LEADING ARTICLE

CAMPYLOBACTER ENTERITIS IN CHILDREN

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The genus *Campylobacter* is widely distributed in nature and includes a variety of species recognised as human and animal pathogens. The common human pathogens include *Campylobacter jejuni, Campylobacter coli, Campylobacter laridis* and *Campylobacter fetus. Campylobacter jejuni, Campylobacter coli* and *Campylobacter laridis* cause acute enterocolitis while *Campylobacter fetus* is an opportunistic organism which causes systemic Campylobacteriosis in immunocompromised patients.

The accompanying article from Malaysia, "*Campylobacter* Enteritis in Children – clinical and laboratory findings in 137 cases", outlines the clinical profile of children with *Campylobacter* enteritis seen in this region[1]. As in previous reports from Malaysia and Singapore, the isolation rate of *Campylobacter* enteritis is low, ranging from 1.2% to 3.8%[2,3].

The age groups of patients in this study are similar to that seen in developing countries, ie majority of cases occur in infancy.

The clinical profile of these children is similar to that reported in other series, with the possible exception of the incidence of abdominal pain which is a characteristic feature of *Campylobacter* enteritis. Abdominal pain which has been reported in up to two-thirds of patients in other series was only reported in approximately 8% of the children in this study. This is probably due to the young age of the patients as explained by the authors as well as the retrospective nature of the study.

HISTORICAL ASPECT

Campylobacter species have been well known to veterinarians as a cause of abortion in cattle and sheep since the initial isolation of Vibroid shaped organisms by McFaydeen in 1909[4].

Levy in 1946[5] reported the first putative cases of an outbreak of acute enteritis due to *campylobacters.* Stool microscopy showed motile "vibrio-like" organisms but no such bacteria was grown on stool culture. Blood culture grew a "spirillum" similar to "vibrio jejuni" which causes bovine diarrhoea.

King in 1957[6] observed that *vibrio foetus* isolates could be divided into two groups. She called the group that grew best at 42°C "related vibrios" (now represented by *Campylobacter jenuni* and *coli*). These isolates were from blood cultures of patients with diarrhoea and attempts to culture them from faeces were unsuccessful due to overgrowth of coliforms.

Veron and Chatelain in 1973[7] proposed that these "related vibrios" be placed in a separate genus *Campylobacter* as these organisms differed from classical cholera organisms in certain fundamental aspects. *Campylobacter* do not ferment carbohydrate and differed in deoxyribonucleic acid composition from vibrio species.

In 1972, Dekeyser and Butzler[8] reported the first positive stool cultures using faecal suspensions passed through a millipore filter which holds back other organisms.

Skirrow in 1977[9] using unfiltered stool specimens on a selective medium (blood agar containing vancomycin, polymixin B and trimethoprim) showed that these organisms are a common cause of diarrhoea.

Since then, *Campylobacters* have been recognised as important enteric pathogens in human diarrhoeal disease throughout the world and are particularly prevalent in the tropics and developing countries. In the developed countries, it is one of the leading causes of bacterial diarrhoea.

RESERVOIRS OF INFECTION

Campylobacteriosis is a zoonosis. The gastrointestinal tract of both wild and domestic animals form the main reservoir of infection. Domestic animals such as cats and dogs especially young animals with diarrhoea, and a wide variety of farm animals such as chickens, pigs and sheep constitute the sources of human infection.

Poorly cooked chicken is probably the most frequent means of infection. *Campylobacter jejuni* can be cultured from chicken and turkey carcasses after slaughter[10]. Red meats are generally much less frequently contaminated although *Campylobacter coli* is particularly associated with pigs.

Raw cow's milk have been associated with outbreaks of *Campylobacter* enteritis[11].

Waterborne outbreaks have also been reported. Untreated water or water supplies contaminated by birds or other small animals are potential sources of infection[10,12].

MODE OF TRANSMISSION

Transmission occurs by the faecal-oral route through contaminated food, water or unpasteurised milk or by direct contact with faecal material from infected animals or humans.

Person to person transmission has occurred when the index cases were young children who were incontinent of faeces. Perinatal transmission from patients who may not be symptomatic has been documented. This may be due to transmission in-utero, during or after delivery.

Most infections appear to be sporadic with no easily demonstrable source.

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EPIDEMIOLOGY

Campylobacter has been isolated from between 4% to 35% of children[13-18] with acute diarrhoea throughout the world. The rates in developing countries are higher than those in developed countries. The epidemiological features of *Campylobacter* enteritis are different in developing and developed countries.

In the developed countries, there is a bimodal age distribution of cases with peaks in infancy and between 10 and 30 years of age[17]. The illness can be severe with fever, bloody diarrhoea and faecal leucocytes. Asymptomatic infection is uncommon (<1%) and the mean duration of convalescent phase excretion after an acute infection is 2-3 weeks.

In the developing countries, *Campylobacter* infection is hyperendemic[15-21]. The peak rate of occurrence is during the first 2 years of life and declines rapidly thereafter[15-18]. Illness may be mild and less frequently accompanied by bloody diarrhoea, and it is found in up to 17% of healthy subjects[16]. The duration of convalescent phase excretion is also shorter.

The different epidemiological characteristics suggest that repeated exposure to infections lead to development of immunity in early life[18]. This may attenuate or modify the illness and decrease the length of excretion time. This view is supported by the observation that serum IgA to cell surface antigens of *Campylobacter jejuni* rises progressively through life among healthy persons in Thailand[18] and Bangladesh[20] and is correspondingly higher than age matched populations in the US. In addition, both *Campylobacter* isolation rates and the case to infection ratio decline rapidly with age in developing countries.

Another suggested contributory factor is the proportion of *Campylobacter coli* strains isolated. *Campylobacter coli* strains cause a milder disease and is not associated with bloody diarrhoea. Hence *Campylobacter* infections may appear to be mild in areas where *Campylobacter coli* is frequently encountered eg Hong Kong (41%)[21] and the Central African Republic (39%)[22]. The proportion of *Campylobacter coli* isolated in Singapore is 10.9%[2], and in this accompanying article from Malaysia, it is 25%[1] while in the United Kingdom and Canada, it is 5%[10] and 3.3%[23] respectively.

The Malaysian study on *Campylobacter* enteritis in this issue of the Singapore Medical Journal reported an isolation rate of 2% in children <12 years of age[1].

This is similar to that observed in children from Singapore 3% (<5 years)[2], Hong Kong 1.4%[21], China 2%[24], and Saudi Arabia 1%[25]. These rates are relatively low compared to those in the neighbouring countries in this region eg Thailand 18%[18] (<5 years) and Indonesia 10%[26] (all ages) and even to the developed countries eg Australia 5%[14], Canada 4.3%[13] and United Kingdom 7.1%[9] (all ages).

PATHOGENESIS

The principal sites of infection of *Campylobacter* enteritis are the jejunum, ileum and colon. Haemorrhagic lesions in the jejunum and first part of the ileum have been reported at autopsy of a patient who died of *Campylobacter* enteritis. Inflammation of the ileum has been observed during laparotomy. Large colon involvement is implicated by the frequent presence of blood, pus and mucus in the stools. Sigmoidoscopic and histologic examinations have revealed inflammatory changes similar to that of inflammatory bowel disease.

The exact mechanism by which *Campylobacters* cause disease is still unknown. Several pathogenic properties have been identified in the various strains of *Campylobacter jejuni*. Some invade the intestinal mucosa, some produce an enterotoxin similar to those of *Vibrio* cholera enterotoxin, some produce a cytotoxin and some have no detectable pathogenic property.

Klipstein et al[27] showed that enteroinvasive strains are associated with bloody diarrhoea and faecal leucocytes with or without red blood cells and the enterotoxigenic strains cause watery diarrhoea. However enterotoxigenic strains were isolated as frequently from asymptomatic children as from children with watery diarrhoea in India[19]. The role of cytotoxin in the pathogenesis of *Campylobacter* enteritis remains uncertain. Hence the clinical and epidemiological significance of toxins in the pathogenesis of Campylobacteriosis remains to be established.

CLINICAL FINDINGS

The clinical presentation of *Campylobacter* enteritis cannot be readily distinguished from that caused by other enteropathogens. *Campylobacter* enteritis is found in all age groups and there is a preponderance of boys over girls up to the age of 14 years. The incubation period is variable, ranging from 1 to 7 days. Clinically, *Campylobacter* infections can be asymptomatic or present as watery diarrhoea, a dysentery-like syndrome mimicking inflammatory bowel disease or rarely as an extraintestinal infection (meningitis, urinary tract infection, cholecystitis).

Typically there is a prodromal period of fever, malaise, headache and myalgia followed by abdominal pain, diarrhoea and nausea.

Diarrhoea is usually present at the onset of illness or develops within 1 to 3 days. The diarrhoea is generally profuse, watery and foul smelling. After 1 to 3 days, many patients have blood streaked stools. The incidence of bloody stools varies from 15.4%[28] to 92%[29].

Abdominal pain may occur at onset or precede the diarrhoea by as much as 2 weeks and may persist after the diarrhoea has subsided. The pain is usually periumbilical or epigastric, colicky. most prominent just before defecation and is relieved by passage of stools or flatus. It may be severe and mimic a surgical emergency eg appendicitis, intussusception or acute peritonitis. Abdominal pain has been reported in up to two-thirds of patients[13, 29].

Fever is a common feature in *Campylobacter* enteritis and has been reported in 86% of patients[29]. It is, however, infrequent in infants less than 6 months of age[30]. Significant vomiting and dehydration are uncommon in *Campylobacter* enteritis. Vomiting has been reported in 30% of children[27]. Bacteraemia is probably more frequent than is clinically reported and the organism has been isolated from the blood during the prodromal phase.

Most patients recover in less than a week although 20% may have a relapse or a prolonged or severe illness. Faeces remain positive for *Campylobacter* for between two to seven weeks.

Death is rare but has been reported in debilitated children and in elderly patients. Complications of *Campylobacter* enteritis include reactive arthritis, Reiter's Syndrome, Guillian Barre Syndrome and erythema nodosum.

DIAGNOSIS

Campylobacter enteritis can be rapidly diagnosed by dark field microscopy or phase contrast microscopy of fresh faecal specimens. *Campylobacter* organisms are distinguished by their rapid darting and spinning motion.

Culture of *Campylobacter* organisms has been made relatively simple with the introduction of various types of selective media. Specimens must be incubated at 42°C under microaerophilic conditions for 48 hours.

Serologic diagnosis may be useful in culture negative cases of *Campylobacter* infection eg reactive arthritis and erythema nodosum.

TREATMENT

Chemotherapy shortens the duration of faecal bacterial excretion from a mean of 2 to 3 weeks to a few days, but does not shorten the duration of diarrhoea unless given early in the course of illness[31].

Generally, *Campylobacter* enteritis is a mild disease and does not warrant chemotherapy. Frequently, by the time a bacteriologic diagnosis is made, the patient is already well on the way to recovery.

Erythromycin is the drug of choice. Other antimicrobial agents which are likely to be useful include tetracycline (contraindicated in those <7 years old), chloramphenicol and gentamicin.

Antibiotic treatment is justified in patients who are seen in the early stages of the disease, for those who may be potential sources of infection for others eg infants with diarrhoea in day nurseries and in the rare patient with systemic spread of the infection.

Resistance to erythromycin has been reported from 9-15%[32] in some countries. In Singapore, erythromycin resistance has been reported in 51% of isolates[2]. The reason for this high resistance rate is uncertain. Whether it is a characteristic of the strains isolated locally or related to the pattern of antibiotic usage in the animal/poultry industry would require further studies to clarify.

Several studies have shown that ciprofloxacin is an effective treatment for *Campylobacter* enteritis. However, the safety of quinolones in children is not established. The newer macrolides (clarithromycin, roxithromycin) with its pharmacological advantages may have a role but further evaluation is required.

Hence should chemotherapy be required, the choice of antibiotics should be based on invitro sensitivity tests.

PREVENTION

Prevention of *Campylobacter* enteritis requires hygienic handling of all raw meats especially poultry in kitchens, control of infection at all stages of poultry production, purification and prevention of contamination of water supplies, heat treatment of all milk sold for human consumption, sensible hygienic precautions in dealing with young domestic pets with enteritis and general public awareness of the hazard.

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