CAMPYLOBACTER ENTERITIS IN CHILDREN: CLINICAL AND LABORATORY FINDINGS IN 137 CASES

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ABSTRACT

One hundred and thirty-seven children with Campylobacter diarrhoea were reviewed. The predominant species was C. jejuni. Ninety-five percent of the children were below 5 years of age with 61% of these being 2-12 months old. A slight male preponderance was noted. About half the cases presented with fever and bloody diarrhoea; vomiting was seen in 28% and abdominal colic in only 8%. Moderate to severe diarrhoea was present in 48% of the children. Thirty-seven percent had a history of recent or concurrent illness. Other bacterial enteropathogens together with Campylobacter were isolated in 15% of the children. Erythromycin, the most useful drug, when indicated for Campylobacter infections, had an MIC_{90} of 2 mg/l with 96.2% of the strains being sensitive.

Keywords: *Campylobacter, enteritis, children, antimicrobial susceptibility, clinical features*

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INTRODUCTION

Campylobacter jejuni and *Campylobacter coli* are well established human enteric pathogens that cause diarrhoea and enteritis in patients in both developing and developed countries. Both species make up the most common bacterial cause for acute diarrhoeal illness in developed countries[1] and there appeared to be a bimodal age distribution of *Campylobacter* infection with the highest incidence in infants and in young adults between 15-27 years[2]. In developing countries, the prevalence in children is particularly high and *Campylobacters* ranked as the third most common cause of acute diarrhoeal disease after rotavirus and enterotoxigenic *Escherichia coli*[3].

The few published reports from Singapore and Malaysia[4-6] give a low isolation rate of *Campylobacters* but the true incidence may be 5-10 times greater than that of the industrialised countries. However, the ratio of illness to infection is probably lower and symptomless excreters are common in developing countries[7]. There is still controversy over the exact pathogenic mechanism(s) by which *Campylobacters* induce diarrhoea but there is no doubt that these organisms are aetiological agents implicated in human diarrhoeal disease.

In this paper, we describe the bacteriological, demographic and some clinical characteristics of *Campylobacter* diarrhoeal cases seen in children at the University Hospital, Kuala Lumpur.

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PATIENTS AND METHODS

From June 1982 to May 1988, 7,221 specimens of stool and rectal swabs from paediatric patients less than 12 years of age, were processed for enteropathogens by standard bacteriological techniques. For the isolation of *Campylobacters*, only bloody and watery stool specimens were inoculated on Skirrow's medium (Oxoid, UK) and incubated at 42°C for 48 hours under microaerophilic conditions using an anaerobic gas generating kit (Oxoid, UK) without the catalyst. Organisms showing typical comma, S or spiral forms in Gram-stained smears, actively motile, oxidase and catalase positive, and sensitive to nalidixic acid but resistant to cephalothin were provisionally identified as *Campylobacter jejuni/coli*. The hippurate hydrolysis test was used to distinguish the two species.

The in-vitro susceptibility of 52 strains of *Campylobacters* to 12 antimicrobial agents was determined by an agar dilution method. Antibiotic powders with known potencies used were erythromycin, cotrimoxazole (trimethoprim: sulphamethoxazole 1:19), chloramphenicol, tetracycline, nalidixic acid, ampicillin and kanamycin (Sigma Chemicals, USA), cefotaxime and gentamicin (Roussel Uclaf Laboratories, France), cefoperazone (Pfizer, USA), norfloxacin (Astra, Sweden) and pefloxacin (Rhone-Poulenc, France). Minimum inhibitory concentrations (MIC) were determined using doubling dilutions of antibiotics prepared in Mueller-Hinton agar (Difco, USA) supplemented with 7% laked horse blood (Oxoid, UK) except for cotrimoxazole where supplemented isosensitest agar (Oxoid, UK) was used. The inoculum was prepared from 48-hour plate cultures diluted in Mueller-Hinton broth to give a final inoculum size of approximately 10^4 organisms per spot when delivered by a Denley multipoint inoculator. Inoculated plates were incubated for 48 hours at 37°C under microaerophilic conditions as described earlier. Controls used in each plate were Oxford *Staphylococcus aureus* NCTC 6571 and *Escherichia coli* NCTC 10418. The MIC was defined as the lowest concentration of antimicrobial agent at which there was complete inhibition of growth or the presence of a barely visible haze. For cotrimoxazole, the concentration which inhibited at least 80% of growth

was interpreted as the MIC.

Patients' records were reviewed for demographic data such as age, sex, ethnic group and the following clinical data: (i) presenting signs and symptoms such as fever, vomiting, abdominal colic, severity of diarrhoea, and bloody stool; (ii) previous or concurrent illness such as measles, upper respiratory tract infections, otitis media, bronchopneumonia and others; (iii) oral or intravenous rehydration; and (iv) antibiotic therapy.

RESULTS

One hundred and thirty-seven separate cases of *Campylobacter* diarrhoeas were recorded during the study period. The total number of paediatric stool processed during the period was 7,221 giving a crude isolation rate of 2%. Seventy-six (55%) of the children were seen as in-patients and 61 (45%) were seen on an out-patient basis. Although 137 isolates had been identified as *C. jejuni/coli*, only 83 of these were available for the hippurate hydrolysis test which distinguished 62 (75%) as *C. jejuni* and 21 (25%) as *C. coli*. There were 85 boys and 52 girls, giving a male to female ratio of 1.6:1. About half the patients (41%) were Chinese, 32% Malays, 25% Indians and 2% were classified as others. The distribution amongst the various ethnic groups is in keeping with the racial composition of the population served by the hospital. The age distribution of these cases is shown in Fig 1; the youngest was a 2-day-old baby and the oldest was 10 years. The largest group (61%) was from the 2-12 month age group, 19% from the 2-5 year group and 14% from neonates.

The results of the in-vitro susceptibility studies are shown in Table I. All strains tested were susceptible to chloramphenicol and gentamicin with 96.2% of the strains being sensitive to erythromycin, the traditional drug recommended for invasive *Campylobacter jejuni* disease. The minimum concentration of erythromycin inhibiting the growth of 50% of the strains (MIC_{50}) and 90% of strains (MIC_{90}) was 2 mg/l. Tetracycline had poor in-vitro activity with a MIC_{50} of 4 mg/l and a MIC_{90} of 128 mg/l. 94.2% of the strains tested were susceptible to nalidixic acid while the newer quinolones norfloxacin and pefloxacin had excellent in-vitro activity with a MIC_{90} of 1.0 mg/l for both drugs. Ampicillin at a breakpoint susceptibility of <32 mg/l[8] was active against 90.2% of the strains and amongst the third-generation cephalosporins tested, good activity was seen with cefotaxime (MIC_{90} 32 mg/l) but no activity was observed with cefoperazone (MIC_{50} >128 mg/l).

Fig 1 – Age distribution in *Campylobacter* enteritis.

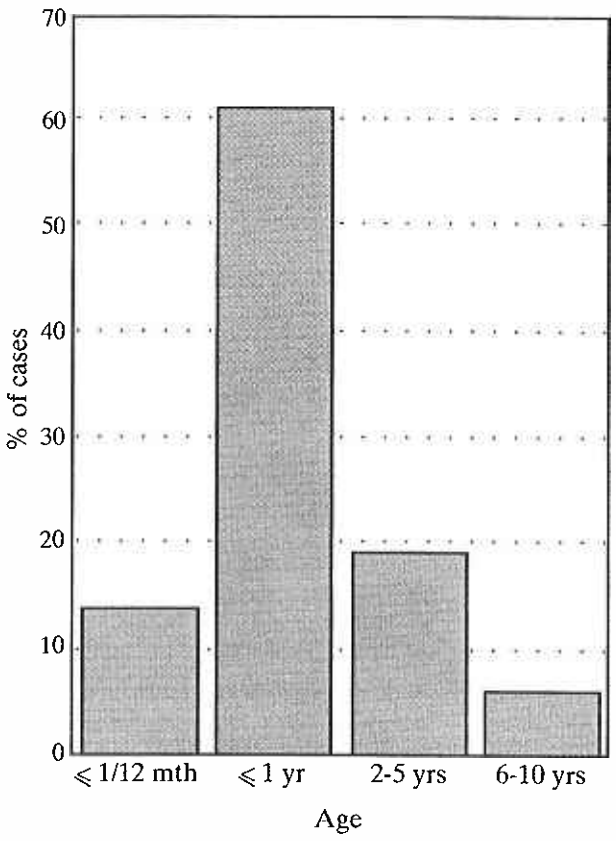

Table I – In-vitro activities of 12 antimicrobial agents against 52 strains of *Campylobacter* species.

Antibiotic (Breakpoint MIC mg/l)[a]	MIC_{50} (mg/l)	MIC_{90} (mg/l)	range (mg/l)	% S
erythromycin (<8)	2	2	0.5 to >128	96.2
cotrimoxazole (<4/76)	1.6/30.4	6.4/121.6	0.2/3.8 to >6.4/121.6	84.6
chloramphenicol (<32)	4	8	1 to 8	100.0
tetracycline (<16)	4	128	0.12 to >128	55.8
ampicillin (<32)	8	16	0.5 to 64	90.2
cefotaxime (<64)	16	32	2 to >128	96.2
cefoperazone (<64)	>128	>128	>128	0.0
gentamicin (<16)	0.12	0.5	0.03 to 1	100.0
kanamycin (<64)	4	>128	0.5 to >128	84.6
nalidixic acid (<32)	8	16	4 to 128	94.2
norfloxacin (<16)	0.5	1	0.03 to 64	98.1
pefloxacin (<8)	0.5	1	0.03 to 16	98.1

a : Breakpoint susceptibility (14)
% S : % susceptible

A little more than half of the children, 74 (54%), presented with fever. The passage of bloody stool was recorded in 70 (51%) of the cases although moderate to severe diarrhoea was recorded only in 66 (48%) children. Other features were vomiting in 38 (28%) cases and abdominal colic was recorded in only 10 (8%) of the children.

Fifty-one children (37%) had a history of recent or concurrent illness such as upper respiratory tract infections in 14, bronchopneumonia 6, post-measles 5, haematological malignancies 4, febrile fits 4, otitis media 3, and surprisingly 9 cases were recorded in children who had been admitted for milk challenge. Other miscellaneous factors such as intussusception, Reye's syndrome and congenital duodenal atresia were recorded in 6 children.

Other bacterial enteropathogens were isolated together with *Campylobacters* in 15% of the children. These were: *Salmonella* species in 11, *Aeromonas* species 3, *Plesiomonas shigelloides* 3, *Shigella* species 2 and enteropathogenic *E. coli* in 2.

Antibiotic therapy for enteritis was administered to 36 (26%) children, these being cotrimoxazole for 10 children, neomycin 9, erythromycin 9, ampicillin 7 and amoxycillin for one.

Rehydration therapy was recorded in 50 (37%) children; of these, 12 required intravenous infusion and 39 were given oral fluids (gesolyte).

DISCUSSION

Most microbiology laboratories are well equipped to isolate and identify *Campylobacters*. Nevertheless, our crude isolation rate of 2% is low compared to published reports from the West. One of the reasons may be that *Campylobacter* diarrhoea is a self limiting disease and only the moderate to severe infections are seen in the hospital. This is supported by the fact that only 55% of our cases needed in-patient treatment, and of these, only 12 required intravenous fluids. Another reason may be that not all stool samples were processed for *Campylobacters* and the true incidence may be higher.

The majority of our isolates (75%) were *C. jejuni* and this confirms published reports of *C. jejuni* being the most common species giving rise to human infection[9]. *Campylobacters* exist as commensals in the intestinal tracts of a wide variety of wild and domestic animals and commercially raised poultry are known to be one of the most common sources of infection[9]. In Malaysia, *Campylobacters* have been isolated from chickens, puppies as well as from poultry for sale[10].

It is not surprising that 75% of the children in our study were less than one year of age. In Thailand, Varavithya et al[11] found *Salmonellae* and *C. jejuni* as the commonest cause of diarrhoea in children less than 6 months of age. *Campylobacter* is a foodborne infection and strict food hygiene is necessary for its prevention, especially in infants and young children. Since the disease is mainly confined to young children in developing countries, repeated exposure probably results in immunity early in life[1]. In our study there were 3 babies less than 3 days old with *Campylobacter* infection, but we were unable to obtain any antepartum history of diarrhoea from the mothers. Perinatal transmission maybe due to exposure in-utero, during passage through the birth canal or during the first days of life[1].

Symptoms and signs of *Campylobacter* infections are not so distinctive to differentiate it from illness caused by other enteropathogens. Published reports indicate that about 50% of patients present with fever which agrees with our figure of 54%. Abdominal colic is said to be a characteristic feature of *Campylobacter* diarrhoea but in our study only 8% had abdominal colic. This low figure is probably a reflection of the age group of our patients as most were less than 1-year-old and hence would have been unable to complain of abdominal pain or discomfort. Vomiting was seen in 26% of children although this is said to be rare in *Campylobacter* infection.

Inflammatory changes accompanied by haemorrhagic lesions have been reported in the jejunum and ileum of patients with *Campylobacter* enteritis[12]. But the frequent finding of bloody stools suggests that mucosal damage of the large intestine is also involved[13].

Bloody stool seen macroscopically was recorded only in 51% of our patients. The type of diarrhoea ie either watery or with blood is probably due to the type of exotoxin produced by the infecting strain whether it is a cytotoxic enterotoxin [14] or a cytotoxin [15]. It is a well known fact that recent debilitating illness can predispose children to infectious diarrhoeas. Fifty-one of the 137 (37%) children gave a history of recent or concurrent illness, the commonest being upper respiratory tract infection, bronchopneumonia and measles.

Isolation of more than one enteropathogen is not infrequent in developing countries and 15% in our study is not too high. But these children with mixed pathogens did not particularly have a more severe infection. Normal carriage of some enteropathogens is possible but very rare in *Campylobacter* being less than 1% [1].

The role of antimicrobial agents in the therapy of diarrhoeas is somewhat controversial. Chemotherapy for most intestinal infections is often considered ineffective and even disadvantageous.

Antimicrobial therapy of invasive disease with *C. jejuni/coli* has traditionally been with erythromycin. However, varying geographical differences have been noted in the in-vitro susceptibility of *C. jejuni* to this macrolide [16]. In our setting, erythromycin with MIC_{90} of 2 mg/l remains a useful drug in the empirical management of invasive disease. Resistance to erythromycin and cotrimoxazole was lower amongst our strains (3.8% and 15.4% respectively) as compared to 12.6% and 30.1% respectively in the study carried out by Michel et al on *C. jejuni* strains isolated in Israel [16]. However, resistance to ampicillin and tetracycline was higher in our study. Gentamicin and chloramphenicol with MIC_{90} of 0.5 mg/l and 8.0 mg/l respectively were active against all the strains tested at our centre but the in-vivo response to these agents is not well documented. The fluoroquinolones, norfloxacin and pefloxacin had high degrees of in-vitro activity (MIC_{90} of 1 mg/l for both) and while both drugs may be useful in the management of severe cases of enteritis, pefloxacin with good serum and tissue levels is an alternative to erythromycin for invasive disease. However, the safety of using quinolones in children is an unresolved issue. The newer macrolide azithromycin, with greater intrinsic activity and improved pharmacokinetic properties needs to be investigated as an alternative therapy.

REFERENCES

1. Butzler JP, Glupczynski Y, Goossens H. *Campylobacter* and *Helicobacter* infections. Curr Opin Infect Dis 1992; 5.80-7.
2. Skirrow MB. A demographic survey of *Campylobacter, Salmonella* and *Shigella* infections in England. Epidem Inf 1987; 99:647-57.
3. Crewe-Brown HH, Greeff AS, Fripp PJ, Bothma MT, Steele AD, Bok HE, et al. In: Aetiology of summer diarrhoea at Ga-Rankuwa Hospital. Proceedings of the symposium on infections in developing countries (South Africa, 1989). Parow: South African Medical Research Council, 1989: 232-3.
4. Puthucheary SD, Lin HP. Bacteraemic enteritis due to *Campylobacter jejuni*. Med J Malaysia 1982; 37:378-80.
5. Lam S. *Campylobacter* enteritis in Singapore. Singapore Med J 1981; 22:173-5.
6. Koe SL, Tay LK, Puthucheary SD, Lam SK. Infectious agents causing diarrhoea in Malaysian children. Mal J Child Health 1991; 3:29-33.
7. Taylor DE, Echeveria P, Pitarangsi C, Seriwatana J, Bodhidatta L, Blaser M. Influence of strain characteristics and immunity on the epidemiology of *Campylobacter* infections in Thailand. J Clin Microbiol 1988; 26:863-8.
8. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. No. 7A. Vol.5. No.22. Villanova. PA, USA 1985:601.
9. Butzler JP. *Campylobacter* infection in man and animals. Florida: CRC Press. 1984.
10. Tay ST. Possible virulence factors associated with *Campylobacter* infections. M Med Sc thesis, University of Malaya, 1993: 47.
11. Varavithya W, Vathanophas K, Bodhidatta L, Punyaratabandhu P, Sangchai R, Athipanyakom S, et al. Importance of *Salmonellae* and *Campylobacter jejuni* in the aetiology of diarrhoeal disease among children less than 5 years of age in a community in Bangkok, Thailand. J Clin Microbiol 1991; 28:2507-10.
12. Goodman DJ, Wise KA. Peritonitis caused by *Campylobacter jejuni* and serologically confirmed in a patient being treated with continuous ambulatory peritoneal dialysis. J Infect 1990; 21:71-5.

13. Blaser MJ, Parsons RB, Wang WLL. Acute colitis caused by *Campylobacter fetus* subsp. *jejuni*. Gastroenterology 1980; 78:448-53.

14. Johnson WM, Lior H. Cytotoxic and cytotonic factors produced by *Campylobacter jejuni, Campylobacter coli*, and *Campylobacter laridis*. J Clin Microbiol 1986; 24:275-81.

15. Johnson WM, Lior H. Toxins produced by *Campylobacter jejuni* and *Campylobacter coli*. Lancet 1984; i:229-30.

16. Michel J, Rogel M, Dickman D. Susceptibility of clinical isolates of *Campylobacter jejuni* to sixteen antimicrobial agents. Antimicrob Chemother 1983; 23:796-7.