

Human Intestinal infection

A range of viruses and bacteria (as well as parasites) can infect the human alimentary canal. Mixed infections of viruses and bacteria are not uncommon, and quite complex physiological changes can result from such infections. This lectures documents the main viruses and bacteria involved in mixed gastroenteritis infections and then survey the frequency and nature of mixed viral-bacterial infections in humans. The literature on the possible mechanisms of such mixed infections is then examined under four headings: (i) the occurrence of asymptomatic infections by viral and bacterial enteropathogens; (ii) the clinical features of natural mixed infections in humans; (iii) the nature of mixed infections in animal models; (iv) relevant in vitro studies of viral-bacterial interaction.

Bacterial Agents of Gastroenteritis in Humans

Ten main bacterial groups associated with human gastroenteritis have been identified in mixed viral-bacterial infections in humans or used in experiments to study such mixed infections. A brief description of their classification and sites of action follows.

Escherichia coli

Six main groups of pathogenic *E. coli* are now known: enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC), enterotoxigenic *E. coli* (ETEC), enterohaemorrhagic *E. coli* (EHEC), enteroaggregative *E. coli* (EaggEC), and diffusely adherent *E. coli* (DAEC). Some pathogenic *E. coli* strains show a particular pattern of adherence to HEp-2 cells referred to as "localized adherence". Many, but not all, of these strains fall into the EPEC category so that strains classified as locally adherent cannot at this stage be further categorized. The pathogenesis of different strains of *E. coli* can vary; e.g., EIEC tends to invade epithelial cells and damage them through multiplication in the cytoplasm, whereas other strains such as ETEC and EHEC do not invade the cell. Toxin production is particularly important in the pathogenesis of noninvasive *E. coli* such as ETEC. Different strains of *E. coli* may also affect different parts of the intestine, e.g.,

ETEC tends to colonize the small intestine, whereas EIEC and EPEC tend to infect both the small intestine and colon.

***Shigella* spp**

Four main species of *shigellae* are commonly recognized in humans: *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*. *Shigellae* normally infect colonic epithelial cells. *Shigellae* can produce a toxin which contributes to their pathogenic effect.

***Salmonella* spp**

Salmonella spp., which are all considered to be potentially pathogenic, currently number more than 2,370 recognized serological types. These bacteria bind to and penetrate the wall of the small intestine. *Salmonellae* produce toxins which contribute to their pathogenic effect.

***Vibrio* spp**

Common species of *Vibrio* associated with food-borne infections include *Vibrio cholerae*, *Vibrio parahaemolyticus*, and *Vibrio vulnificus*. *V. cholerae*, the most studied of this group, colonizes the small intestine, where pathogenesis of several strains is assisted by the production of toxins.

***Campylobacter* spp**

The genus *Campylobacter* includes a number of species which can cause gastroenteritis, notably *C. jejuni*. *C. jejuni* principally infects the colon, but infection may also involve the small intestine. Bacterial toxin production may facilitate cell damage.

Yersinia enterocolitica

Bacteria related to *Y. enterocolitica* include many species which are usually referred to as the *Yersinia enterocolitica* group. These bacteria bind to and penetrate the small intestinal mucosa; they then colonize the Peyer's patches and can then spread to other organs. The

pathogenesis of *Y. enterocolitica* is related in part to production of a toxin. *Y. enterocolitica* infection can cause a wide range of clinical symptoms, including diarrhea.

***Aeromonas* spp**

Infection with many species of the genus *Aeromonas* can be associated with gastroenteritis, particularly in children. Pathogenesis of the bacteria appears to be related to several factors, including toxin production in the host gut.

***Clostridium* spp**

Three main species are commonly associated with human disease: *Clostridium difficile*, *C. perfringens*, and *Clostridium botulinum*. *C. difficile* can colonize the colon and induce diarrhea following the production of toxins. *C. perfringens* is a common cause of food poisoning; these bacteria can secrete a toxin during the process of sporulation within the intestine. *C. botulinum* is also an important cause of food poisoning. This bacterium can multiply and produce a neurotoxin in the intestine.

***Bacillus* spp**

Some species of the genus *Bacillus* are occasionally associated with outbreaks of food-borne illness. *Bacillus cereus* infection can involve either the small intestine or the colon. *B. cereus* produces a number of toxins which may contribute to the development of diarrhea.

***Listeria* spp**

Two species of the genus *Listeria*, *Listeria monocytogenes* and *Listeria ivanovii*, are considered pathogenic in humans and can affect the gastrointestinal tract.

Viral Agents of Gastroenteritis in Humans

Nine main virus groups associated with human gastroenteritis have been identified in mixed viral-bacterial infections or have been used in studies of such mixed infections. A brief description of the classification and site of action of human gastroenteritis viruses follows.

Rotaviruses

Rotaviruses are a major cause of gastroenteritis, particularly in children. The virus, which measures about 70 nm in diameter, is classified in the genus *Rotavirus* in the family *Reoviridae*. Rotavirus infects villus epithelial cells in the small intestine; although recent evidence indicates rotavirus can also produce a toxin.

"Norwalk-like" Viruses

"Norwalk-like" viruses (NLV) are an important cause of gastroenteritis in humans and are currently classified in the genus "Norwalk-like viruses" in the family *Caliciviridae*. The particles measure about 35 nm in diameter. The virus appears to infect the epithelium of the small intestine.

Adenoviruses

Adenoviruses, particularly serotypes 40 and 41, are an important cause of gastroenteritis in humans, especially in children. These viruses are classified in the genus *Mastadenovirus* in the family *Adenoviridae* and measure about 70 to 90 nm in diameter. The viruses appear to infect the duodenal mucosa.

Astroviruses

Astroviruses are a major cause of gastroenteritis in humans, particularly children. These viruses, which measure about 27 nm in diameter, are classified in the genus *Astrovirus* in the family *Astroviridae*. Astroviruses appear to infect the duodenal epithelium in the lower third of the villi.

"Sapporo-like" Viruses

The "Sapporo-like" viruses comprise a genus within the family *Caliciviridae* and represent an important cause of illness, particularly in children. They measure about 31 nm in diameter. The term "human calicivirus" has also been applied to this group, although the term is now often used to collectively describe the Norwalk-like viruses and Sapporo-like viruses. The pathogenesis of this virus does not appear to have been described in detail.

Toroviruses

Toroviruses are pleomorphic particles, about 100 to 140 nm in diameter, often with surface projections about 10 nm in length. These viruses are classified in the genus *Torovirus* in the family *Coronaviridae*. The pathogenesis of toroviruses in humans is not well established, but the animal torovirus, Breda virus, replicates in intestinal epithelial cells. Toroviruses have been detected in children with gastroenteritis.

Coronaviruses

"Coronavirus-like particles" (CVLP), i.e., the fringed membranous particles sometimes detected in human feces, may be neither pathogenic in humans nor viral in nature. The occasional identification of true coronaviruses in humans with gastroenteritis appears to be the exception rather than the rule.

Picornaviruses

A series of studies by Yamashita and colleagues has established that Aichi virus, a member of the family *Picornaviridae*, is a cause of gastroenteritis in humans. Reports have also linked infections with viruses of the genus *Parechovirus* within the family *Picornaviridae* with gastrointestinal symptoms in humans.

Herpesviruses

Herpesviruses, notably cytomegalovirus (CMV), have been found in humans with gastroenteritis, particularly patients infected with the human immunodeficiency virus (HIV). CMV can infect the human gastrointestinal tract with resultant gastrointestinal symptoms.