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Escherichia coli that cause diarrhea

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Although *Escherichia coli* plays an important role in maintaining normal gut physiology, there exist within this species primary pathogens that cause various syndromes of diarrheal disease. Five categories of diarrheagenic *E. coli* are now recognized which manifest distinct virulence properties, interact with the intestinal mucosa in different ways, cause distinct clinical syndromes, differ in their epidemiology, and fall into distinct O : H serotypes.

The five categories of diarrheagenic *E. coli* include 1. Enteropathogenic (EPEC; a frequent cause of infant diarrhea) 2. Enterotoxigenic (ETEC; major cause of traveler's diarrhea and infant diarrhea in less-developed countries) 3. Enteroinvasive (EIEC; cause dysentry) 4. Enterohemorrhagic (EHEC; cause of hemorrhagic colitis and hemolytic uremic syndrome) 5. Enteroadherent-aggregative; (EA-Aggec) common cause of infant and traveler's diarrhea).

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While the five categories of diarrheagenic *E. coli* are quite distinct, they nevertheless have certain underlying commonalities from the point of view of pathogenesis.[1] These include the importance of plasmids in encoding critical virulence properties; characteristic interactions with intestinal mucosa; the production of enterotoxins or cytotoxins; a marked propensity to fall within certain O : H serotypes.

In the 1940s, Kauffman[2] proposed a scheme to differentiate *E. coli* on the basis of lipopolysaccharide O, flagellar H and polysaccharide K antigens. We presently recognize 171 O serogroups and 56 H types. Together these designate the O : H serotype which is important role in studying the epidemiology and pathogenesis of *E. coli* infection.

Enteropathogenic (*E. coli*)

Enteropathogenic *E. coli* was the term coined by Neter[3] to refer to certain *E. coli* strains identified in the 1940s and 1950s by serological methods and incriminated as causes of infantile diarrhea both in out-

breaks and in sporadic cases.[4] The major O serogroups that contain EPEC serotypes are shown in the Table. Except for O142, this list represents a compilation from reports of Ewing et al[5] and Taylor[6] who, in the 1950s, headed the enteric reference laboratories at the Center for Disease Control in Atlanta and at the Central Public Health Laboratory in Colindale, respectively; these O serogroups represent "classical" (Class I) EPEC O serogroups. O142 EPEC were described in the late 1960s and early 1970s.[1,4] Certain other O serogroups were recognized by both Ewing *et al* and Taylor as being less strongly incriminated as pathogens; these include O18, O44, O112 and O114, among others (Table).

Volunteer studies in the early 1950s established the pathogenicity of several common classical EPEC O serogroups, including O55, O111 and O127 strains.[4] However, by the tests and animal models available up to the mid 1960s, it was not possible to differentiate these *E. coli* from normal flora strains and the virulence properties by which they cause diarrhea remained unknown. Therefore, until the 1970s, O serogrouping remained the only diagnostic tool to detect EPEC.

EPEC strains do not elaborate heat-labile (LT) or heat-stable (ST) enterotoxins of ETEC nor do they exhibit the epithelial cell invasiveness of EIEC.[1,4] Rather, they cause diarrhea by other mechanisms.[7] EPEC cause a distinctive

Table. Features of the five distinct categories of *E. coli* that cause diarrhea

Category	O Serogroups	Clinical syndromes	Plasmid-mediated virulence properties
Enterotoxigenic	6, 8, 15, 20,25 27, 63, 78, 80 85, 115, 128ac, 139, 148, 153 159, 167	Infant diarrhea in less-developed countries; Adult traveler's diarrhea	LT & ST; fimbrial colonization factors
Enteroinvasive	28ac, 29, 124 136, 143, 144 152, 164, 167	dysentery, all ages	Shigella-like invasiveness of epithelial cells
Enteropathogenic			
Class I	55, 86, 111, 119, 125, 126, 127 128ab, 142	Acute and protracted infant diarrhea	Attachment to epithelial cells
Class II	18, 44, 114	Acute infant diarrhea	?
Enterohemorrhagic	26, 111, 157	Hemorrhagic colitis, hemolytic-uremic syndrome, all ages	Novel colonization fimbriae
Enteroadherent-aggregative	O untypable (new O groups)	Infant diarrhea in less developed countries	O antigen and novel fimbriae

ultrastructural histopathological lesion in the intestine which involves destruction of the microvilli, typically without further invasion. Bacteria are often closely adherent to the membrane of the enterocyte with the membrane partially enveloping the bacterium.[4] A very important practical observation (because it provides an alternative diagnostic tool to serotyping) is that EPEC adhere to HEp-2 cells in tissue culture in a characteristic pattern of microcolonies called localized adherence, a property not found among other *E. coli*.[8-11] The name EPEC Adherence Factor, or EAF, has been given to this property and the genes that encode it are found in certain plasmids. Localized adherence to HEp-2 and HeLa cells must be differentiated from diffuse adherence,[9-11] more recently, a third pattern of adherence to HEp-2 cells, the "aggregative" pattern, has been described and identifies a distinct new category of diarrheagenic *E. coli* Enteroadherent-aggregative *E. coli*[21].

The EAF plasmid is necessary for full expression of the pathogenicity of most (but not all) EPEC strains.[13] The EAF plasmid enodes the expression of a bacterial surface (outer membrane) protein that appears to be critical in the pathogenesis of EPEC diarrhea and perhaps in mediating protective immunity.[13] This protein has been found in all the important EPEC serotypes, such as those in serogroups O55, O111, O119, O127, and O142, but it is not found in other pathogenic *E. coli*. An attempt to purify the 94 Kd protein is underway to prepare a potent and plentiful antibody to it that could be used in a simple diagnostic test such as one based on agglutination.

Some EPEC strains have been reported to elaborate moderate quantities of a cytotoxin very similar (or identical) to *Shigella dysenteriae* I toxin. It has been suggested that this toxin may play a role in the pathogenesis of EPEC disease.[14,15]

Clinically, EPEC illness is characterized by fever, malaise, vomiting and diarrhea with prominent amounts of mucus but without gross blood. EPEC illness tends to be clinically more severe than many other diarrheal infections in infants, some of whom develop prolonged diarrhea that persists for more than 14 days. Recent studies from several countries in South America where improved diagnostic techniques were employed have shown EPEC to be either the first or second most important bacterial cause of diarrhea in infants.[16,17] EPEC illness is rare beyond infancy.

Unfortunately, at present, Class I EPEC can be identified only by O serogrouping, recognition of localized adherence to HEp-2 cells in tissue culture or by use of the EAF gene probe.

Enterotoxigenic *E. coli*

ETEC came to prominence in the late 1960s and early 1970s, largely based on work carried out in Calcutta.[18,19] ETEC are a major cause of infant diarrhea in less-developed countries (some reports of infants prospectively followed by frequent household surveillance suggest that as many as 2-3 clinical ETEC infections per child/year occur during the first 2-3 years of life),[20] one of the main bacterial causes of dehydrating infant diarrhea in developing areas;[21] and an infection correlated with adverse nutritional consequences.[22] ETEC are also the most frequent agent responsible for traveler's diarrhea.[23-25] Within developed countries ETEC infection is rare, although occasional outbreaks have been reported.

ETEC infection is acquired via the ingestion of contaminated food or water which allows the bacteria to reach the proximal small intestine, the critical site of host-parasite interaction. Here they colonize by means of fimbrial colonization factors and elaborate LT or ST. LT closely resembles cholera toxin in structure and action and immunologically.[26] ST is a small polypeptide that is not immunogenic in the course of natural infection.[26] The clinical features of ETEC infection are watery diarrhea, nausea, abdominal cramps and low-grade fever. Occasionally, particularly with strains that are prevalent in the Indian subcontinent, severe cholera-like purging can occur.

ETEC from diverse geographic areas fall within a limited number of O : H serotypes.[1] While many other serotypes can also be toxigenic, the recurrent O : H serotypes appear to be successful ETEC clones that have spread far and wide. Usually these serotypes elaborate both LT and ST and possess fimbrial colonization factors.[1] The major O serogroups associated with ETEC are shown in Table.

ETEC possess attachment or colonization factors that allow them to overcome the peristaltic defense mechanism of the small intestine. Heretofore, all the characterized colonization factors have proven to be fimbriae, i.e. hair-like, filamentous organelles on the surface of the *E. coli* that are notably thinner than flagellae.

ETEC are identified by detecting the presence of LT or ST or the genes that encode these toxins. Several practical tests for LT are available, including enzyme-linked immunosorbent assays (ELISAs[27] immunodiffusion assays,[28] latex particle tests, tissue culture cell lines that change their morphology in the presence of LT (Y-1 adrenal and Chinese Hamster Ovary cells), and DNA probes.[29] Tests for ST are less practical and include ELISA,[30] the infant mouse assay[31] and DNA probes.[29]

Enteroinvasive *E. coli*

Certain *E. coli* strains cause an invasive, dysenteric form of diarrheal illness. These strains, of serotypes distinct from ETEC and EPEC (Table 1), were found to closely resemble *Shigella* in many ways. Like *Shigella*, their cardinal pathogenetic feature is the capacity to invade and proliferate within epithelial cells, leading to cell death. The invasive capacity of both EIEC and *Shigella* is dependent on the presence of large plasmids which code for the production of several outer membrane proteins involved in the invasiveness process;[1] the proteins are antigenically closely related (if not identical) in EIEC and *Shigella*. EIEC often resemble *Shigella* in being unable to ferment lactose and non-motile. Furthermore, EIEC and *Shigella* O antigens show many cross-reactions.

EIEC have a predilection for colonic mucosa as the favored site of host parasite interaction. Clinically, the illness is marked by fever, severe abdominal cramps, malaise, toxemia, and watery diarrhea followed by gross dysentery consisting of scanty stools of blood and mucus. A simple stain of the fecal mucus reveals sheets of polymorphonuclear leukocytes.

EIEC can be diagnosed by serotyping suspect *E. coli* strains,[32] by an ELISA based on detection of the invasiveness-associated outer membrane proteins[33] and by DNA pobes that detect the invasiveness genes.[34]

Enterohemorrhagic *E. coli*

In 1982 an outbreak of hemorrhagic colitis in the USA drew attention to an unusual clinical syndrome of diarrheal disease and a new bacterial enteric pathogen[35] the causative organism, *Escherichia coli* 0157 : H7, was a serotype not previously recognized as a cause of diarrheal disease in humans. The clinical syndrome was notable in that bloody but copious diarrhea, unaccompanied by fecal leukocytes, was seen in afebrile patients;[35] these features distinguish it from classic dysentery due to Shigella or enteroinvasive *Escherichia coli* (EIEC) which are characterized by fever and scanty stools of blood and mucus containing many fecal leukocytes. Since 1982, some knowledge has been gleaned on the epidemiology of 0157 : H7 infections as they occur in North America and Europe and considerable progress has been made on elucidating its pathogenesis. There has also been a strong incrimination of 0157 : H7 as a cause of hemolytic-uremic syndrome (HUS).[1,36] O157 : H7 has emerged as an enteric pathogen of public health importance in Canada and the USA with multiple reports of outbreaks of hemorrhagic colitis, hemolytic uremic syndrome and diarrhea in nursing homes, day care centers, schools, and the community.[1] So far, little is known of the epidemiology of EHEC in less-developed countries.

O157 : H7 strains from persons with hemorrhagic colitis and HUS have been shown to elaborate phage-encoded potent cytotoxins active on HeLa and Vero cells.[1,36] One of these toxins, so-called Shiga-like toxin 1 (SLTI) or Verotoxin 1 (VT1), is apparently identical to the potent cytotoxin/neurotoxin/enterotoxin produced by *S. dysenteriae* 1 (Shiga toxin and reacts with and is neutralized by Shiga antitoxin.[1] Many strains also elaborate a second potent cytotoxin (Shiga-like toxin 2 or Verotoxin 2) that is not neutralized by Shiga antitoxin.[1] In addition, O157 : H7 strains possess a plasmid that plays a role in virulence by encoding the production of a newly-recognized variety of fimbriae that mediates attachment to gut-derived epithelial cells in tissue culture.[37]

Several animal models have been developed which demonstrate the pathologic features of O157 : H7 infection.[1] In electron photomicrographs,[38] attached and effaced enterocytes are evident with destruction of the microvilli, a lesion resembling that due to classic serotype enteropathogenic *E. coli* (EPEC). Nevertheless, in gnotobiotic piglets, the two types of infection, EHEC versus EPEC, can be clearly differentiated by anatomic site of involvement, severity of lesions, and degree of polymorphonuclear cells infiltration. EPEC involve the entire intestine of piglets, EHEC only the cecum and colon; EPEC lesions are generally less severe; some infiltration by leukocytes is seen with EPEC, but not with EHEC, infection.

The term EHEC refers to strains such as O157 : H7 which manifest the above-mentioned clinical, epidemiologic and pathogenetic features. Heretofore, it has been difficult to undertake studies of the epidemiology of EHEC infections, other than outbreak investigations, because of the lack of suitable methods for screening large numbers of stool cultures for O157 : H7 strains and because of the lack of knowledge regarding what other serotypes may also be enterohemorrhagic

and how to identify them as well. One other serotype, in particular, 026 : H11, is now recognized as EHEC; this serotype was previously considered to be EPEC. O26: H11 is usually as abudant producer of VT, possesses a plasmid that does not hybridize with the EPEC EAF gene probe, and sometimes is associated with bloody diarrhea. Preliminary studies have shown considerable homology among the O157 : H7 and O26 : H11 plasmids and have led to the development of a sensitive and specific DNA probe to identify EHEC.[136]

Enteroadherent-aggregative *E. coli*

The newest category of diarrheagenic *E. coli* are strains that show a characteristic "aggregative" pattern of adherence to HEp-2 cells. In this pattern, the bacteria form aggregates that give a "stacked brick" appearance.[12] Bacterial clusters are visible on the glass, as well as attached to HEp-2 cells. Enteroadherent aggregative *E. coli* (Auto EC) do not elaborate LT or ST, do not manifest Shigella-like invasiveness, do not cause the histopathological lesion of EPEC and are negative with the EPEC, EPEC, EIEC and ETEC DNA probes.EA -AggEC cause a distinct histopathological lesion of the intestine discernable by light microscopy.[39] AutEC occur in distinct O : H serotypes but the O antigens are new and as yet untypable. Plasmids encode cirtical virulence properties.

EA-AggEC have been found to be an important cause of acute diarrhea in young children in South America and are suspected to cause protracted diarrhea in young children. At least one of the "enteroadherent" *E. coli* strains fed to volunteers by Mathewson et al[40] is now known to be EA-AggEC. It is likely that many of the "enteroadherent" *E. coli* referred to by Mathewson et al are in fact EA-AggEC strains.

While EA-AggEC can be readily identified by their characteristic pattern of adherence to HEp-2 cells, antisera and DNA probes are also being prepared to facilitate epidemiologic studies.

From the early days of the 1940s when *E. coli* were first convincingly associated with human diarrhea, there has come to exist an impressive fund of knowledge on the several categories of diarrheagenic *E. coli*, including information on their clinical features, epidemiology, O : H serotypes and, their pathogenesis. From a previous state of some confusion about their role as enteric pathogens, diarrheagenic *E. coli* are now recognized as being among the best understood bacterial enteropathogens.

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