

GUT INFECTION CAUSED DUE TO VIRAL MICROBIOTA

Abstract

Human gut microbiota is a complex ecosystem with several functions integrated in the host organism (metabolic, immune, nutrients, absorption etc.) Human microbiota is composed by bacteria, yeasts, fungi and, last but not least, viruses, whose structure, composition, nature, pathogenic role and immunological and genetic predisposition have not been completely described. Among these, majority of the microbiota resides in the gastrointestinal tract and plays an important role in health and diseases in human. According to medical literature on pathogenicity of viruses, the human GI tract harbors bacteriophages and viruses derived from plant. New metagenomics methods have enabled the reconstruction of whole viral genomes from the genetic constituent distributed in the human GI tract, shedding light to understand the composition of gut virome and it's possible therapeutic applications. This chapter summarize the most recent evidence on the composition and nature of gut "virome", also its potentials pathological and future therapeutic uses in human health, diseases, and it's an attempts to clarify the role of the gut "virome" in the larger microbial ecosystem.

Keywords: Human gut microbiota, gastroenteritis, post-infectious irritable bowel syndrome (PIBS), viral agents causing gastroenteritis, acute gastroenteritis

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I. INTRODUCTION

Colonization of diverse microbial community is called microbiota. The human gut microbiome promotes the expression of genes that are essential for nutrient synthesis as well as the metabolism of amino acids, carbohydrates and lipids. Several factors including host genetics, eating habits, lifestyle, co-morbidities, chemotherapy and antibiotics can upset this equilibrium and may contribute to disease progression.¹ Food or other ingested substrates affect the composition and density of the microbiota as well as their functional roles and also help us to digest food for conditioning of our immune system and provide protection from invading foreign bodies. A majority of the microbiota resides in the gastrointestinal tract and plays an integral role in health and disease.² These microbes are in a situation to influentially affect our science since they are numerous, diverse, differ between individuals, and interact with the host and each other over an extensive stretch of time.³

Inflammation of the gastro-intestinal tract (GI) may cause nausea, vomiting and diarrhea and commonly known as gastroenteritis. Gastroenteritis kills 2 to 3 millions of people each year, making it one of the leading cause of mortality not just only in children's in develop and developing nations but also immuno-compromised individuals who suffer from diarrhea. While bacterial and parasitic gastrointestinal infections are declining due to regular practice of sewage disposal and safe drinking water, viral gastroenteritis is not declining particularly in developing countries due to the unknown aetiology.⁴

- 1. Host Cell Interaction:** Virus evolution and survival promotes due to interaction between different virome because of their lytic and latent life cycles. The human gastrointestinal tract is an interface between the host and complex microbial ecosystems.⁵ Viruses are holoparasite with single-stranded or double-stranded genetic material. Viral infection starts when binding occur between surface and receptor proteins on the host cell surface, this followed by replication and lysis but on the other hand due to adverse conditions, some viruses remain dormant until conditions become favorable for replication and host cell lysis. It should also be highlighted that few viruses might have wide host adaptability, while protein-protein interactions between virion and host are very often in most of the cases. The curation of the human virome is mainly based on dsDNA (double stranded deoxy-ribose nucleic acid) viruses, but few research has focused on the RNA viral fraction, which includes the majority of the eukaryotic virome.¹ There is an incredible interest for explaining how the microbiota can influence immune homeostasis *in-vivo* and *in-vitro* of the gut, this physiological process has important involvement in the pathogenesis and treatment of inflammatory gut disorders.²
- 2. Virome Composition of Human Gut:** For more than a century, viral pathogenesis of GI tract has been known and reported. Pathogenic composition of viruses such as Norwalk, Rotavirus, and Enterovirus can contribute into the human gut virome. They are the well-known infective agents that cause human gastroenteritis. They can cause acute gastrointestinal infections with symptoo like nausea, vomiting, diarrhea and weight loss, but they can persist for prolonged periods of time, leading to chronic gastrointestinal disorders ; dyspepsia and post-infectious irritable bowel syndrome (PIBS) as shown in table-1.^{4,6,7}

Table 1: Viruses causing Gastroenteritis and different method of Diagnosis

Virus	Family	Morphology	Epidemiological Features	Detection Methods
Group A rotavirus	Reoviridae	wheel-like capsid, 70 nm in diameter, double-stranded RNA genome	The most important cause of acute gastroenteritis in infants and young Children. Vaccines are available	EM, ELISA, PAGE, PCR
Group B rotavirus	Reoviridae	wheel-like capsid, 70 nm in diameter, double-stranded RNA genome	Reports from China, India, and Bangladesh. Affects both children and adults	EM, PAGE, PCR
Group C rotavirus	Reoviridae	wheel-like capsid, 70 nm in diameter, double-stranded RNA genome	Sporadically reported. Affects more often school-age children	EM, ELISA, PAGE, PCR
Norovirus	Caliciviridae	Indistinct substructure of virion surface, 27–32 nm in diameter, single-stranded (+) RNA	Causes gastroenteritis in all age groups. Major cause of food-borne gastroenteritis	EM, ELISA, PCR
Sapovirus	Caliciviridae	cup-like depression on the surface, 27–32 nm in diameter, single-stranded (+) RNA	Similar age distribution of cases as group A rotavirus	EM, PCR
Enteric adenovirus	Adenoviridae	icosahedrons, 70 nm in diameter, double-stranded DNA	Serotypes 40/41- Causes sporadic cases of acute gastroenteritis	EM, ELISA, PCR
Astrovirus	Astroviridae	star-like structure on the surface, 27–32 nm in diameter, single-stranded (+) RNA	Causes sporadic cases of acute gastroenteritis	EM, ELISA, PCR
Klassevirus/salivirus	Picornaviridae	--	significantly associated with diarrhea	EM, ELISA, PCR, NGS
MX/MW/S TLPolyomavirus	Polyomaviridae	--	With and without diarrhea from Mexico, United States and Chili	EM, ELISA, PCR, NGS
Bufavirus	Parvoviridae	--	Causes diarrhea in Thailand and Turkey	--
Tusavirus	Parvoviridae	--	Tunisia with unexplained Diarrhea in children	--

AGE (acute gastroenteritis), **EM** (electron microscopy), **PAGE** (polyacrylamide gel electrophoresis), **NGS** (Next-generation sequencing)

II. PATHOGENESIS OF VIRAL INFECTIONS

The identification of the new viruses mentioned in the table-1 in stools samples of human certainly increased our knowledge and etio-pathogenesis of viruses, even from different parts of the body they can be detect in faeces, but out of these new viruses it is still remain uncertain to determine the genuine enteropathogens. yet still continued to be a most significant cause of worldwide mortality and morbidity.⁴ Worldwide, diarrhea is the second leading cause of mortality for children under 5 years of age, 70% of childhood gastroenteritis is viral because viruses are already the most common pathogens responsible for diarrhea.^{8,9} As discussed, there are a number of viruses responsible for viral gastroenteritis but mainly nine virus groups are associated with human gastroenteritis. In this section, we will discuss a

brief classification, pathogenesis and immune response of these potential pathogenic viruses follows.¹⁰

- 1. Rotaviruses:** Infection with rotavirus in newborns and young children can cause severe diarrhea, dehydration, electrolyte imbalance, and metabolic acidosis.¹¹ The virus enters the body through the oral route. Viral replication occurs in the villous epithelium of the small intestine. Recent evidence indicates that up to two-thirds of children with severe rotavirus gastroenteritis showed the presence of rotavirus antigen in serum (antigenemia). Infection may result in decreased intestinal absorption of sodium, glucose, and water, and decreased levels of intestinal lactase, alkaline phosphatase, and sucrose activity, and may lead to isotonic diarrhea.¹²

Children who are immune-compromised because of congenital immunodeficiency or because of bone marrow or solid organ transplantation may experience severe or prolonged rotavirus gastroenteritis and may have evidence of abnormalities in multiple organ systems, particularly the kidney and liver.^{13,14} The immune correlates of the protection from rotavirus are poorly known. The serum and mucosal antibodies against VP7 and VP4 are likely significant for the protection against the infection. As illustrated in Figure-1, cell-mediated immunity most likely plays a role in infection recovery and disease protection.^{9,12}

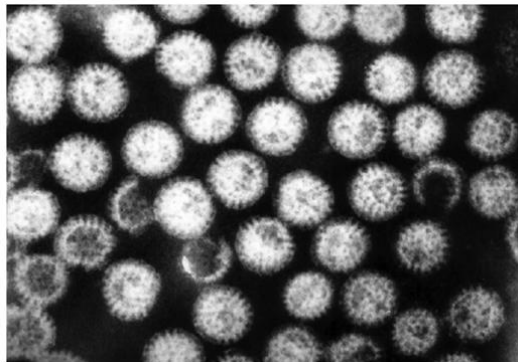


Figure 1: Electron microscopy structure of Rotavirus in stool sample

Rotavirus found in substantial quantities in the stool of infected individuals. Transmission occurs via the faecal-oral pathway, which involves both close person-to-person contact and fomites (such as toys and other environmental surfaces contaminated by stool). Transmission of rotavirus through contaminated food and water appears to be infrequent.^{12,15} Rotavirus diarrhea has a short incubation period, usually less than 48 hours. The clinical signs of infection vary and depending on whether it is the first or reinfection. The first infection after three months of age is usually the most serious. Infection might be asymptomatic, result in self-limited watery diarrhea, or produce severe dehydration diarrhea followed by fever and vomiting. A temperature of 102°F (39°C) or higher may be present in up to one-third of affected children. The gastrointestinal symptoms usually resolve within 3 to 7 days.¹³

According to National Rotavirus Surveillance Network, several studies from India, different settings and methods to know the proportion of children admitted with

diarrhea. It is estimated that; 34% children were admitted with the complaint of diarrhea in a hospital setting, community acquired Rotavirus up to 15%, in outpatients it is 16% and in neonatal ranged from (22% -79%) of Rotavirus infection has been found.¹⁶ The clinical features and stool characteristics of rotavirus diarrhea are nonspecific, and similar illness may be caused by other pathogens. As a result, confirmation of a diarrheal illness as rotavirus requires laboratory testing by serology and molecular tests.¹⁷

2. **Noroviruses:** Several strains can cause gastroenteritis in humans. Noroviruses commonly identified as Norwalk like viruses in the family *Caliciviridae* (NLVs and SLVs). Other strains those belongs with the same group are Southampton virus, Desert storm virus, Toronto virus, Bristol virus, Hawaii virus, Snow mountain virus and Jina virus; they all comes under NLVs and there are several species which comes under SLVs includes London virus, Parkville virus and Sapporo virus.¹⁸ These viruses can be transmitted easily through direct contact, touching contaminated surfaces, contaminated food and comprises approximately 60% of all sporadic diarrhea cases.⁴ The genomic constitution of NLVs consist positive sense, single stranded RNA arranged into three ORFs (open reading frames) as shown in figure Figure-2. ORF-1 encodes non-structural proteins while ORF-2 encodes structural proteins of capsid and ORF-3 encodes proteins with unknown function.^{19, 20}

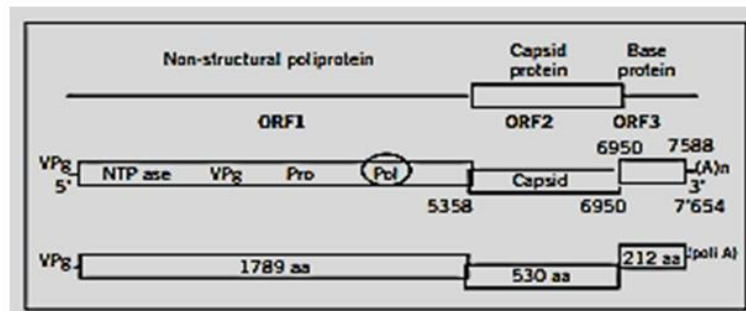


Figure 2: Norovirus Genomic Organization

The incubation time for Norovirus is 24-48 hours, and the average duration of mild to moderate illness lasting 12-60 hours and clearing up within few days. The symptoms are similar to those of rotavirus, including nausea, vomiting, non-bloody diarrhea, mild cramps, and fever.⁸

Among seven outbreaks of calicivirus reported in literatures, four outbreaks affected children in an orphanage and school in Japan, other affected infant-mother hospital unit and school in England. Three outbreaks reported in nursing-home settings in England and Japan. This calicivirus affected 50% to 70% of the population where outbreaks happen.²¹

The norovirus pathogenesis has been demonstrated *in-vitro*. Diarrhea developed in most of the cases without blood after given filtrated Norovirus to healthy individuals. It is very difficult to culture norovirus like other viruses, yet study done by Jones et al. in 2014, it has been explained the culture of norovirus in B-cells and enteric viruses; *in vitro* co-factors such as histo-blood antigen exhibit enteric bacteria are probably required.^{22,23}

As due to lack of fortified antiviral agent to treat norovirus associated infection, there should be focus on prevention and treatment of the secondary dehydration. The isotonic fluid given orally is usually help to maintain fluid balance. Hospitalization required in case of a severe dehydration, although this is rare. Analgesic and antipyretic drugs are prescribed to control the symptoms such as headache, myalgia, and nausea.²⁴

- 3. Adenoviruses:** The adenoviruses are an important group of widely prevalent human pathogens. In humans and other primates they can cause gastroenteritis while, in children's they cause severe diarrhea and are play an important viral pathogens in immune-compromised adults and also associated with high morbidities and mortalities in both age groups.^{25,26} DNA has a double-stranded linear structure composed by two major core proteins and 55-kDa protein covalently bonded to its 5' end. Adenoviruses with over 100 antigenic types have been found, in which 47 human adenovirus types are classified till date and 5 more genotypes are recently observed.²⁷ Further, it has been classified that human adenoviruses sub-classified into six subgenus groups (A–F) on the basis of their physical, chemical and biological properties as shown in table-2.^{27, 28}

Table 2: Human Adenovirus Types

S.NO.	SUBGENUS	SEROTYPES
1.	A	12,18,31
2.	B	3,7,11,14,16,21,34,35
3.	C	1,2,5,6
4.	D	8,9,10,13,15,17,19,20,22-30,32,33,36-39,42-47
5.	E	4
6.	F	40,41

Adenoviruses are unusually resistant to chemical or physical agents and in an adverse pH condition, which allow them for prolonged survival *in vitro*. A study conducted by WHO on water recreation and disease in the year 2005 showed that the adenovirus has been highly resistant against both tertiary treatment and UV radiation of urban wastewater.²⁹

Many of the adenovirus serotypes can multiply in the mucosal lining of small intestine, but only types 40 and 41 have been strongly associated with gastroenteritis, leads to atrophy of the villi and compensatory hyperplasia in the crypts resulting in fluid loss and mal absorption. The incubation time is usually a few days, but it might be longer in some circumstances.¹⁸ In most cases, specific antibodies arise after adenovirus infection, and non-neutralizing antibodies are valuable for assessing the host's immune response. The specific neutralizing antibodies can provide protection both in the acute illness and in case of reinfections caused due to the same serotype. Despite the fact patients may continue to eliminate the virus after an effective humoral response in their feces for a month.³⁰

Adenovirus infection begins similarly to rotavirus infection and DNA replication is bi-directional and atypical with 80- to 87-kDa polypeptide primer. Several host proteins, as well as encoded DNA polymerase, pTP, and the viral E2A protein, catalyze

adenovirus DNA replication.²⁷ Adenovirus genes are transcribed by the host DNA-dependent RNA polymerase II in a complex transcriptional pathway. This mechanism is regulated by the nucleotide sequences and the structured viral promoters. In adenovirus, the regulatory genes in the E1A region of genome are the first to be transcribed. This quick viral response can also activate or deactivate certain other cellular genes and influencing adenoviral infection pathogenesis.²⁷

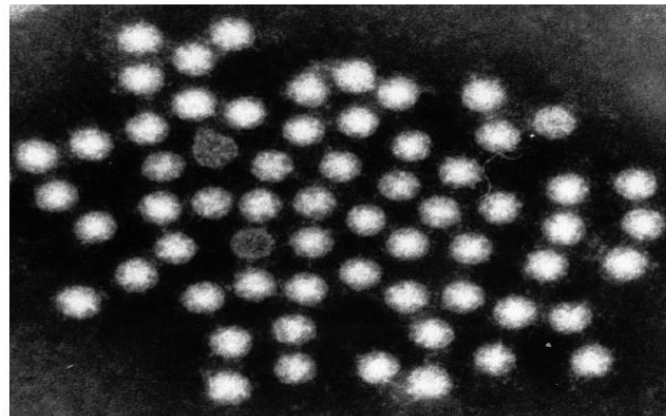


Figure 3: Human astrovirus particles observed by transmission immune-electron microscopy in feces

- 4. Astrovirus:** Astrovirus (star like appearance) was first recognized by electron microscopic during examination of diarrheal stool samples from infants. It can cause severe gastroenteritis, especially in infants and children as shown in figure-3.³¹

The virus contains a positive-sense, single stranded RNA genome of approximate size of 7.2 kb and contain ORF1a and ORF1b encode viral protease and polymerase respectively. ORF2 encodes viral protein capsid precursor.^{18,32} The virus replication takes place in human embryonic kidney cells.⁴ The astrovirus are transmitted through the oral-fecal route and the incubation period is ranging from 1 to 5 days. The signs and symptoms include diarrhea, nausea, vomiting, fever, abdominal pain, headache, and malaise.⁸ The structural protein in astrovirus includes 87-kDa poly-proteins and 30 kDa smaller proteins. They can classify into seven genotypes on the basis of nucleotide sequences of 348-bp region of ORF2 as shown in figure figure 4.^{18,31}

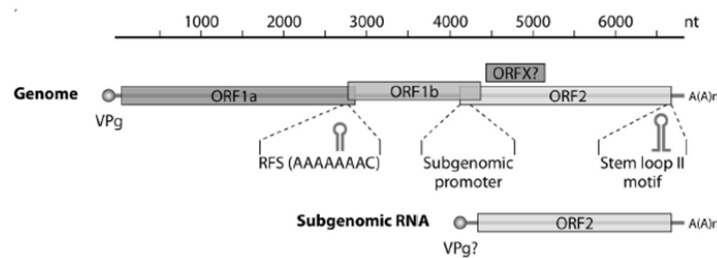


Figure 4: Genome organization and polyprotein products of human astrovirus

The pathogenesis of the virus remains to be determined, but on the basis of several studies, which about 2-10% of endemic pediatric gastroenteritis cases are caused by astrovirus infection. Blacklow et al in 1995 reported that astrovirus was the causative agent of nosocomial outbreaks of infant diarrhea in Swedish children's hospital and endemic childhood diarrhea in Bangkok, Thailand in their study.^{33,34} Mainly children's were affected with astroviral infection but pathogenic mechanism in an adult not yet to be clear.

III. OTHER VIRUSES CAUSING GASTROENTERITIS

- 1. Torovirus:** It is a genus sorted inside the Coronaviridae family. The study was conducted in 1984 by Beards et al; elaborated the first time detection of Torovirus in the feces of patients suffering with gastroenteritis.³⁵ The envelope sizes of these viruses are of 100–140 nm, with a capsid and positive sense single-stranded RNA genome. It is associated with acute diarrhea in children due to the persistent of viruses in gut and later this infection play an important cause of nosocomial diarrhea in childrens.^{36,37}
- 2. Coronavirus:** Another virus belongs to the Coronaviridae family known as Coronavirus. The size of the virus is in between 60 and 220 nm, it form a spiculated envelope that gives them crown like appearance.³⁸ Positive monocatenary RNA constitutes the genome and it was first time appeared in 1975 causing diarrhea in humans, but still there is no evidences till date, to establish a definite etiological role of coronavirus in humans gastroenteritis.^{39,40}
- 3. Picornaviruses:** Pereira et al. reported these viruses for the first time in 1988. They are small, without an envelope, and have a capsid with icosahedric symmetry. Its genomic structure is made up of two or three bicatenary RNA segments.⁴¹ They cause diarrhea in both children and adults and have more strong association among immuno-compromised patients.⁴²
- 4. Herpes Viruses:** It's commonly known as cytomegalovirus (CMV) and has been found in humans causing gastroenteritis, and is especially harmful to patients infected with human immune-deficiency virus (HIV). CMV has the ability to human gastrointestinal tract with resulting in gastrointestinal symptoms including upset stomach, indigestion, nausea, vomiting etc.⁴³

In a case study conducted by Boulton et al. in 1982, reported that *Herpes simplex* virus, which belongs to the herpes virus group, has also been one of the agents of infection in the upper gastrointestinal tract in immune suppressed patients and was extracted from the ileum region of the patient suffering with diarrhea. So, it was considered that the patient's suffering with terminal diarrhea was probably due to presence of herpes simplex virus colitis but it has been suggested that immunosuppressive therapy may be a factor in triggering the systemic spread of herpes simplex virus because in these patients have mucocutaneous manifestations, which was not appeared in their study.⁴⁴

IV. PREVENTION AND TREATMENT

The treatment of viral gastroenteritis disease is symptomatic, primary goal is to keep the dehydrated, in order to control water and minerals deficit, it is very essential to increase liquid intake.¹⁸ Oral rehydration solutions may be the good choice in cases of mild and moderate dehydration are as effective as or better than intravenous rehydration and can be easy to utilized in all kind of clinical settings but for rapid treatment of severe dehydration, intravenous rehydration may be required. Live, attenuated rotavirus vaccines derived from a single common strain and re-assorted bovine-human rotavirus are considered highly effective in preventing severe gastrointestinal disease. It is recommended that rotavirus vaccines should be included in all national immunization programmes.¹¹ There is no role of antibiotics but the anti-inflammatory salicylates (eg. olsalazine, mesalazine), laxative and non-specific anti-diarrheal will be helpful in the management of uncomplicated viral gastroenteritis.⁴⁵ Earlier it was limited to the use of laxative, antispasmodics, antacids and has changed markedly in past few years. The use of histamine H₂ receptors (ranitidine, nizatidine etc) is now in the use to treat peptic acid disorders.⁴⁶

V. CONCLUSION

In this review we presented different viral agents causing gastroenteritis infections, to understand the causative viral agents associated with the human gut and have explained the genetic structure, function and pathogenesis of the human gut viruses in a variety of diseases. Hopefully this will be helpful us to reduce the transmissibility of infection, morbidity and mortality of several known viral infections. Recent technological innovations and continuous efforts in the field of medical research have led to a tremendous development in the knowledge of the human gut virome database. Enteroviruses, norwalk and rotaviruses are a prevalent component of the human gut virome and are known to cause infectious gastroenteritis. These viruses can cause acute infections followed by gastrointestinal complaints such as nausea, vomiting, diarrhea and weight loss. If they persist for long-term with the symptoms, it may lead to functional dyspepsia and post-infectious IBS. More efforts and research required further to characterize the role of the viral microbiota of gut and the immunological mechanisms associated with host-microbe interactions to provide a better understanding of gut viral infectious diseases.

VI. AUTHOR CONTRIBUTIONS

Mr.Vivek Gaur designed and contributed to the writing of the manuscript. Dr. Amresh Kumar Singh was provided the final version of the review and proof reading. Dr. Ankur Kumar contributed to the editing and for corrective actions. All authors contributed to the article and approved the submitted version. Authors also like to thanks the Residents and all technical staff of the Department of Microbiology, BRD Medical College, Gorakhpur, Uttar Pradesh, India for their immense support during this research work.

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