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INFECTIOUS GASTROENTEROCOLITIDES IN CHILDREN
An Update on Emerging Pathogens

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Infectious agents have long been known to cause acute enterocolitis, particularly in infants and young children; however, a proportion of both children and adults have clinical symptoms typical of acute enterocolitis in the absence of an identifiable microbial pathogen. Failure to isolate pathogenic organisms from the infected stools of such patients does not conclusively demonstrate that the illness was not infectious. For instance, these individuals may have been infected but the organism cleared from the gut at the time the samples were obtained for testing. For cost-containment purposes, some diagnostic laboratories do not test for all known enteropathogens but focus their isolation procedures on those organisms that historically have been identified most commonly in the local community. For example, despite increasingly widespread acceptance of enterohemorrhagic Escherichia coli as a recognized cause of disease, not all medical centers or commercial laboratories routinely test for these organisms in standard stool cultures. The presence of unrecognized enteropathogens may provide an-

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other explanation for the failure to identify an infectious agent in the stool. For example, *Campylobacter jejuni* and *Campylobacter coli* infections were not recognized as a major health concern until the organisms could be cultured routinely on selective medium under microaerophilic culture conditions. The selective media that are used contain antibiotics to suppress the growth of the fecal microflora while permitting the replication of resistant campylobacters. The limitation of the technique is that intestinal campylobacters that are sensitive to the antibiotics in the selective culture medium are not identified. For example, *Campylobacter upsaliensis* likely is an important cause of disease that is underdiagnosed because standard methods for culturing intestinal campylobacters use antibiotics to which this organism is sensitive.

The lack of suitable culture techniques to successfully grow some microbes is another possible reason for the failure to identify enteropathogens. The polymerase chain reaction (PCR) has been used to identify nonculturable microbial pathogens, including, for example, the Whipple's bacillus in intestinal biopsy specimens. This technology also has demonstrated that microbial pathogens can cause gastric disease in the absence of enterocolitic symptoms.

This review highlights selected, recently recognized and emerging bacterial and viral pathogens that infect the gastrointestinal tract. Protozoal, helminthic, and fungal infections are not considered in this review. These are, nevertheless, important causes of disease involving the gastrointestinal tract, especially in the immunocompromised host. Several of these agents, including cryptosporidia, microsporidia, cyclospora, and possibly *Dientamoeba fragilis* and *Blastocystis hominis* have increasingly been recognized as human enteropathogens. The interested reader is referred to an accompanying article by Winter and Chang in this issue and to several recent relevant reviews.

Some newly recognized agents may ultimately prove not to be true causes of disease. Nevertheless, several considered in this review likely are to be proven as important gastroenteric pathogens in children. They also are considered to emphasize that much remains to be learned about the interactions of the gastrointestinal tract with the multitude of microbes that enter into it on a daily basis.

A recent review provides a summary of the therapeutic approach to acute infectious diarrhea, including, most importantly, oral rehydration therapy. The future promises the development, field testing, and widespread delivery of mucosal vaccines for use in preventing gastroenteric infections in humans.

### THE STOMACH

**Bacteria**

*Helicobacter pylori*

*Helicobacter pylori*, a gastric pathogen, was first successfully cultured from mucosal biopsies obtained from the antrum of patients in the
early 1980s by Marshall and Warren in Perth, Western Australia. The presence of this urease-producing, gram-negative, microaerobic organism was correlated with histopathologic evidence of chronic-active (type B) gastritis (Table 1). Specificity of the infection for certain subtypes of gastritis, resolution of gastritis with antibacterial therapy, and the induction of type B gastritis in both human volunteers and in the appropriate experimental animals fulfill each of Koch's postulates and thereby establishes *H pylori* as a human pathogen. Infection of the stomach also is strongly correlated with recurring peptic ulcer disease and with gastric cancers. Readers are referred to Chapter 21 in this volume for a more detailed review of *H pylori* infection.

**Helicobacter heilmannii**

*Helicobacter heilmannii*, a urease-producing, spiral-shaped organism, also is associated with gastritis in both the antrum of infected humans and in domesticated animals, including cats. As shown in Figure 1, the organism can be distinguished from *H pylori* both with brightfield microscopy and by using transmission electron microscopy because *H heilmannii* is longer and more tightly coiled, presenting with a corkscrew-like appearance. Formerly referred to as *Gastrospirillum hominis*, *H heilmannii* is identified in inflamed antral tissues less commonly than is *H pylori*. The incidence of infection by this organism is likely underestimated because it cannot be cultured yet. The organism has been identified by staining with silver of mucosal biopsies in the stomachs of children and adolescents. A study is needed to determine the prevalence of *H heilmannii* infection in children with and without type B gastritis.

**Viruses**

*Cytomegalovirus*

In adults, Ménétrier's disease (hypertrophic gastritis) is a chronic remitting and relapsing disease that seems to be related to an excessive production of transforming growth factor-alpha in the gastric mu-

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**Table 1. RESULTS OF SILVER STAINING, CULTURE, AND UREASE TESTING FOR HELICOBACTER PYLORI IN ANTRAL BIOPSY SPECIMENS FROM 67 CHILDREN**

| Group                              | No. of Subjects | Silver Stain-Positive | Culture-Positive | Urease-Positive |
|-----------------------------------|----------------|-----------------------|-----------------|-----------------|
| Normal antral histology           | 49             | 0                     | 0               | 0               |
| Type B gastritis                  | 6              | 10                    | 7               | 7               |
| Secondary gastritis               | 8              | 0                     | 0               | 0               |

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Figure 1. A, Gastric biopsy demonstrating several long corkscrew-like organisms typical for “Gastrospirillum hominis” overlying the mucosa (hematoxylin and eosin, original magnification, × 1250). B, Transmission electron photomicrograph showing tightly coiled H heilmannii with corkscrew appearance. Dark stained gastric mucin vacuoles are shown in the mucosa on the top left (original magnification, × 20,000). (Reproduced with permission of Van Zanten SJO, Malatjalian DA, Desmormeau LM, et al: Gastritis induced by the helicobacter ‘Gastrospirillum hominis.’ Can J Gastroenterol 8:257, 1994.)

cosa (Fig. 2). In contrast, childhood Ménétrier's disease is a short-lived, acute event recently suggested to be of an infectious etiology. Several investigators have identified the cytomegalovirus (CMV) virions and genomic DNA in the antral mucosa of children with a protein-losing gastropathy and the hypertrophic gastritis that is characteristic of Ménétrier's disease. A cluster of cases of CMV-associated Ménétrier's disease was reported by Kovacs and colleagues in five children under 4 years of age; however, restriction enzyme DNA fingerprinting did not support the hypothesis that the gastric infections were due to a single virulent strain of the virus. In fact, at least four different CMV strains were identified among the five infants.

SMALL INTESTINE

Bacteria

Vibrio cholerae O139

The past 2 years have seen the emergence of a new Vibrio cholerae serogroup, O139, that has caused epidemic diarrheal disease primarily
Figure 2. Histology of gastric mucosa in a 3-year-old with Ménétrier's disease reveals glandular epithelial cell (closed arrow) with cytomegalovirus inclusion and positive immune reactivity for early antigen by immunoperoxidase using monoclonal antibody against cytomegalovirus early antigen and counterstained with hematoxylin-eosin (original magnification, × 300). These consist of large cells with a large prominent eosinophilic intranuclear inclusion surrounded by a thin clear halo. A dilated gland (open arrow), regenerative epithelium (arrowhead), and mixed acute and chronic inflammatory cell infiltrate are present in the lamina propria. (From Eisenstat DDR, Griffiths AM, Cutz E, et al: Acute cytomegalovirus infection in a child with Ménétrier's disease. Gastroenterology, 109:592, 1995.)

in the Indian subcontinent. Although the lipopolysaccharide and, hence, the serogroup of this strain is distinct from classic O1 epidemic strains, V cholerae O139 contains the same virulence operon (i.e., cholera toxin, toxin-coregulated pilus) as the O1 organisms traditionally causing worldwide cholera pandemics.

The severe dehydration of cholera is related to the Gs-protein-mediated activation of cyclic adenosine monophosphate by cholera toxin that causes reduced sodium-chloride-coupled absorption in villus enterocytes and increased chloride secretion in crypt cells. Recent studies show that these effects are mediated through the enteric nervous system and immunocytes. Increasingly, a complex interaction of nerves, muscle, mast cells, T cells, and B cells with the host epithelium is recognized to ultimately modulate the host response to the infecting organisms and their toxins. Indeed, the concept has sponsored the formation of a new multidisciplinary field of investigation referred to as neuroimmunophysiology.

Deletion of the genes encoding for the A (active adenosine diphos-
Enteroaggregative Escherichia coli

Enteroaggregative E. coli (EAEC) are characterized by their pattern of bacterial adhesion to infected tissue culture cells. These organisms produce enterotoxins that are heat-labile and heat-stable. Epidemiologic studies provide supportive evidence for the pathogenic role of EAEC in disease, especially as a cause of persistent diarrhea. In some studies, the organism is identified in the stool samples of children with diarrhea more frequently than in age-matched controls. For example, Cravioto and colleagues identified EAEC in 51% of Mexican children under 2 years of age with protracted diarrhea but in only 5% of asymptomatic age-matched infants. The relative importance of EAEC as a cause of disease in the United States remains to be established. The biologic relevance of the in vitro adhesion properties and toxins produced by these bacteria also need to be addressed in further experimental evaluation.

Diffusely Adherent Escherichia coli

Diffuse adherence E. coli (DAEC) are characterized by binding of organisms evenly over the surface of tissue culture cells in in vitro adhesion assays. DAEC have been associated with acute and chronic diarrhea in some case-controlled epidemiologic studies. The reproducibility and generalizability of these findings now need to be defined. Genetic probes to defined bacterial adhesins, such as F184 and AIDA-I should help in achieving these goals.

Enterotoxigenic Bacteroides fragilis

Although generally considered a constituent of the normal colonic microflora, some investigators report that a toxin-producing variant of Bacteroides fragilis is enteropathogenic. Additional studies are required to fulfill each of Koch’s postulates for this organism. The recognition that a normal constituent of the fecal flora can cause disease is not, however, without precedent. For example, Clostridium difficile can be a part of the normal colonic microflora. Toxin-producing C difficile colonize in normal infants without apparent ill effect, perhaps because the receptor(s) required for binding of the toxins that are elaborated by the...
organism are not present until later in life. Alteration of the normal flora by the use of antibiotics can create a microenvironment in which the organism proliferates and, in the susceptible (i.e., age-appropriate) host, ultimately results in disease. The concept that the commensal microflora influences health also has been used to develop medical biotherapy in which nonpathogenic organisms, such as *Saccharomyces boulardii*, *Bifidobacterium bifidum*, and *Lactobacillus* species, are used to treat and prevent infectious enterocolitides.

**Viruses**

**Astrovirus**

In addition to rotaviruses, adenoviruses of serotype 40 and 41, Norwalk virus, and related 27 nm enteritis-associated viruses, recent epidemiologic studies have demonstrated that the astrovirus is an etiologic agent of childhood enteritis. In controlled studies in Thailand using a monoclonal antibody-based immunoassay, astrovirus was detected in 8.6% of symptomatic children compared with 2.0% of asymptomatic, age-matched controls (*P* < 0.001, Table 2). Comparable findings have been reported in day-care centers in North America. The recently derived sequence of the astrovirus RNA genome reveals that this agent is sufficiently unique to be classified in its own family as *Astroviridae*.

**Calicivirus**

The RNA genomes of the Norwalk virus, several Norwalk-like viruses (also termed *small round structured viruses* [SRSV]), and the calicivirus have been sequenced. The RNA sequences of these viruses are related, and these agents are now considered members of the family *Caliciviridae*. Using reverse transcription-PCR, the SRSV can be sub-classified into four distinct genotypes that can also be identified by

**Table 2. FREQUENCY OF ASTROVIRUSES, GROUP A ROTAVIRUSES, ENTERIC ADENO VIRUSES, AND NONENTERIC ADENO VIRUSES AS ETIOLOGIC AGENTS OF ENTERITIS IN THAI CHILDREN**

|                      | Enteric Tested | No. Enteric Astrovirus | Group A Rotavirus | Enteric Adenovirus | Nonenteric Adenovirus |
|----------------------|----------------|------------------------|-------------------|-------------------|----------------------|
| With diarrhea        | 1691           | 146 (9)*               | 322 (19)*         | 44 (3)*           | 25 (2)*              |
| Without diarrhea     | 1459           | 30 (2)                 | 15 (1)            | 8 (1)             | 16 (1)               |

*Difference between groups with and without intestinal symptoms, *P* < 0.001.

$t$Difference between groups with and without intestinal symptoms, *P* = not significant.

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immunoelectron microscopy. This has greatly simplified our understanding of the classification of these agents.

**Torovirus**

Fringed, pleomorphic particles resembling toroviruses were first reported in stool specimens of children with diarrhea by Beards and colleagues. Because of their pleomorphic structures, electron microscopy alone was not sufficiently convincing for these agents to gain immediate acceptance as viral enteropathogens. The more recent finding that torovirus-like particles are reactive in an immunoassay using antiserum to a well-established, morphologically similar Breda virus of calves has provided supporting evidence that these particles are indeed toroviruses. Preliminary evidence shows that torovirus-like particles (Fig. 3), which also may be reported as coronavirus-like agents, are commonly found in stool samples of children with diarrhea. During a 9-month period beginning in October, 1993, torovirus-like particles accounted for more than half of all stool specimens that were positive for viruses when examined by electron microscopy. By contrast, torovirus was identified in only 4 of 49 stool specimens obtained in age-matched children without intestinal symptoms. Additional investigations at multiple centers are now required to confirm the enteropathogenicity of toroviruses and to clarify the epidemiology of infection.

**COLON**

**Bacteria**

*Brachyspira aalborgi*

Intestinal spirochetosis refers to colonization of the large bowel mucosa by *Brachyspira aalborgi* or related spirochetes. The organism is identified in biopsies of colonic mucosa obtained at colonoscopy (Fig. 4). Although some investigators report that the spirochetes are a cause of bloody diarrhea, appropriately controlled studies have not been performed to ascertain the prevalence of *B. aalborgi* adherent to colonic mucosa in asymptomatic children. In fact, some studies in adults indicate that asymptomatic colonization of the large bowel does occur. Additional studies to characterize the presence of potential virulence properties, such as toxin production, invasion potential, and the ability to induce a signal transduction response following adhesion to colonicocytes, are clearly warranted.

*Enterohemorrhagic Escherichia coli*

Enterohemorrhagic *E. coli* (EHEC) refers to *E. coli* of a limited number of serotypes, including O157:H7 and O26:H11. These bacteria cause
hemorrhagic colitis and systemic complications, including the hemolytic uremic syndrome (i.e., microangiopathic hemolytic anemia, thrombocytopenia, and renal failure) and thrombotic thrombocytopenic purpura (i.e., microangiopathy with neurologic involvement). The morbidity, mortality, and immense financial implications of this food-borne infection are only now being fully appreciated. Hemorrhagic colitis and the systemic complications of the disease also can be caused by infection with other *E. coli* serotypes, albeit less frequently than by O157:H7. All strains are characterized by the production of one or more phage-encoded cytotoxins variously referred to as *Shiga-like toxin* or *Verocytotoxin*. These toxins function as an N-glycosidase that depyrimidates a
Figure 4. Brightfield microscopy photomicrograph showing spirochetes adherent to surface epithelial cells (arrows) in the transverse colon of a 16-year-old male adolescent with hematochezia. The infection may have been incidental, however, because a juvenile polyp was observed in the rectum and removed by snare polypectomy (hematoxylin and eosin, original magnification, × 150).

specific residue (adenine 4324) on 28S ribosomal RNA and thereby block eukaryotic cell protein synthesis, ultimately resulting in cell death.\(^{14,49}\)

The precise role of the cytotoxin in EHEC-induced disease is currently under active investigation. Studies using animal models have reported evidence both for\(^{86,89}\) and against\(^{63,111}\) the role of Verocytotoxins in experimentally induced enterocolitis. If these toxins are important in beginning the cascade that results in a systemic disease, preventing toxin binding to enterocyte receptors may interrupt the pathophysiology of this disease. The hypothesis that receptor analog therapy is an effective and safe form of treatment to prevent the systemic complications of EHEC infection is now being tested.\(^{93}\) This or other novel treatment approaches are required because antimicrobial agents are of unproven benefit. Theoretically, antibiotics could cause harm because the cytotoxins are released from the periplasm of the organism following exposure to agents that disrupt the prokaryotic outer membrane. An increased
prevalence of antibiotic resistance among EHEC isolates also has been recently described.51

EHEC attach to infected epithelial cells in vitro and in experimental animals in a morphologically distinct pattern referred to as attaching and effacing adhesion (Fig. 5).29,108 The attaching and effacing lesion is dependent on a chromosomally encoded bacterial outer membrane protein.22 The role of the outer membrane protein in mediating EHEC-induced diarrheal disease is under active investigation because the adhesin is a potential vaccine candidate. Whether all cytotoxin-producing strains induce the attaching and effacing lesion is doubtful. The authors have reported, for example, that Verocytotoxin-producing E coli of the serotype O113:H21 does not contain a homologous gene for the outer membrane adhesin and does not cause attaching and effacing adhesion either in vitro or in vivo.28

As is typical of infectious colitis, the lamina propria of large intestine is infiltrated by polymorphonuclear leukocytes following EHEC infection. Using a lapine model, Elliot and colleagues34 showed that a mono-

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Figure 5. Transmission electron photomicrograph of Verocytotoxin-producing E coli, serotype O121:H-, adherent to the eukaryotic cell plasma membrane in an attaching and effacing phenotype with loss of the microvillus membrane and collection of electron-dense material (F-actin, alpha-actinin) below the adherent organisms (arrows). (From Sherman P, Soni R, Karmali M: Attaching and effacing adherence of Verocytotoxin-producing Escherichia coli to rabbit intestinal epithelium in vivo. Infect Immun 56:756, 1988; with permission.)
clonal antibody against C18 vascular adhesion epitopes on leukocytes reduces the secretory response of the colon to \textit{E coli} O157:H7 infection. Thus, anti-inflammatory molecules might serve to provide novel therapy regardless of the role of cytotoxin and outer membrane protein in the etiopathogenesis of EHEC infection.

**SUMMARY**

The recognition that bacterial infections induce signal transduction responses in infected epithelial cells also provides new avenues to consider as novel forms of therapy. For example, the chemokine interleukin-8, which attracts neutrophils to sites of mucosal infection, is produced by epithelial cells of gastric and intestinal origin in response to bacterial infection. Inhibitors of chemokine production or inhibition of the biologic effects of neutrophil chemoattractants have the potential to reduce both mucosal inflammatory responses and the attendant clinical sequelae. Eukaryotic cells also respond to infection with elevations in cytosolic second messengers, including inositol triphosphate (IP3) and calcium ([Ca$^{2+}$]). In intestinal epithelium, these second messengers can mediate the diarrheal response to infection.

Calcium/calmodulin inhibitors may have a beneficial effect in treating those gastrointestinal infections mediated through changes in the level of cytosolic free calcium. DuPont and colleagues showed, for example, that oral therapy with zaldaride maleate relieves symptoms of disease and shortens the duration of diarrhea in travelers with ETEC-induced diarrhea. Evaluation of additional signal transduction responses to microbial infections should provide both new insights into the pathogenesis of gastrointestinal infectious diseases and novel approaches to consider for the prevention and therapy for these human illnesses.

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