World Journal of Virology

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World J Virol 2023 June 25; 12(3): 136-150

DOI: 10.5501/wjv.v12.i3.136

ISSN 2220-3249 (online)

REVIEW

Gastrointestinal tract and viral pathogens

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Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Perse M, Slovenia

Received: December 7, 2022
Peer-review started: December 7, 2022
First decision: March 1, 2023
Revised: March 17, 2023
Accepted: April 27, 2023
Article in press: April 27, 2023
Published online: June 25, 2023

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Abstract

Viral gastroenteritis is the most common viral illness that affects the gastrointestinal (GI) tract, causing inflammation and irritation of the lining of the stomach and intestines. Common signs and symptoms associated with this condition include abdominal pain, diarrhea, and dehydration. The infections commonly involved in viral gastroenteritis are rotavirus, norovirus, and adenovirus, which spread through the fecal-oral and contact routes and cause non-bloody diarrhea. These infections can affect both immunocompetent and immunocompromised individuals. Since the pandemic in 2019, coronavirus gastroenteritis has increased in incidence and prevalence. Morbidity and mortality rates from viral gastroenteritis have declined significantly over the years due to early recognition, treatment with oral rehydration salts, and prompt vaccination. Improved sanitation measures have also played a key role in reducing the transmission of infection. In addition to viral hepatitis causing liver disease, herpes virus, and cytomegalovirus are responsible for ulcerative GI disease. They are associated with bloody diarrhea and commonly occur in immunocompromised individuals. Hepatitis viruses, Epstein-Barr virus, herpesvirus 8, and human papillomavirus have been involved in benign and malignant diseases. This mini review aims to list different viruses affecting the GI tract. It will cover common symptoms aiding in diagnosis and various important aspects of each viral infection that can aid diagnosis and management. This will help primary care physicians and hospitalists diagnose and treat patients more easily.

Key Words: Virus diseases; Gastroenteritis; Enterocolitis; Rotavirus infections; Norovirus; Adenoviridae infections; Digestive system diseases

Core Tip: Viral gastroenteritis is a common condition that affects the gastrointestinal (GI) tract. These viruses can affect people of all ages and are a significant public health concern. Dehydration resulting from the infection is the primary reason for emergency department visits in both children and adults. Our review discusses other GI viruses such as cytomegalovirus, herpes simplex virus, and hepatitis virus that cause manifestations such as hepatitis, gastritis, and bloody diarrhea. Both immunocompetent and immunocompromised individuals can be affected by these GI viral pathogens. Understanding the various viruses that cause GI manifestations can help with early diagnosis and appropriate management. This is a concise review of GI viral pathogens.

Citation: Jagirdhar GSK, Pulakurthi YS, Chigurupati HD, Surani S. Gastrointestinal tract and viral pathogens. *World J Virol* 2023; 12(3): 136-150
URL: https://www.wjgnet.com/2220-3249/full/v12/i3/136.htm
DOI: https://dx.doi.org/10.5501/wjv.v12.i3.136

INTRODUCTION

Viral pathogens cause gastrointestinal (GI) manifestations such as watery diarrhea, bloody diarrhea, and various other manifestations like hepatitis, ulcerative diseases, motility disorders, and neoplastic diseases of the GI tract in both immunocompetent and immunocompromised individuals. Infectious gastroenteritis is a major illness worldwide, especially in developing nations and viruses account for most of the illnesses. Globally, Norovirus is the leading cause of acute gastroenteritis outbreaks. Besides diarrhea, viruses are also responsible for causing diseases like hepatitis and ulcerative diseases. Asymptomatic and symptomatic co-infections with these pathogens listed are also mentioned in prior literature. Our paper is the first-of-its-kind mini-review summarizing most of the GI viral pathogens and their varied manifestations to update existing reviews[1,2]. We consolidated information on viruses that cause both diarrheal illness and non-diarrheal manifestations. Our paper will concisely summarize each entity to equip clinicians with accurate information and aid in correct diagnosis and management. As gastroenteritis is the most common disease caused by these viruses, we will be categorizing the paper based on this presentation. This categorization may also help with forming a differential diagnosis when patients present to health care centers and hospitals with the infection. We categorized the manuscript into: (1) Diarrheal illnesses further subdivided into non bloody diarrhea and bloody diarrhea; and (2) viruses associated with other non-diarrheal illnesses-hepatitis, ulcerative disease, and neoplasms (Table 1 shows common viruses that affect the GI system).

NON-BLOODY DIARRHEA FROM VIRAL GASTROENTERITIS

Norovirus

Norovirus is an RNA virus belonging to the *Caliciviridae* family and consists of forty-nine genotypes. According to Centers for Disease Control and Prevention (CDC), Norovirus is the leading cause of acute gastroenteritis among all age groups in the United States[3]. However, high-risk groups include young children, the elderly, travelers, military personnel, and the immunocompromised. On average, each year in the United States, Norovirus causes 109000 hospitalizations. Outbreaks usually occur in congregant environments like healthcare centers, cruise ships, and restaurants *via* fecal-oral transmission through food, water, or person-to-person contact. It is typically a self-limiting disease with symptoms like diarrhea, nausea/vomiting, and abdominal cramps that resolve within two to four days. It is primarily a clinical diagnosis. However diagnostic modalities include electron microscopy, polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and immunochromatographic testing[4]. Diagnostic testing for Norovirus is rarely used given the short-lived nature of the disease. Currently, no drug has been clinically approved to treat norovirus infection owing to its mild state of disease. Complications of this illness include electrolyte imbalances, chronic gastroenteritis, irritable bowel syndrome, inflammatory bowel disease, convulsions, and encephalopathy (especially in children)[5]. Vaccinations are not currently licensed for norovirus infection prevention, but many trials are underway to assess the impact and efficacy of vaccines on disease prevention and transmission.

Rotavirus

Rotavirus, an RNA virus, and a member of the Reoviridae family is the major cause of diarrhea in children younger than five years. Reports from the Global burden of disease showed that 128530 deaths occurred due to Rotavirus infection alone[6]. Rotavirus contributed to 29.3% of total diarrheal deaths in 2015[6]. Younger age groups (< 5 years) and lower socioeconomic status seem to be the targets of the

Table 1 Common viruses affecting the gastrointestinal system

Virus	Route of infection	Population affected	Type of disease	Diagnosis	Treatment
Norovirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Rotavirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Adenovirus	Fecal-oral, fomites	Any age group, especially children	Gastroenteritis	Self-limited	Supportive
Hepatitis A	Fecal-oral, fomites	Any age groups; international travelers to endemic countries, IV drug users, men who have sex with men	Gastroenteritis, acute viral hepatitis, and fulminant liver failure	Serology	Supportive
Astrovirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Sapovirus	Fecal-oral, fomites	Children < 5 yr	Gastroenteritis	Self-limited	Supportive
Coronavirus	Fecal-oral, fomites	Any age group	Gastroenteritis; respiratory infection	Self-limited, viral rapid antigen, PCR can be performed	Supportive; for COVID-19-antivirals (nirmatrelvir/ritonavir, remdesivir), steroids, biologics (tocilizumab, baricitinib)
Hepatitis E	Fecal-oral, Fomites	15-40 yr	Gastroenteritis, acute hepatitis, and acute liver failure	Serology	Supportive
Cytomegalovirus	Contact with bodily fluids and organ transplantation	All ages	Colitis, toxic megacolon, and peritonitis	Viral PCR	Ganciclovir, valganciclovir, ganciclovir resistant-foscarnet, cidofovir
Herpes simplex virus	Sexual contact	MSM	Proctitis and anal ulcerations	Viral PCR	Acyclovir, valacyclovir, and famciclovir
HIV	Contact through bodily fluids like sexual contact, injection drug use, perinatal transmission	All ages	Acquired immunodeficiency syndrome, HIV enteropathy-diarrhea	2-step testing-combination antigen-antibody test followed by HIV 1/2 differentiation assay	HAART-combination therapy with Tenofovir, Emtricitabine, raltegravir, and bictegravir
Hepatitis B and D	Contact through bodily fluids like sexual contact, injection drug use, perinatal transmission	Usually adults, but all age groups can be affected	Hepatitis, cirrhosis, hepatocellular carcinoma	Serology, DNA load	Acute infections usually resolve; in some cases, tenofovir, entecavir
Hepatitis C	Contact through bodily fluids like sexual contact, injection drug use, transfusion, or perinatal transmission	Usually adults, but all age groups can be affected	Hepatitis, cirrhosis, hepatocellular carcinoma	Serology, RNA load	Combination therapy specific for genotypes; includes sofosbuvir/velpatasvir, glecaprevir/pibrentasvir
Varicella Zoster	Droplet, and contact infection	Commonly in children but can occur in any age group. Reactivation common in immunocompromised	Erosive disease of the stomach and intestines, motility problems	Clinical diagnosis, but RNA PCR is used for atypical presentations	Acyclovir, valacyclovir, and brivudin
Epstein-Barr virus	Contact with bodily fluids, especially saliva; sexual transmission, blood transfusion, organ transplantation	Individuals aged 15-24 yr	Gastritis, Enteritis, esophageal disorders, and gastric cancer	Mostly clinical diagnosis but can be diagnosed by serology	Symptomatic treatment, acyclovir in some cases
HHV-8	Sexual transmission, contact with saliva, blood transfusion, and organ transplantation	All age groups	Maculopapular and polypoid lesions of the GI tract	Endoscopy and biopsy	Radiation, intralesional chemotherapy, or systemic chemotherapy with liposomal doxorubicin and paclitaxel
HPV	Sexual transmission-oral, vaginal, anal sex	15-49 yr	Oropharyngeal, esophageal, gastric, colorectal, and anal cancers	Cytology and viral testing	Cancer-specific treatment

HIV: Human immunodeficiency virus; HPV: Human papillomavirus; HHV: Human herpesvirus 8; MSM: Men who have sex with men; PCR: Polymerase chain reaction; GI: Gastrointestinal.

disease[7]. Diarrhea caused by the virus is thought to be *via* two mechanisms: (1) Osmotic diarrhea due to malabsorption secondary to enterocyte damage; and (2) secretory diarrhea from activation of the enteric nervous system and non-structural protein-4[7]. The disease is transmitted through fecal-oral routes and fomites. Clinical manifestations include diarrhea, vomiting, and fever. Clinical morbidity is due to severe dehydration requiring hospitalization and can sometimes also lead to necrotizing enterocolitis[8]. ELISA can detect the virus until 1 wk after the onset of diarrheal illness whereas real time PCR (RT-PCR), being more sensitive can detect the virus until longer periods[7]. Fluid and electrolyte resuscitation remains the mainstay of treatment. Symptomatic management with Antiemetics and Antidiarrheal drugs decreases fluid losses thus fastening recovery and preventing death. Routine use of antivirals is not recommended for this infection. The advent of Rotarix and RotaTeq around 2006-2008 brought about a notable change in the morbidity and mortality of rotaviral disease. Mortality among children younger than 5 years of age has decreased by more than 45% since the mid-2000s[6]. It is prudent to say that, although there has been a shift from rotaviral illness being a fatal disease to a non-fatal disease, continued efforts are necessary to widen vaccination coverage and improve water and sanitation facilities.

Adenovirus

Adenovirus is a double-stranded DNA virus belonging to the Adenoviridae family. HAdV-F40 and F41 are the enteric serotypes implicated in causing acute gastroenteritis[9]. According to the re-analysis done by Global Enterics Multicenter Study, adenovirus was the second most common cause of diarrheal illness after Rotavirus in infants[9]. Infections caused by Adenovirus include febrile respiratory illness, pharyngoconjunctival fever, keratoconjunctivitis, and gastroenteritis. Transmission routes include aerosols, fecal-oral, and fomites. Adenovirus infections occur in congregate settings like daycare centers, summer camps, college campuses, and military camps. Symptoms of adenoviral gastroenteritis are like any other gastroenteritis including diarrhea, vomiting, and abdominal cramps. However, a multicenter study done in 8 Low-resource countries showed that fever was more commonly associated with adenoviral infection compared to other viral infections other than rotavirus[10]. Diagnostic methods are not often used but consist of antigen detection, PCR, and serology. No specific treatment is available for the infection but measures like rehydration, adequate food intake, and zinc supplementation are essential, especially in low to middle-income countries. Complications of adenoviruses include intussusception, hepatitis of unknown cause (adenovirus type 41), chronic lung disease, meningoencephalitis, and cystitis[11,12]. Currently, vaccination against Adenovirus type 4 and 7 is FDA-approved to prevent febrile acute respiratory disease for military populations aged 17 years to 50 years.

Astrovirus

Astroviruses are single-stranded RNA viruses belonging to the family of Astroviridae. Astroviruses are responsible for 0.5%-15.0% of diarrheal outbreaks across the world[13]. Transmission is through the fecal-oral route and fomites. Like any other gastroenteritis-causing virus, outbreaks happen in communal settings like schools, nursing homes, and swimming pools[14]. The incubation period is long (4.5 d) and it causes mild diarrhea lasting for about 2 d to 3 d associated with symptoms like fever, anorexia, and vomiting[15]. Diagnostics include electron microscopy, cell culture, immunoassays, and RT-PCR, with the latter being the most commonly used modality[16]. This infection is self-limited and usually resolves with fluid and electrolyte replacements. Immunocompromised adults and the elderly have longer-lasting symptoms with rare occurrences of complications like meningitis and encephalitis [17].

Sapovirus

Sapoviruses are single-stranded RNA viruses belonging to the same family as Norovirus, *Caliciviridae*. According to the Etiology, Risk Factors, and Interactions of Enteric Infection and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study, sapovirus had the second-highest incident rate of acute diarrhea after Shigella. The study attributed an incidence rate of 22.8 cases per 100 child years to sapovirus with a 95% confidence interval ranging from 18.9 to 27.5[18]. Transmission occurs through fecal-oral contact, contaminated food/water, and fomites[19]. They are known to cause gastroenteritis in humans, specifically aged < 5 years, and animals[20]. Outbreaks occur in communal settings like daycare centers, hospitals, nursing homes, and schools[21]. While the usual clinical symptomatology is the same as any gastroenteritis-causing virus, it has also been implicated in causing chronic diarrhea, especially in immunocompromised populations. Definitive diagnosis by PCR detection, however, is not indicated due to the self-limiting nature of the disease and the cost considerations[21]. No antivirals are warranted, World health organization (WHO) guided treatment for diarrhea viz rehydration, zinc supplementations, and adequate nutrition is considered the treatment of choice[22]. Interestingly, Nitazoxanide has been tried in transplant patients with some benefits[23]. Cases of Sapoviruses causing septic shock and intestinal obstruction have been reported in the literature[24,25].

Enterovirus

Enteroviruses are single-stranded RNA viruses belonging to the Picornaviridae family. Enterovirus

genus consists of viruses like Poliovirus, Coxsackie virus, Echovirus, rhinovirus, and other enterovirus subtypes. According to the CDC, it is estimated that around 10-15 million non-polio-enterovirus infections occur annually[26]. They can be transmitted *via* the fecal-oral route or through respiratory secretions. Infants, children, and teenagers are more likely to get affected than adults[27]. They generally have a secondary tissue tropism and spread to other target tissues after they infect the GI system[28]. Non-Polio enteroviruses are known to cause diseases like aseptic meningitis, hand-foot-mouth disease, flaccid paralysis, myocarditis, pancreatitis, *etc*[28,29]. Some non-specific GI manifestations are less common but include abdominal pain, vomiting, and diarrhea and are self-limited. Enteroviruses can be detected in stool, pharynx, blood, and CSF using techniques like PCR, serology, and cell culture. Treatment is usually symptomatic care and no targeted therapies have been developed yet. Some of the dreaded complications of enteroviruses include meningitis, encephalitis, myocarditis, and acute flaccid paralysis[30,31]. The only enteroviral vaccine is the polio vaccine to prevent poliomyelitis.

Coronavirus

Coronaviruses are single-stranded RNA viruses belonging to the Coronaviridae family. SARS-CoV-1 emerged in 2002-2003 and caused a global outbreak that affected over 8000 people in 26 countries, with a case fatality rate of approximately 10%[32]. MERS-CoV emerged in 2012 and has since caused sporadic outbreaks in the Middle East and other regions, with a case fatality rate of approximately 34%[33]. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019 and has since spread globally, causing a pandemic that has affected millions of people worldwide. As of April 21, 2023, there have been over 435 million confirmed cases and over 5.8 million deaths reported globally[34]. Coronaviruses are transmitted through multiple routes, mainly through droplets, contact with infected persons, and contaminated surfaces.

Human Coronaviruses are known to cause respiratory infections, but they also cause GI symptoms including diarrhea, nausea, vomiting, and abdominal pain. The majority of HCoV infections like diarrhea occur in neonates, infants, and children. Also, they co-infect with other enteric viruses like norovirus and rotavirus. SARS-CoV and MERS-CoV, members of the coronavirus family have also been implicated in causing the above symptoms[35]. SARSCoV2 causing COVID-19 also presents as diarrhea, nausea, vomiting, and abdominal pain along with respiratory symptoms and sometimes even in the absence of respiratory manifestations[36]. GI manifestations were speculated to be caused due to the high expression of ACE2 receptors in the gut which is the binding site for SARS-CoV-2[37]. Changes in the gut microbiota have also been observed in COVID-19-infected patients. Although they are respiratory viruses, interestingly, the GI transmission of this group of viruses has also been proven as many studies have mentioned the detection of RNA in stool samples[35]. Currently, no specific antivirals are indicated in SARS and MERS infections, whereas COVID-19 treatment entails various therapies like antivirals, steroids, biologics, *etc*. The most common complications of COVID-19, caused by SARS-CoV-2, include pneumonia and acute respiratory distress syndrome (ARDS), which can lead to respiratory failure and death in severe cases[38]. COVID-19 can also cause a range of other complications, including cardiovascular and neurological complications, blood clots, and multisystem inflammatory syndrome in children[39]. MERS-CoV infections are also associated with severe respiratory illness and complications such as pneumonia, ARDS, and septic shock[40]. SARS-CoV-1 infections can cause similar respiratory complications, as well as complications such as liver and kidney failure[41]. Currently, several vaccines against the COVID-19 have been developed. Pfizer-BioNTech and Moderna mRNA vaccines have reported efficacies of over 90% in preventing symptomatic COVID-19[42,43].

Hepatitis E virus

Hepatitis E virus is a single-stranded RNA virus belonging to the family Hepeviridae. According to the WHO, there are an estimated 20 million HEV infections worldwide every year[44]. hepatitis E caused approximately 44000 deaths in 2015 (accounting for 3.3% of the mortality due to viral hepatitis)[44]. Hepatitis E is mainly transmitted through food and water contamination, also through perinatal transmission, and blood transfusions[45]. Pregnant women, especially those in their third trimester, and individuals with pre-existing liver disease are the most vulnerable groups for developing severe HEV infection[46-48]. Other groups that may be at increased risk of HEV infection include travelers to endemic areas, healthcare workers, and individuals who consume undercooked or raw pork[49]. It is usually a self-resolving illness but can sometimes occur with symptoms like fever, anorexia, jaundice, nausea, vomiting, hepatomegaly, and abdominal pain[50]. Diagnosis is by serology, enzyme immunoassay, or RNA detection by PCR. Acute hepatitis E does not require treatment, however, if liver failure occurs then liver transplantation is an option[51]. Chronic hepatitis E can be treated with Ribavirin for 12 wk[52]. In pregnant women, HEV infection can lead to fulminant hepatic failure, which has a mortality rate of up to 30%[46]. Other complications include acute liver failure, chronic HEV infection, and neurological complications like Guillain-Barre syndrome, myelitis, and neuropathy to name a few[53]. Vaccines are not yet commercially available for prevention except in China[54].

BLOODY DIARRHEA FROM VIRAL GASTROENTERITIS

Cytomegalovirus

Cytomegalovirus (CMV) is a double-stranded DNA virus and a member of the Herpesviridae family with a prevalence ranging between 40%-100% in the adult population[55]. Latent phase reactivation occurs in immunocompromised individuals, including transplant recipients, patients on immunosuppressive agents, and those with inflammatory bowel disease (IBD) treated with steroids[56]. CMV is transmitted by contact with infectious body fluids like saliva, urine, respiratory droplets, sexual contact, blood transfusion, and solid organ transplants. Symptomology of CMV colitis could range from bloody diarrhea, abdominal pain, fever, weight loss, and lymphadenopathy to toxic megacolon. Few studies show that the severity of CMV is related to age and could cause Toxic megacolon and pan peritonitis in the elderly[57]. Although histology of tissue analysis is considered the gold standard for diagnosis, RT-PCR has the highest sensitivity and detection rate for infection. The most used antivirals are intravenous ganciclovir and valganciclovir. Foscarnet and cidofovir are used in ganciclovir-resistant cases. Some studies showed that although CMV is reactivated in IBD patients, it spontaneously disappears even without antiviral treatment[58,59]. Complications associated with CMV colitis may include ischemic colitis, perforation of the large bowel, toxic megacolon, and formation of pseudomembranous. Currently, there are no vaccines available for CMV. As per European Crohn's and Colitis Organization guidelines, if severe systemic CMV is detected, immunomodulators should be discontinued and screening for CMV is not routinely performed before starting immunomodulators in IBD[60].

Herpes simplex virus

Herpes simplex virus (HSV) is a double-stranded DNA virus belonging to the Human Herpesviridae family. HSV proctitis is the second most common sexually transmitted cause of infectious proctitis in homosexual males and could be caused by HSV-1 or HSV-2, but 70% of cases are due to HSV-2[61,62]. Prevalence of HSV-1 and HSV-2 have decreased over time linearly from 59.4 % & 18.0% in 1999-2000 to 48.1% & 12.1% in 2015-2016[63]. HSV is transmitted by intimate person-to-person contacts like men who have sex with men (MSM), unprotected receptive anal, and oral sex. Clinical symptoms of HSV proctitis include rectal bleeding, tenesmus, anorectal pain, and mucous discharge. The absence of external HSV lesions should not diminish suspicion of HSV infection as only 32% of men with HSV proctitis have external anal ulcerations[64,65]. Due to the high seropositivity for HSV worldwide, serological analysis plays a minor role in the diagnosis. PCR has been used to accurately diagnose and quantify the HSV DNA from clinical biopsy specimens[66]. Immunofluorescence staining of colonic specimens with HSV-type specific monoclonal antibodies against glycoproteins is highly specific to confirm the diagnosis. CDC recommends antiviral treatment with acyclovir, valacyclovir, or famciclovir in acute proctitis if the HSV infection is suspected or confirmed. Complications of HSV proctitis can result in symptoms such as constipation, severe anorectal pain, difficulty urinating, sacral paresthesia's, and diffuse ulcerations of the distal rectal mucosa. Currently, there are no vaccines approved for the prevention of HSV. Infectious proctitis must be considered before starting immunosuppressant therapy for presumed IBD, as the immunosuppressive medications may result in a lack of improvement or symptomatic worsening of infectious proctitis. HSV-induced anogenital ulcers will lead to a 1.5 to 7.0-fold increase in human immunodeficiency virus (HIV) transmission due to associated mucosal barrier breach, hence HIV screening is important. Individuals with acute proctitis along with HIV and/or painful perianal ulcers should receive presumptive treatment for anogenital HSV[67].

VIRAL GASTROINTESTINAL PATHOGENS ASSOCIATED WITH DIARRHEA AND OTHER GASTROINTESTINAL MANIFESTATIONS

Hepatitis A virus

Hepatitis A virus (HAV) is an RNA virus and a member of the Picornaviridae family. According to a report published in 2017, the incidence of acute hepatitis A was 170 million cases globally[68]. It is commonly transmitted through the fecal-oral route *via* contaminated food and water consumption. Transmission through sexual contact, person-to-person contact, and illicit drug use also exist in the literature[69]. Case fatality was higher in males, older than 50 years, and coexisting chronic liver disease raised the risk of developing fulminant hepatitis after an HAV infection[69]. From prior literature, > 70% of children under six years of age do not develop symptoms whereas > 70% of adults manifest symptoms[70]. Symptoms include fever, malaise, nausea, vomiting, abdominal discomfort, and jaundice. Physical examination findings include hepatomegaly and jaundice[70]. Hepatitis A generally follows a benign course, however chronic relapsing hepatitis for as long as 1 year is a possibility. Diagnosis is through serology by measuring the IgM antibody. IgG detection is useful when the question of immune status arises. Owing to its self-limited nature, this infection does not require treatment. According to the CDC, Hepatitis A vaccination is recommended for all infants. It is also recommended for those at substantial risk of exposure to hepatitis A infection, those at risk of

progressing to fulminant hepatitis, those experiencing homelessness, and HIV-infected persons.

Human immunodeficiency virus

Human immunodeficiency virus (HIV) is an RNA virus, belonging to the family Retroviridae. According to recent statistics, around 1.5 million individuals acquired HIV in 2021[71]. High-risk groups include gay and bisexual populations of all races and ethnicities, African Americans, injection drug users, and transgender populations[72]. It is transmitted *via* body fluids through sexual contact, needle sharing, breast milk, and perinatal transmission. In addition to the wide range of clinical manifestations, it is interesting to note how this virus affects the GI system. A specific term, "HIV enteropathy" has been coined to define the GI manifestations caused by this virus[73]. It causes alteration of epithelial ionic balances and enterocyte apoptosis resulting in inflammation, change in permeability, and malabsorption[73]. Histologically, villous atrophy, crypt hyperplasia, and epithelial hyperproliferation ensue. All of this culminates in causing diarrhea secondary to HIV enteropathy. HIV also leads to other GI effects by the virtue of its immunodeficiency, thus paving the way for opportunistic infections. Antiretroviral therapy (ART), especially protease inhibitors itself, can also cause diarrhea in HIV[74]. GI complications range from Esophageal disorders, gastric illnesses to colitis, enteritis, and anorectal disease. Most of these are caused by secondary/opportunistic bacterial, fungal, and viral infections and HIV-induced neoplasia of the GI tract. Also, the GI tract is a favorable site for HIV replication and GI CD4 destruction[75]. Pancreatic and hepatobiliary complications include pancreatitis, exocrine pancreatic insufficiency, hepatitis, and non-alcoholic fatty liver disease[76]. Diagnosis is fourth generation antigen-antibody assay followed by HIV 1/2 differentiation assay. Stool samples for ova and parasite examination should be done to identify the causative pathogen given the high chance of opportunistic infections like Cryptosporidium, Isospora, Giardia, *etc*[74]. If a cause cannot be identified yet, endoscopy with biopsy is an option[74]. Highly ART (HAART) causes the reconstitution of peripheral circulating plasma CD4 cells, but studies have found that it is not successful in the replenishment of GI CD4 cells[77].

Hepatitis B and D virus

Hepatitis B virus (HBV) is a partially double-stranded DNA virus and belongs to the family of Hepadnaviridae. According to the CDC statistics, globally, 296 million people are infected with Hepatitis B. High-risk groups include veterans, healthcare professionals, MSM, injection drug users, persons with HIV, hepatitis C virus (HCV) co-infection[78]. hepatitis B can be transmitted perinatally, through sexual contact, percutaneous or person-to-person contact with infected body fluids[79]. The incubation period ranges from 1 mo to 4 mo. The acute phase of hepatitis B infection presents as a serum-sickness-like illness characterized by fever, rash, and arthralgia followed by jaundice, nausea and vomiting, and other constitutional symptoms[79]. It causes elevation of alanine aminotransferase (ALT) more than aspartate aminotransferase (AST) and bilirubin. Diagnosis is by serum viral biomarkers[79]. It is known that Hepatitis B is implicated in the causation of Hepatitis and its plethora of clinical manifestations including hepatocellular carcinoma (HCC). HCC contributes to 80% of global liver cancers in 2018[80]. Pathogenesis of HCC in hepatitis B is: (1) Direct-due to the oncogenic viral protein activating proto-oncogenes, transcriptional pathways (MAP kinase and JAK/STAT), and inhibition of tumor suppressor genes (p53); (2) chronic inflammation, cirrhosis, and regeneration[81,82]. It is also worth noting the other GI disorders caused by this virus. According to a cumulative analysis performed by Yang *et al*[83] involving 7027546 individuals across 13 studies-10 studies reported data on hepatitis and gastric cancer, and it was found that the risk of gastric cancer was 26 times higher in the hepatitis B population[83] (pooled HR, 1.26; 95%CI, 1.08-1.47; P = 0.003). This can be attributed to chronic inflammation, tumorigenesis, and alteration of the tumor suppression process due to oncogenic viral proteins [84,85]. Another study observed that Hepatitis B is associated with gut microbiota disturbance, especially in the cirrhosis population[86]. Acute HBV is self-limited and does not require treatment. Special cases like acute liver failure, complicated course (prolonged PT and marked elevation of jaundice are treated[87]. Treatment of chronic hepatitis B depends on factors like the presence or absence of cirrhosis, ALT level, and HBV DNA level. Therapy includes drugs like Tenofovir, Entecavir, and Interferon[87]. Complications of acute hepatitis B are mainly due to immune complex reactions occurring in various parts of the body manifesting as glomerulonephritis, polyarteritis nodosa, cryoglobulinemia[88], *etc.* Sequelae of chronic hepatitis B are well known including cirrhosis and HCC. Hepatitis B prevention is achieved with recombinant vaccines that require either three or two doses. Combined vaccination, along with diphtheria, pertussis, tetanus, and hepatitis A is also in use currently in the United States.

Hepatitis D virus (HDV) is a defective RNA virus requiring the presence of the Hepatitis B virus for its replication and assembly of virions. It belongs to the Kolmioviridae family. The global disease burden of hepatitis D/hepatitis B co-infection is 62-72 million[89]. HDV requires HBV to replicate and therefore the HBV population is the target group for this infection. The mode of transmission is the same as HBV infection. Hepatitis D infection can occur as a co-infection with hepatitis B occurring simultaneously which usually leads to spontaneous resolution[90]. On the other hand, superinfection in already infected HBV persons usually leads to conversion to chronic hepatitis D infection which is considered a severe form of chronic hepatitis. Symptoms of acute hepatitis D are indistinguishable from

other forms of viral hepatitis. However, superinfection with HBV can lead to fulminant liver failure[91]. In addition, the risk of progression to cirrhosis is 3 times higher in superinfection than in infection with HBV alone[92]. Diagnosis is through the detection of IgM and IgG Anti HDV antibodies and confirmed by testing for HDV RNA[93]. The current treatment strategy utilizes Pegylated interferon for at least 1 year[94]. However, several emerging therapies like myrcludex B and Lonafarnib are gaining popularity in the treatment of hepatitis D.

HCV

HCV is a hepatotropic, single-stranded RNA virus belonging to the family of Flaviviridae. The prevalence of Hepatitis C is 0.5%-2.5% with the highest being in the eastern Mediterranean region and Europe[95]. It was recorded that 399000 individuals died in 2016 due to complications from chronic hepatitis C[95]. Injection drug users, HIV, healthcare professionals, prior recipients of blood products (before 1992), and hemodialysis patients are at risk of acquiring HCV[96]. Modes of transmission include injection drug use, blood transfusion, sexual contact, and perinatal transmission[97]. Acute hepatitis C infection is usually asymptomatic and can consist of symptoms like fever, abdominal pain, and jaundice[97]. Only 15%-20% resolve completely whereas the remaining percentage of infected patients go on to have chronic hepatitis C[97]. Chronic hepatitis C is characterized by the presence of HCV RNA for more than 6 mo. Sequelae of chronic hepatitis C are liver fibrosis, Cirrhosis, and Hepatocellular Carcinoma. A decision analytical model done by Chen *et al*[98] predicted that the cumulative incidence of HCC among HCV-infected persons would be 583000 cases between 2012 to 2040. Several extrahepatic manifestations affect the quality of life in chronic hepatitis C like mixed cryoglobulinemia, glomerulonephritis, skin disease (porphyria cutanea tarda and lichen planus), thyroid disease (Hashimoto's disease and Grave's disease) to name a few[99]. Diagnosis is made by serology either by the presence of HCV RNA or anti-HCV antibody[100]. Guidelines suggest treatment with direct-acting antiviral agents (DAA) after acute infection to prevent progression to chronic infection and due to the high likelihood of loss to follow-up to test for spontaneous clearance of the virus[101]. Chronic hepatitis C is treated with DAA regimens based on the genotype and also the presence of advanced liver disease. Some of the pan-genotype regimens include Sofosbuvir and velpatasvir for 12 wk and glecaprevir and pibrentasvir for 8 wk[102]. Vaccination for hepatitis C is under development and prevention of hepatitis C solely depends upon the prevention of high-risk behavior like injection drug use and adopting safe sexual practices.

Varicella zoster virus

Varicella-zoster virus (VZV) is a double-stranded enveloped DNA virus belonging to the α-herpesviruses subfamily. Adults, young children, and immunocompromised are at risk of developing the severe disease with primary varicella infection[103]. According to the CDC report, 4 million cases occurred annually in the United States during the pre-vaccine era. After the introduction of vaccines, incidence declined by around 97%[104]. Transmission is through droplets, aerosols, and direct contact with respiratory secretions or zoster lesions[105]. Reactivation of latent VZV from dorsal root ganglia leads to herpes zoster (shingles), which presents as localized cutaneous eruption associated with neuralgic pain. GI VZV lesions could present as multiple erosions occurring in the stomach, duodenum, and small and large intestines[106]. Skin findings often precede visceral involvement. In a study, 42 of 131 patients with herpes zoster [not specified as bone marrow transplant (BMT) or malignancy patients] progressed to visceral involvement[107]. The mortality rate from GI VZV ranges from 28.6% to 50.0% in BMT recipients despite antiviral therapy[108]. GI manifestations of herpes zoster are extremely rare. Constipation secondary to motility issues (visceral neuropathy) has been reported in some case reports [106,109]. Skin findings and concomitant GI symptoms should raise suspicion in predisposed patients. Elevated liver enzymes and abnormal imaging findings also aid in diagnosis. Diagnosis can be confirmed through immunohistochemical staining of biopsy specimens VZV. Although shingles is a clinical diagnosis, PCR (highly sensitive) and immunoassays are used for the diagnosis, especially in atypical presentations[110]. Treatment options include IV Acyclovir, valacyclovir, famciclovir, and brivudine. If clinical resistance to Acyclovir is suspected, foscarnet could be used. Complications of primary varicella infection are bacterial infections of the skin and soft tissues, pneumonia, and cerebellar ataxia[111]. Reactivation of VZV (Herpes zoster) is complicated by chronic pain, encephalitis, post-herpetic neuralgia, myelopathy, *etc*[112]. Varivax, a two-dose vaccine, is licensed for children above 12 mo of age to protect against chicken pox. Shingrix is an FDA-approved recombinant vaccine to reduce the risk of shingles in people aged 50 years or more.

Epstein-Barr virus

Epstein-Barr virus (EBV) is a double-stranded DNA virus belonging to the Herpesviridae family. It is estimated that more than 90% of the worldwide population has been infected with EBV[113]. It is associated with a wide range of clinical manifestations, the most common one being infectious mononucleosis (IM), prevalent among teens and adults[114]. It is spread through saliva and presents with fever, malaise, sore throat, and lymphadenopathy[114]. Chronic active EBV (CAEBV) is a condition where IM symptoms persist for more than 3 mo and is commonly seen in Asia[115]. EBV has also been

implicated in the pathogenesis of multiple sclerosis and rheumatoid arthritis[115]. Also, chronic EBV has been linked with gastritis, enteritis, and esophageal disorders, oral hairy cell leukoplakia[116-119]. A separate clinical subset of diseases EBV has been strongly associated with is lymphoproliferative cancers like Burkitt's Lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, and post-transplant lymphoproliferative disorder. Besides lymphoproliferative cancers, EBV has been implicated in causing other cancers like gastric cancer, nasopharyngeal cancers, and breast cancer. Some key features of EBV-associated gastric cancers are they can occur in the gastric fundus, cardia, and body, unlike non-EBV-associated gastric cancers which happen in the antrum. EBV-associated cancer starts as a lesser fibrotic nodular ulcer compared to the non-EBV type[119]. Microscopically, EBV-associated gastric cancer shows a monoclonal proliferation infected latently with EBV, suggesting the role of the virus in the early stages of tumorigenesis[119]. IBD patients on immunosuppressants like thiopurines have a high incidence of EBV and some studies also showed that patients taking these medications also have a higher incidence of lymphoproliferative disorders than those who are not on treatment for IBD [120,121]. EBV can be diagnosed by the detection of antibodies against various antigens like viral capsid antigens, EBNA; enzyme immunoassays, Western blot, PCR, heterophile antibody agglutination, *etc* [122]. There is no targeted therapy for EBV. Symptomatic treatment has been a cornerstone for the treatment of EBV. Several anti-viral drugs including acyclovir, and cidofovir have been tried with good invitro activity and with no clinical benefit[123].

Human herpesvirus 8

Human herpesvirus 8 (HHV 8) is a double-stranded DNA virus belonging to the Human Gamma herpesvirus family. It is also commonly known as Kaposi Sarcoma-associated herpesvirus due to the disease it causes, Kaposi's Sarcoma (KS). It is common in HIV, MSM, Mediterranean, Ashkenazi jews, and sub-Saharan African populations[124,125]. According to seroprevalence, Uganda has the highest seroprevalence worldwide where KS is endemic. No more than 6% seroprevalence has been reported in the United States[126]. KS is a low-grade vascular tumor that involves mucocutaneous sites and visceral locations, predominantly the respiratory and GI systems[125]. GI Kaposi sarcoma is usually asymptomatic but on progression, can present as abdominal pain, nausea, vomiting, and GI bleeding. Diagnosis is through endoscopy and biopsy[127]. It is most common in the stomach and small intestine and endoscopically appears as a maculopapular lesion to a nodular or polypoid mass which can sometimes bleed on touch[127]. In HIV Kaposi, HAART is the mainstay of treatment with or without chemotherapy. In classic Kaposi's sarcoma, treatment options include local therapy with radiation or intralesional chemotherapy; systemic chemotherapy with liposomal doxorubicin or paclitaxel[124]. Besides KS, HHV 8 is implicated in the causation of lymphoproliferative disorders like primary effusion lymphoma and multicentric Castleman's disease[128].

Human papillomavirus

Human papillomavirus (HPV) is a double-stranded DNA virus belonging to the Papillomaviridae family. It is estimated that around 13 million persons acquired HPV infection in 2018 in the United States and over 77 million had a prevalent infection during the same year[129]. It is primarily a sexually transmitted disease (vaginal, anal, and oro-genital) but can also be transmitted through skin-to-skin contact and vertical transmission[130]. High-risk sexual behaviors, multiple sexual partners, and previous history of STDs increase the risk of HPV acquisition. Clinical manifestations of HPV include cutaneous warts, anogenital warts, and respiratory papilloma's caused by HPV 6,11 *etc* genotypes along with cancer precursor lesions (intraepithelial neoplasia's) and cancers caused by HPV 16,18 genotypes. HPV is an oncogenic virus and has been associated with a multitude of cancers including GI cancers like esophageal cancer, stomach cancer, colorectal cancer, anal cancer, and liver cancer[131]. The other cancers to which it has been linked are cervical, penile, vulvar, vaginal, and oropharyngeal cancers [132]. HPV causes cervical cancer near the transformation zone where there is a transitional/transformational zone (squamocolumnar junction). In the same fashion, HPV also causes cancerous lesions in the anal region because of the presence of a squamocolumnar junction which is a site of multipotent embryonic cells. However, the incidence rates of cervical cancer and anal cancer are much different (17:1). Colposcopy, Biopsy, HPV DNA detection, PCR, and pap smear are some of the methods by which HPV can be diagnosed[133]. Treatment depends on the type of disease. Warts can be treated with topical medications like salicylate, imiquimod, trichloroacetic acid, cryosurgery, and electrocautery. Precancerous and cancerous lesions require detailed workup and surgical excision of lesions[134]. Current FDA-approved vaccines are Bivalent (for types 16 and 18), quadrivalent (for types 6, 11, 16, and 18), 9 valent (for types 6, 11, 16, 18, 31, 33, 45, 52, and 58) protect against genital warts, precancerous lesions of vulva, cervix and anus, oropharyngeal cancers and are approved for males and females aged 9-45.

CONCLUSION

After conducting a comprehensive review of the literature on viruses and the GI tract, these pathogens

play a significant role in both acute and chronic GI diseases. While many viruses can cause mild symptoms, such as diarrhea and vomiting, some can lead to severe and even life-threatening conditions. The importance of early detection and appropriate management of viral gastroenteritis cannot be overstated.

Several studies have highlighted the need for better prevention and control measures, including improved hygiene practices and the development of effective vaccines. It is crucial to continue researching the relationship between viruses and the GI tract to better understand how these pathogens operate and to develop more targeted treatments.

Overall, this review provides clinicians with a differential diagnosis when they encounter patients with GI manifestations. It emphasizes the importance of recognizing the different presentations of viruses on the GI tract and understanding the prevention, diagnosis, and treatment of these illnesses.

FOOTNOTES

Author contributions: Jagirdhar GSK, Pulakurthi YS, and Chigurupati HD contributed to literature review and write the original manuscript; Surani S wrote the original manuscript, revised the paper, and approved the final version.

Conflict-of-interest statement: None of the authors have any conflict of interest to disclose.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Liu JH

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