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Mini-symposium **Alimentary**

Gastro-intestinal pathogens of recently discovered significance

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Gastro-intestinal infection is an important cause of morbidity and mortality, particularly in children. Although significant advances have taken place in the diagnosis of gastroenteritis approximately 5 million deaths due to this condition occur each year in the developing world in children under 5 years.

During the 1970s rotavirus was identified as one the most important pathogens in childhood diarrhoea increasing the specific diagnosis for diarrhoea from 10–20% to 40–70%. Since then a further diverse group of organisms have been implicated as gastrointestinal pathogens. Some like *Helicobacter pylori* are definitely pathogenic, whereas considerable controversy still surrounds the role of others such as Aeromonas and Plesiomonas in gastrointestinal disease. We review the clinical, epidemiological and laboratory features of these infections and discuss their importance in children.

Aeromonas

Aeromonas has been recognised as a pathogen in immunocompromised hosts since 1968.[1] There now exists a large body of mainly epidemiological evidence implicating Aeromonas as enteric pathogens in the normal host, particularly in children.

Microbiology

The organisms are gram negative facultative anaerobic, motile, bacilli with a single flagellum. Three species are recognised — *A. hydrophilia*, *A. sobria* and *A. caviae*.

Isolation of Aeromonas from stool requires a selective media supplemented with ampicillin to which, at low concentrations, most Aeromonas species are resistant.

Epidemiology

A. hydrophilia and *A. sobria* account for most infections. A recent study of the secretory IgA(sIgA) response in subjects with diarrhoea shedding Aeromonas species supports their role as human enteropathogens. There was a significant sIgA titre rise in response to diarrhoea associated with *A. hydrophilia* and *A. sobria* but not with *A. caviae*. Nonetheless some studies implicate *A. caviae* as a significant pathogen in children.[2,3,4] Aeromonas species are found in fresh water, sewage, animal faeces and a variety of foods including ground beef, pork, shellfish, poultry and raw milk.[3] Untreated drinking water is a risk factor for the acquisition of Aeromonas enteritis and antibiotic therapy has also been implicated.[3,4]

Virulence determinants

A major difficulty in confirming this organism as a gastro-intestinal pathogen in humans has been the inability to correlate pathogenicity with specific virulence factors. Cytotoxin and enterotoxin production, the expression of haemagglutinins and the ability to adhere to and invade epithelial cells have all been implicated. However presence of these virulence factors does not correlate with infection in humans.[2,5] In addition challenge studies in human volunteers are not conclusive. In one study diarrhoea was induced in only 2 of 57 volunteers using Aeromonas strains with known toxin activities.

Clinical features

An acute self limited watery diarrhoea associated with fever and cramps is the most common manifes-

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tation of infection with Aeromonas sp. Diarrhoea persisting beyond 14 days is unusual. Chronicity of diarrhoea has been documented but this would seem to be more common in the older age group.[3,4,6]

The finding of a predisposition in the younger age group to Aeromonas suggests that primary exposure to enteropathogenic strains of this organism, before the development of enteric immune defense systems, is most likely to manifest as disease. Aeromonas hydrophilia associated diarrhoea has been described in the neonatal period.[7]

Blood does not generally occur in the stools (although occult blood is found in up to 33%[8] and Challipalli et al noted frank blood in 25% of their study). Leucocytes are rarely present in stools.[9] Transmission of Aeromonas infection between close contacts is unusual.[2,3] Asymptomatic carriage has been documented to be as high as 27%,[6] but most studies record rates of less than 10%. Chronic post infection carriage has also been documented.

The self limiting nature of most cases of Aeromonas associated diarrhoea means supportive treatment is all that is necessary. Specific guidelines for antibiotic treatment of this condition do not exist. Most of these organisms are resistant to penicillins and first generation cephalosporins and to a lesser degree to erythromycin. Aminoglycosides, chloramphenicol, kanamycin and trimethoprim-sulphamethoxazole are all effective in-vitro and the latter has been used effectively in a number of patients. Prolonged or severe disease warrants a course of antibiotic treatment.[10]

Plesiomonas

Aeromonas and *Plesiomonas shigelloides* belong to the family Vibrionaceae and share many similiarities. The name Plesiomonas is derived from the Greek word for neighbour, referring to their close relationship. The evidence linking this organism with enteric disease is mainly epidemiological and more tenuous than for Aeromonas.

Microbiology

This is a gram-negative facultative anaerobic rod. It grows well on Salmonella-Shigella and MacConkey agars and can be differentiated from enterobacteriaceae by a positive oxidase test.

Epidemiology

Plesiomonads have been isolated from up to 17% of diarrhoeal stools in contrast to less than 0.1% of stools from persons without evidence of enteric infection.[11] They have been implicated as pathogens in both immunocompetant and immunodeficient hosts[12] and have been linked with consumption of raw oysters[11] and foreign travel, particularly to Mexico.[11] Holmberg et al noted the onset of diarrhoea and prolonged symptoms in two patients who took ampicillin to which their Plesiomonas strains were resistant and the elimination of symptoms in seven patients who took antibiotics to which plesiomonas strains were sensitive suggesting pathogenicity of Plesiomonas in these cases. However two recent reports[13,14] finding little laboratory evidence for the pathogenicity of these organisms have highlighted the uncertainty surrounding their place in human gastrointestinal disease.

Virulence determinants

Enteroinvasive[11] and enterotoxic[15] aetiologies have been suggested by different authors on clinical grounds. Abbott et al could not find supportive evidence for either.[13]

Clinical features

Most reports suggest that a mild, self limiting, watery diarrhoea is usual. However bloody and mucousy stools and stools with faecal leucocytes have been reported[11] as have abdominal cramping and vomiting.

Most isolates appear sensitive to trimethoprim-sulphamethoxazole, aminoglycosides and chloramphenicol and the former has been used in a limited number of patients with apparent success.[11] It is probably prudent to treat prolonged or severe cases but the routine administration of antimicrobials in Plesiomonas associated diarrhoea is not justified.

Enterohaemorrhagic *Escherichia coli*

Escherichia coli, first described in 1885, has become the most thoroughly understood free-living organism on earth. *E. coli* can be subdivided into four groups according to the manner in which they cause illness, enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC) and enterohaemorrhagic *E. coli* (EHEC). *E. coli* are important enteric pathogens mainly in the developing world. However strains of enterohaemorrhagic *E. coli* (classically *E. coli* O157:H7) which elaborate a specific cytotoxin termed verotoxin have recently been implicated as an important cause of haemorrhagic colitis and haemolytic uraemic syndrome (HUS) in developed countries.[15,17]

Microbiology

E. coli is a gram-negative motile bacillus which is an important part of the normal colonic flora. Most verotoxin producing *E. coli* (VTEC) can be distinguished from other strains of *E. coli* by their inability to ferment sorbitol. Positive isolates are confirmed as O157 by tube agglutination. Some VTEC belonging to serogroups other than O157 must be distinguished from other *E. coli* by directly demon-

strating verotoxin production (a cytotoxic effect on Vero cells).

Epidemiology

VTEC have been identified in up to 40% of ground beef samples, and may also be found in raw milk poultry, pork and lamb. Dairy cattle are a major reservoir for human infection. Family and day care centre outbreaks have occurred. Household contacts of children with haemolytic uraemic syndrome are commonly colonised with verotoxin producing *E. coli*[18] indicating that person-to-person spread is an important mode of transmission. Age and seasonal patterns are similiar for HUS and *E. coli* O157:H7 gastroenteritis.[19] There is a higher incidence of HUS among children in upper socioeconomic groups and this could be due to an immune related protective effect of early infection in lower socioeconomic groups.[20]

Virulence determinants

The exact pathogenic mechanism by which VTEC cause disease is not yet known but is presumably related to the verotoxins VT-1 and VT-2 which they produce.[21] VT-1 is structurally indistinguishable from Shiga toxin produced from *Sh. dysenteriae* and is also called Shiga-like toxin-1.

Clinical features

A spectrum of illness may result from infection with VTEC including asymptomatic infection, mild diarrhoea, haemorrhagic colitis and haemolytic uraemic syndrome. Haemorrhagic colitis typically presents with abdominal cramps and watery diarrhoea progressing to bloody diarrhoea. Fever is conspicuously absent. Pai et al found *E. coli* O157:H7 in 40% of patients presenting to a casualty department with bloody diarrhoea.[19]

HUS is the leading cause of acute renal failure in children and has a significant case fatality rate.[20,22] HUS typically presents following an acute 'prodomal' bloody diarrhoea. This is followed 5 days to 2 weeks later by hypertension, oliguria, azotaemia, anaemia and thrombocytopaenia. Further complications may ensue in the severely affected patient including coma, seizures, cardiac failure and bleeding. Death occurs in 5% and 15% will have residual renal impairment. There is now an overwhelming body of information linking classical HUS with VTEC infection.[16–21] VTEC is isolated from up to 88% of stools from patients with HUS.[21] Asymptomatic carriage has been widely reported in HUS family contacts but a chronic carrier status is unlikely.[18]

The diagnosis of VTEC infection is by isolation and serotyping of the organisms from faecal specimens. These may however be absent later in the course of the disease. Recently an ELISA method for detection of serum antibodies to the lipopolysaccharide of *E. coli* O157:H7 has been shown to be a useful diagnostic tool.

Treatment of VTEC related diarrhoea with antibiotics has not yet been adequately addressed.[23]

Helicobacter pylori

Helicobacter pylori is the major cause of chronic antral gastritis in adults and children. The organism is also of major importance in the development of duodenal ulcer disease. Recent reviews have dealt with the role of this organism in both children and adults.[24,25]

Microbiology

H. pylori is a spiral or curved, gram negative, motile bacillus which has multiple unipolar flagellae and produces large amounts of urease. The organism grows well under conditions of reduced oxygen. It has a very long incubation period of up to 7 days. A haemin source is always necessary for growth. The organism can be cultured on solid media such as charcoal, blood or Skirrows medium.

Epidemiology

The prevalence of *H. pylori* colonisation of the gastric mucosa increases with age. While in developed countries less than 10% of children are infected in the first decade, up to 50% of 60-year olds are colonised. The infection is more common in individuals living in poor socio-economic circumstances. Children in developing countries are often colonised at an early age. The organism has only been identified on gastric tissue. Infection appears to be clustered within families and in institutions for the mentally handicapped. The precise mode of transmission is not known.[25]

Virulence determinants

H. pylori is motile and can penetrate the gastric mucus layer. It produces urease which may be important as a virulence factor. It also produces cytotoxins the importance of which have not yet been determined. *H. pylori* adheres to the gastric mucosa in a classical effacing type manner. The organism elaborates a substance which is capable of inhibiting parietal cell acid production. The relevance of this parietal cell inhibition to the virulence of the organism is not known.

Clinical features

H. pylori colonisation of the gastric mucosa is always associated with histological evidence of gastritis.[26] This gastritis may not be apparent at endoscopy but in children a nodular appearance of the gastric mucosa is identified in some cases.[27] When primary

duodenal ulcer disease is present, in children and adults, *H. pylori* colonisation of the gastric mucosa is always present.[28]

At this time there is no convincing evidence to suggest that *H. pylori* associated gastritis is a cause of symptoms. The prevalence of *H. pylori* associated gastritis is not increased among individuals with recurrent abdominal pain. Furthermore *H. pylori* gastritis is present in large numbers of asymptomatic children.

The organism is important in relation to duodenal ulcer disease. Studies in adults demonstrate that if *H. pylori* is eradicated from the gastric mucosa duodenal ulcers do not relapse.[25] Preliminary studies in children confirm that this is also true in the paediatric age group. Recently epidemiological studies have demonstrated that early infection with *H. pylori* may be an important risk factor for the subsequent development of gastric carcinoma.

H. pylori can be eradicated from the gastric mucosa using a combination of colloidal bismuth subcitrate and ampicillin or metronidazole. Such treatment should be undertaken in all children with duodenal ulcer disease. Whether *H. pylori* gastritis without duodenal ulcer disease requires treatment is presently not determined.

Cryptosporidium parvum

While much of the literature on human infection with this organism concerns infection in immunocompromised individuals the organism was first recognised as a human pathogen in an immunocompetant 3-year old in 1976.[29] Prior to this it had long been recognised as an enteric pathogen in veterinary medicine. Cryptosporidium is definitely associated with diarrhoea in the immunocompromised host. There is still controversy regarding its pathogenicity in immunocompetent individuals. It appears to cause diarrhoea in malnourished children.

Microbiology

Cryptosporidium is a coccidian parasite with a complex life cycle which it can complete within the human host. Within the small intestine the sporozoites (excysted from the ingested oocyst) attach to the epithelium and are enveloped by the microvilli; unlike other intestinal protozoa, further development is intracellular.[30] Oocysts can be identified in stools using hematoxylin-eosin, Giemsa or more specialised staining techniques. Examination of small bowel aspirates or of histological sections may also be useful in establishing the diagnosis.

Epidemiology

Cryptosporidium sp. are found throughout the world but are generally more prevalent in developing countries. Asymptomatic carriage is common. In India 22% of asymptomatic normal children under 6 months had the organism present in stools.[31] In the same study 13% of children less than 4 years with acute diarrhoea had cryptosporidium isolated from stools. In developed countries isolation rates in diarrhoea are of the order of 1–7%.[32] Animals act as reservoirs for human infection but transmission in humans is probably mainly person-to-person and via contaminated water supplies. Day care facilities are probably a risk factor for children.

Virulence determinants

No specific virulence factors have been identified. There is not overt invasion of the intestinal epithelium. The marked variation in clinical spectrum might be accounted for by the elaboration of different cytotoxins by various strains of cryptosporidia as is seen with *Entamoeba histolytica.*

Clinical features

In the immunocompetent, host diarrhoea follows an incubation period of 1–7 days and lasts 3 days to 3 weeks with a mean duration of 6 days.[30,33,34] Vomiting is frequent as is cramping and fever and there may be a cough. Diarrhoea is offensive and watery. Dehydration occurs in a significant proportion. Thompson et al have noted that the disease is more common, and dehydration more significant in older infants (>2 years). Chronicity in the immuncompetant host is recognised.

A spectrum of histological changes in the small intestine ranging from partial to subtotal villous atrophy is seen.[33] Some studies have noted malabsorption occurs in both animals and humans. The disease is more severe in malnourished children. In immunodeficient patients, and particularly in patients with acquired immune deficiency syndrome (AIDS) cryptosporidiosis is associated with more severe and prolonged diarrhoea, with a high case fatality rate. The life cycle of the organism in immunodeficient hosts is different and infection may be widespread throughout the gastrointestinal tract.[30] Clifford et al noted that the disease was more severe in HIV sufferers than in renal transplant patients on immunosuppressive treatment and suggest that this may be due to preexisting gastrointestinal damage. Cryptosporidiosis is a rare cause of cholecystitis, sclerosing cholangitis and pancreatitis in the immunodeficient host.

Treatment of cryptosporidiosis is supportive in mild cases. In severe disease the macrolide Spiramycin has been evaluated but is not proven to be effective,[23] except perhaps in the early stages of HIV infection.

Newer treatments with bovine and cow milk immunoglobulin are being studied. The somatostatin analogue Octreotide has been used to control severe intestinal fluid loss in AIDS patients.

Isospora belli

This is another coccidian protozoan. Although recognised as a cause of travelers diarrhoea and implicated in several institutional outbreaks of enteritis the organism is mainly of interest at present as a cause of diarrhoea in HIV infection.

Microbiology

Isospora oocysts are similiar to cryptosporidia but can be differentiated by their elliptical shape and larger size.

Epidemiology

These organisms are recognised in up to 15% of Haitians with HIV and will probably be increasingly documented in HIV sufferers in the developed world when looked for routinely. Sources of infection are uncertain but person to person transmission, transmission from animals and from contaminated water supplies have been implicated.

Clinical features

As in cryptosporidiosis there is watery diarrhoea with abdominal cramps and weight loss. It is usually self limiting but may become chronic in the immunocompromised patient. Recurrences are a common feature of infection in AIDS patients. Small bowel pathological changes including villous atrophy and infiltration of the lamina propria with eosinophils have been documented.

Trimethoprim-sulfamethoxazole is an effective treatment in Isosporiasis and is also useful as a suppressive treatment to prevent recurrences in HIV sufferers.

Viruses

The clinical, pathophysiological and epidemiological features of rotavirus, first described in 1973, have been well documented. In the last decade a number of other viruses have been identified as possible gastrointestinal pathogens in children. These include enteric adenovirus, Norwalk and Norwalk-like agents, astrovirus, calici and calici-like virus, coronavirus and other small round viruses which are of presumed but as yet unproven pathogenicity. These agents share many features in common and will be considered together.

Virology

These organisms are all classified as small round viruses (SRVs). The Norwalk virus is the best characterised of the group. It is a small 27 nm particle which has been found in the stools of patients with diarrhoea during epidemics and after transmission to human volunteers. They are difficult to visualise on electron microscopy and cannot be propagated in vitro. However an enzyme-linked immunoassay has recently been developed which will facilitate their detection. The human calicivirus has a distinctive 6-pointed star appearance and astrovirus a 5- or 6-pointed star on the surface. Coronavirus is an RNA virus with multiple surface projections.

Adenovirus types 40 and 41 are icosahedral DNA viruses of similar size to rotavirus. Much of the strong evidence linking them to diarrhoea comes from direct electronmicroscopic studies.

Epidemiology

Further studies are required on many of these viruses in relation to their role in childhood diarrhoea. Human calicivirus may cause up to 5% of infantile diarrhoeas. Enteric adenoviruses may be associated with up to 17% of diarrhoea in children in developed countries. Enteric adenovirus antibodies are seen in over 30% of children.

Norwalk and Norwalk-like agents may cause gastroenteritis outbreaks in children but, as with coronaviruses, do not appear to be important as causes of severe gastroenteritis in young infants. Norwalk agent serum antibody levels increase gradually over time reaching 50% by the fifth decade. Infected food handlers, shell-fish and contaminated water supplies have all been implicated as sources for infection.[35] It is as yet uncertain as to whether astroviruses and other SRV are important in diarrhoeal illness in children.

Virulence determinants

These viruses invade epithelial cells in the small intestine. The virus multiplies within the enterocytes and these cells are damaged and shed within 24 h. Repopulation with less functionally mature cells arising from the crypts occurs within the next 48 h. The absorptive capacity of the relatively undifferentiated replacement enterocytes is diminished. Glucose and glucose-stimulated sodium absorbtion as well as disaccharidases and the Na, K- ATPase pump are all affected.[35] The repair process takes 5–10 days but animal studies have documented delayed recovery in protein-calorie malnutrition. These pathophysiological features observed in animal models are felt to be similiar in rotavirus infection and other viral enteritides.

Clinical features

In Norwalk and Norwalk-like virus infection nausea, vomiting and abdominal cramps are common but diarrhoea, which is usually mild, occurs in only 40–50% and fever is not a prominent feature.[35] Enteric adenovirus infection has an incubation period of approximately 1 week and is followed by moderate

diarrhoea and vomiting. The diarrhoea associated with viral enteritis in general is watery without blood or faecal leucocytes.

The management of these infections revolves around attention to hydration and nutrition and prevention of further transmission. These agents do not usually cause chronic disease except in immunodeficient patients.

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