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REVIEW ARTICLE

Rotavirus Structure, Genomics, Types, Pathophysiology, Management and Prevention: Review Article

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ABSTRACT

Background: Children under the age of five are most commonly affected by severe, dehydrating gastroenteritis brought on by infections with rotavirus. Despite the common usage of rotavirus immunizations more than ten years ago, rotavirus infections still cause more than 200,000 fatalities each year, primarily in developing nations. Rotavirus predominantly affects enterocytes and causes diarrhea by destroying absorbent enterocytes (resulting in malabsorption), stimulating intestinal secretion by activating the enteric nervous system, and viral non-structural protein 4. Furthermore, rotavirus infections can result in viremia and antigenaemia, both of which are connected to more severe acute gastroenteritis symptoms. Although this is uncommon, rotavirus can also replicate in systemic areas. Rotavirus reactivations are frequent throughout life, however they lessen the severity of the illness. Although both aspects—protection against rotavirus reinfection and recovery from infection—involve rotavirus-specific immunoglobulin A, the immunological implications of these processes are poorly understood. Although the use of antiviral and antiemetic medications may be necessary in rare circumstances, Dehydration must be avoided and treated in order to manage rotavirus infection.**Conclusions**: Rotavirus causes acute dehydrating diarrhea associated with high global mortality in particular among under five-year children. The introduction and expanded use of the two oral attenuated rotavirus vaccines have already contributed to reductions in rotavirus-attributable child death and hospitalization.

Keywords: Rotavirus structure; pathophysiology; management; Lanzhou Lamb Rotavirus; triple-layered particle

INTRODUCTION

Rotavirus is the most typical cause of severe gastroenteritis in kids under the age of five. In 1973, rotavirus was discovered in human patients' feces and duodenal biopsies. Even though there is a rotavirus vaccine, it nevertheless results in more than 200,000 fatalities per year. In contrast to impoverished countries, where it continues to be a major cause of life-threatening diarrhea in newborns and young children under the age of five, rotavirus infection is less common in wealthy countries with regular vaccination programs than it is in such countries [1].

Rotavirus symptoms include profuse diarrhea, vomiting, fever, malaise, and rarely neurologic features such as convulsions, encephalitis, or encephalopathy. The most common symptoms are diarrhea and vomiting, leading to significant dehydration and reduced oral intake, which can necessitate hospitalization and lead to death if not treated [2].

In this review, we will summarize the previous and recent insights into rotavirus (RV) structure, classification, and epidemiology and current status of RV vaccination around the globe.

Rotaviruses structure:

The triple-layered particle (TLP) created by the rotavirus's Double-shelled, single-shelled, and core particles are stacked in concentric rings and becomes the infectious form of the virus. Single-shelled, core, and double-shelled particles are, respectively, 76.5 nm, 70.5 nm, and 50 nm in size **[3].**

A non-enveloped icosahedral ds RNA virus is a rotavirus. The rotavirus genome is composed of 11, distinct double helix RNA (dsRNA) molecules, totaling 18,555 nucleotides. Each helix, or portion, represents a gene and is numbered 1 through 11 by decreasing size. Except for gene 9, which codes for two proteins, each gene only produces one. A three-layered icosahedral protein capsid surrounds the RNA. Although not contained, viral particles can have a diameter of up to 76.5 nm (figure 1) [4].

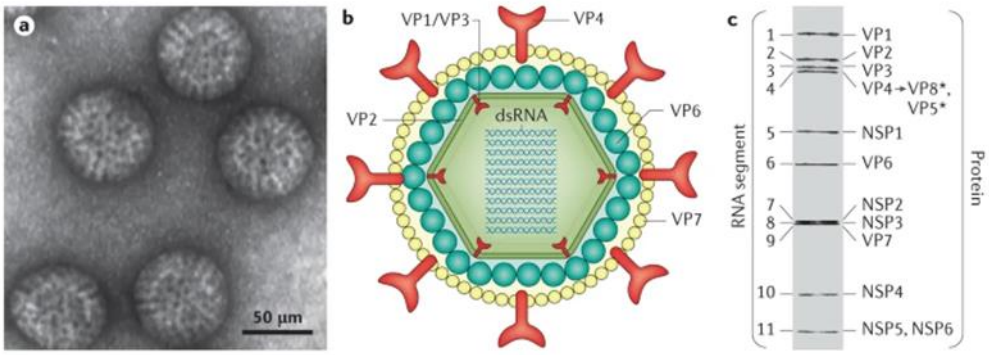

Figure (1): The rotavirus particle resembles a wheel with short spokes and a smooth outer rim. **a** | Electron micrograph of rotavirus triple-layered particles. **b** | Cross-sectional schematic of the rotavirus triple-layered particle. This structure consists of the inner capsid layer (viral protein (VP)2), the middle capsid layer (VP6) and the outer capsid layer (VP7 and the spike protein VP4). VP4 is proteolytically cleaved into VP8* and VP5*. The structural protein VP2, the enzymes VP1 and VP3 and the viral genome compose the virion core. The middle capsid layer protein (VP6) determines species, group and subgroup specificities. The outer capsid layer is composed of two proteins, VP7 and VP4, which elicit an immune response in infected hosts, leading to the production of rotavirus-specific antibodies. **c** | Electrophoretic migration profile of the 11 segments of rotavirus double-stranded RNA (dsRNA) and the encoded proteins for simian rotavirus SA11 strain. NSP, non-structural protein.

Types of Rotavirus:

The nine rotavirus species are designated the letters A, B, C, D, F, G, H, I, and J. rotating virus Species that primarily affect people. A through I, H in pigs, D, F, and G in birds, I in cats, and J in bats are the species that transfer disease. The rotavirus A has numerous serotypes, which are often referred to as strains. The virus is categorized using two proteins on its surface, just like the influenza virus. The glycoprotein VP7 and the protease-sensitive protein VP4 each determine a specific serotype [5, 6].

The two genes that determine G-types and P-types can be passed on separately to progeny viruses, leading to the discovery of new combinations. Using whole genome genotyping, the origin of rotavirus A atypical strains has been identified. Individual G- and P-type prevalence varies over time, across nations, and between years. There are at least 51 P types and 36 G types, although only a few G and P type combinations prevail in

infections of humans. Their designations are G1P, G2P, G3, G4, G9P, and G12P [1].

Epidemiology & Transmission:

Rotaviruses are spread all over the world and typically infect children by the age of five. Infection rates are comparable around the world, however, low-income areas around the world are more prone to experience deadly infections. This is probably a result of inadequate healthcare facilities, rising malnutrition rates, and restricted access to hygienic, clean hydration therapy. Rotavirus is typically considered to be a winter illness, notably in the world's temperate regions[7].

The epidemiology of the rotavirus sickness has significantly changed since the virus's vaccines were created. Children under the age of five were most frequently infected with rotavirus before the creation of the vaccination. Due to widespread immunization campaigns, Rotavirus seems to affect older, unvaccinated children more frequently. The prevalence of rotavirus infections seems to be steady in low-income nations where rotavirus vaccinations are not widely available. In these places, sickness usually worsens due to malnutrition [7].

Transmission:

Contact with infected hands, surfaces, and objects, the fecal-oral route, and probably the respiratory route are the three main ways that rotaviruses spread. The spread of viral diarrhea is very common. The feces of an infected person can contain more than 10 trillion infectious particles per gram; fewer than 100 of these are required to transmit the infection to another person [5, 6].

Rotaviruses can be identified at rates of up to 1–5 infectious particles per US gallon in estuarine samples because they are stable in the environment. The viruses can endure low temperatures for nine to nineteen days. Given that the prevalence of rotavirus infection is the same in nations with high and low standards for health, sanitary practices that are successful in getting rid of parasites and bacteria don't seem to work as well in reducing rotavirus Figure 2 [2, 7].

Pathophysiology:

Rotaviruses reproduce across the small intestinal lumen in mature enterocytes. Osmotically active food is transported into the large intestine as a result of this change in the small intestine's epithelial cells, which impairs water absorption in the large intestine. The usual watery diarrhea associated with rotavirus infections is consequently brought on by impaired water reabsorption. Increased intestinal motility is another potential contributing factor to rotavirus-induced diarrhea, though the reason for this is still unknown Figure 3 [1].

The virus engages in a variety of processes that lead to rotavirus diarrhea. One explanation is that enterocytes' endoplasmic reticulum and mitochondrial engorgement, severe mononuclear cell infiltration, intestinal brush boundary enzymes, as well as like lactase, maltase, and sucrase are all results of the virus' extensive replication and large intestinal epithelium cellular necrosis [9]. This causes nutritional, electrolyte, and fluid malabsorption, which in turn causes an increase in gut lumen osmotic pressure, and the subsequent beginning (D-xylose and lactose near an acute infection) of diarrhea. Following the procedure, reactive crypt-cell hyperplasia may speed up the flow of fluids, worsening the diarrhea[1, 10].

Rotavirus (RV)-infected cells produce the viral enterotoxin NSP4, which uses phospholipase C to communicate with intestinal epithelial cells after binding to them. The stimulation of signaling pathways that result in age- and calcium-dependent chloride release into the intestinal lumen is a second mechanism driving RV diarrhea. High chloride ion concentrations provide an osmotic gradient that encourages water to enter the intestinal lumen, which ultimately

causes secretory diarrhea[1].

The Sodium-Glucose-Lactose-Transporter Proteins System (SGLT1), which facilitates the reabsorption of water, sugar, and body electrolytes, is rendered inactive by the NSP4 protein, which inhibits the activity of brush-border membrane disaccharidases and may even activate the calcium ion-dependent secretory reflexes of the enteric nervous system [11].

Normal enterocytes release lactase into the small intestine, which aids in the breakdown of lactose. However, a lactase shortage that can linger for several weeks affects a child's ability to tolerate milk in rotavirus infections. Lactose in the gut is fermented by bacteria, which results in such a youngster developing recurrent diarrhea once milk is reintroduced into their diet [5].

A third mechanism is based on the viral enterotoxin's activation of the enteric nervous system. Human enteroendocrine cells secrete Serotonin (5-HT), commonly known as 5-hydroxytryptamine, as a result of the increase in intracellular calcium concentration caused by NSP4. These chemicals cause the small intestine's enteric nerves to become active, boosting intestinal motility, which is linked to the beginning of diarrhea. Evidence studies have demonstrated a connection between the relief of diarrhea and medications that prevent such stimulation [4].

The mechanisms that trigger vomiting usually seen in an early illness may be the result of early cytokine release acting centrally or delayed gastric emptying. Whether the latter is a result of an increase in gastrointestinal hormones (e.g., secretin, gastrin, and cholecystokinin) or vagal nerve activation associated with rotavirus infection remains an area for future study to look at [2, 12].

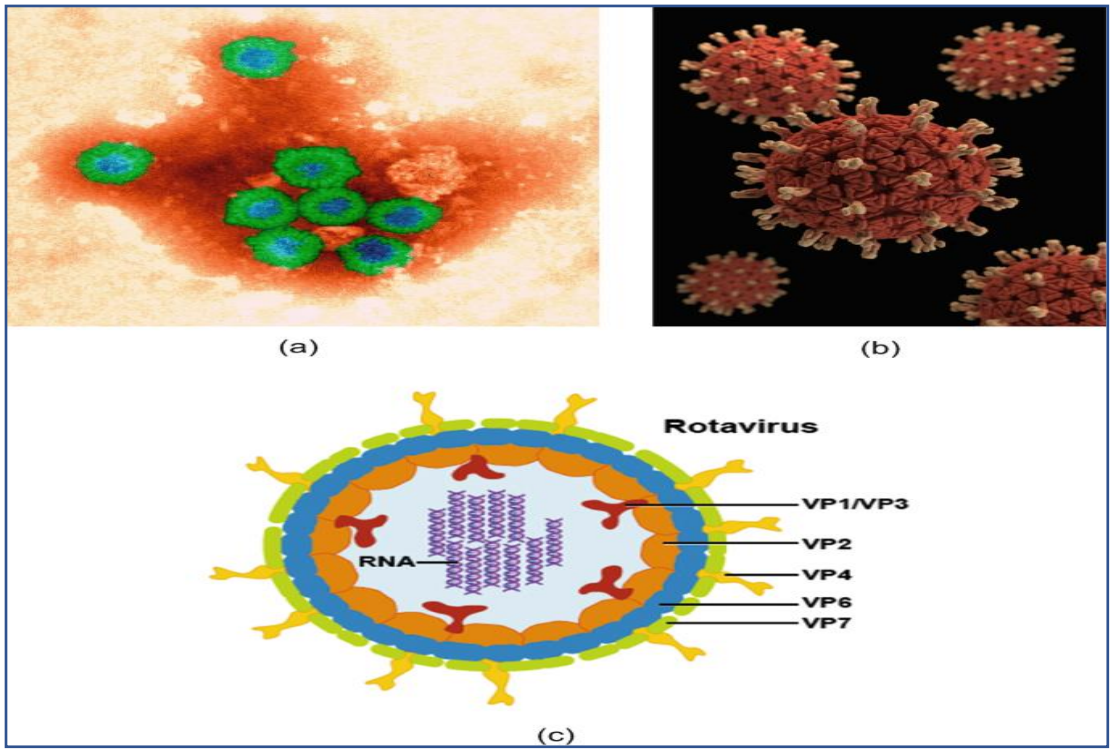

Figure 2: Rotavirus structure [8].

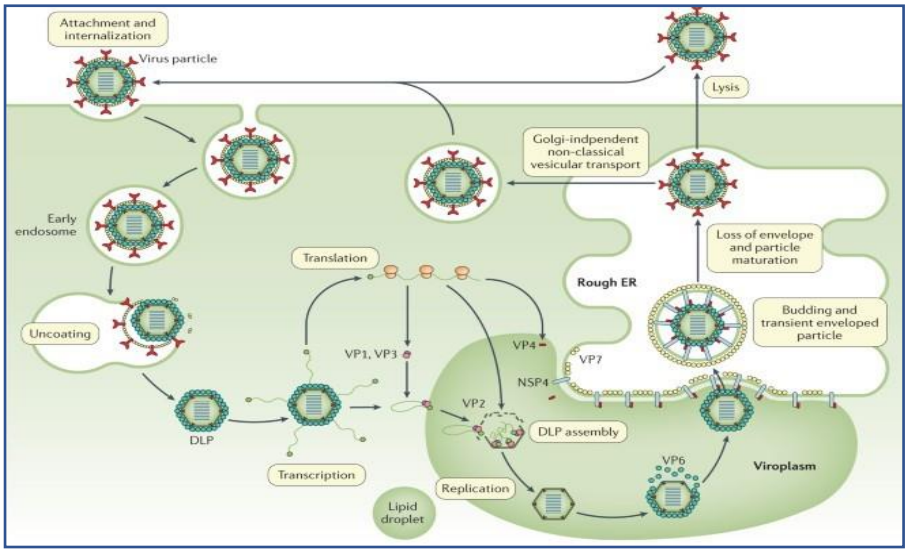

Figure (3): Rotavirus virulence [9].

Immune response to Rotavirus

Innate immune response to Rotavirus:

The activation of interferon (IFN) production, which is mediated by viral dsRNA, starts the innate immune response to rotavirus. The host receptors known as retinoic acid-induced gene-1 (RIG-1), Toll-like receptor-3 (TLR-3), or melanoma differentiation-associated gene 5 (MDA-5) immediately identify rotaviral replication after the virus has entered the host cells. Rotavirus nucleic acid substantially stimulates the RIG-I, MDA-5, and TLR3 components of the host pattern recognition receptor (PRR) machinery [13, 14].

Academic Press. In the absence of 5′-caps, RV (+) RNAs are more likely to be detected by RIG-I, increasing the production of IFN and an antiviral response. Two transcription factors, nuclear factor kappa light chain enhancer of activated B cells (NF-B) and interferon regulatory factor 3 (IRF3), are activated as a result of this link [4].

The interferon-stimulated genes (ISGs) are activated as molecules are transported to the nucleus. During viral replication, NSP1 production may result in the degradation of IRF3, and rotavirus-dependent and independent processes may be used to stop the translocation of NF- to the cell nucleus [1].

It's interesting to note that the NSP1 protein's anti-interferon type I function differs depending on the rotavirus strain, targeting either the beta transducing repeats-containing protein (TrCP beta) or IRF 3, 5, or 7. This distinction explains why the animal rotaviruses have a broader attack surface against the IFN-signaling pathway since NSP1 from these viruses focuses mostly on the IRFs 3, 5, and 7. For instance, it has been demonstrated that human rotaviruses predominantly depend on NSP1-mediated degradation of IRF5 and IRF7 to obstruct IFN- signalling [13, 14].

Protein kinase R (PKR), a dsRNA-dependent enzyme, and INF transcription regulation of further INF production occur throughout the course of the illness. Signals produced by this series of events, which results in the autocrine synthesis of IFN, activate the transcription of STAT1 and STAT2 as well as IRF9, the interferon regulatory factor. These molecules will localize to the gut to prevent extraintestinal transmission of the virus and travel into the cell nucleus, enhancing the transcription of interferon-stimulated genes (ISG) and interferons (INF), generating an antiviral state

to clear the virus [5].

Elevated levels of TNF-, IL-6, IL-8, IL-12, and MCP-1, as well as proinflammatory cytokines and chemokines (IFN-, IFN-, IFN-, and IFN-) are indicators of the pattern recognition receptors (PRRs) mediated activation in the intestinal mucosa. By creating an antiviral state, attracting and activating immune cells, and growing dendritic cells (DCs), IFNs and cytokines released by intestinal epithelial cells and immune cells assist in the establishment of protective immunity[11].

Maturated DCs are better at connecting the innate and adaptive arms of the antiviral immune response through the priming and activation of T and B cell responses. The fact that MyD88, an essential convergent adaptor in signaling from the various TLRs, enhances viral infectivity, the severity of diarrheal morbidity, and decreases humoral immunity points to a critical role for TLR-mediated defense against rotavirus [2].

When a cell is infected by rotavirus, The immunological route involving RNase-L and 2′-5′-oligoadenylate synthetase (OAS) is activated. The interaction of viral dsRNA with 2′-5′-oligoadenylate synthetase results in the destruction of both viral and cellular RNAs by RNase-L. [10, 14].

Rotavirus and humoral immunity:

Both local (sIgA) and systemic (IgA and IgG) immune responses are brought on by rotavirus. By blocking the IgG and IgA responses that are brought on by the immunogenic outer layer proteins (VP7 and VP4), children and adults are protected against disease. Virus-specific antibodies have also been found in the sera of patients who are recovering, but they are not neutralizing against the RV proteins VP2 and VP6's immunodominant epitopes [3].

Although the small intestine continues to be the primary site for rotavirus infection and replication reports have shown that viral escape from the digestive tract does occur. Antigenemia and genomia associated with systemic and mucosal humoral reactions have consequently been documented. Following the initial naturally occurring or vaccine-induced rotavirus infection in newborns and young children, homotypic immunity induces neutralizing antibodies against the predominant G serotype of the infecting strain [15, 16].

Both homotypic and more pronounced heterotypic antibody reactions are brought on by rotavirus infections (against strains that belong to various G serotypes). Re-infection with a similar strain protects kids far better than re-infection with a different G serotype. According to the theory, only antibodies produced against different RV-encoded proteins or non-neutralizing, conserved epitopes of the same proteins require repeated exposure. This is because the VP7 and VP4 epitopes that are exposed to the surface initially generate humoral reactions [4].

The presence of both homotypic and heterotypic systemic antibodies is associated with resistance to rotavirus infection. However, findings from animal studies and adult volunteers have shown that measurement of local antibodies is better for mucosal surrogates of immune protection against rotavirus illness [5].

Rotavirus and cell-mediated immunity:

In children who have been exposed to rotaviruses, Th1 and rarely Th17 responses are predominantly responsible for inducing CD4 and CD8 T-cell responses. Particularly when activated, IFN- and IL-17 from CD4 and CD8 T-cells exert an immune-protective response by inducing a direct antiviral state and luring inflammatory cells prepared to wipe out viruses [11].

During rotavirus infection, the regulatory T-cells subpopulations (IL10+ and FOXP3+ regulatory T-cells) are sometimes involved in the suppression of pro-inflammatory immune response to preserve mucosal homeostatic balance in response to rotavirus. Although the B lymphocytes play a major role in the protection against reinfection from the wild-type virus, viral clearance during primary infection is facilitated by the CD8+ T cells

[1].

Immunological cells' cellular component secretes cytokines like IFN- and TNF, which act as antiviral defenses by either preventing either by preventing virus infection or by managing a number of host immune responses. In addition to protecting the host in the acute phase before other elements of the immune response, such as the serum antibody responses, take effect, this reaction may allow the host to contain or eradicate the virus [16].

For instance, type 1 IFNs (IFN/) are generated to boost NK cell cytotoxicity and activity, activate dendritic cell costimulatory molecules, and stimulate the growth of particular memory CD8 + T cell subsets [2].

Some young children who were prospectively followed-up showed robust proliferative T cell responses to RV without a rise in RV antibodies, suggesting that seroconversion may not always be a reliable marker of early viral exposure because some infections may go undetected [11].

Undeveloped immune systems coupled with short exposure histories in young children lead to reduction in production of circulating memory cells. Seroconversion is proposed to be a stronger predictor of protection against rotavirus, this is supported by the finding that antibody responses to RV often remained high with advancing age [5].

Clinical picture:

After an incubation period of one to three days, the rotavirus symptoms manifest fast and in a variety of ways. Although rotavirus infections are frequently more severe, the signs and symptoms of an infection are remarkably similar to those of other gastrointestinal illnesses. Fever, diarrhea, and vomiting are the three symptoms that manifest themselves most frequently. The symptoms of the infected patients vary, ranging from mild diarrhea that lasts just a short time to severe diarrhea that lasts for a long time and is accompanied by fever and vomiting [2].

Vomiting frequently starts a rotavirus infection off, and then watery diarrhea follows. Approximately 33% of infected persons have fever. Five to 7 days pass between the start of the illness and the full resolution of symptoms. Usually, the results of a physical examination cannot reliably identify rotavirus from other viruses that are known to often infect the gastrointestinal tract [1].

People with rotavirus infection may exhibit clinically such as fever, stomach pain, tiredness, and indications of dehydration such dry mucous membranes, decreased skin turgor, tachycardia, decreased urine output, and extended capillary refill [9].

Rotavirus infection can result in either asymptomatic or symptomatic individuals, depending on a number of viral and host variables. The most important host factor that affects how clinically an RV infection turns out is age. Due to maternal antibodies obtained through the placenta, infants infected with rotavirus do not necessarily show symptoms of the illness [16].

The age at which newborns are most susceptible to developing severe cases of rotavirus sickness frequently coincides with the reduction in maternal antibodies. The infant is still susceptible to infection until the age of five, at which point a robust immunity to virus infection starts to emerge. Despite the rarity of severe symptoms, rotavirus can infect adults as well. Adults may become infected after contracting an uncommon viral strain or after being exposed to very high virus dosages [9].

Children experiences repeated exposures from birth to old age, though natural and/or vaccine-induced immunity usually makes further infections mild or asymptomatic following natural infection or vaccination. Malnutrition is another factor that potentiates the severity of rotavirus diarrhea by delaying the restoration of the damaged intestinal epithelial barrier and also modifying the intestinal inflammatory responses [3].

The diarrheal illnesses brought on by other gastrointestinal infections such Salmonella, Escherichia coli, enteric adenoviruses,

noroviruses, and astroviruses are all clinically similar to those brought on by rotavirus. In most circumstances, a history and physical exam are sufficient evaluations [1].

Symptoms that point to rotavirus infection include a slight temperature along with nausea and diarrhea that is watery. The symptoms of rotavirus-induced gastroenteritis are more likely to include fever, an acid-reducing component low serum bicarbonate levels, and in the feces. Gross bloody diarrhea suggests that another organism is more likely to be the source of acute gastroenteritis [17].

Bacterial and protozoal causes of gastroenteritis can potentially mimic symptoms of viral gastroenteritis but often require a different treatment approach and may carry higher morbidity potential. Pathogens such as Salmonella, Escherichia coli, Shigella, Campylobacter, Giardia lamblia, and Clostridium difficile may be potential causes in those patients who present with atypical symptoms of viral gastroenteritis [18].

Laboratory diagnosis:

Testing whether the virus, viral-specific antigen, or RNA is present. is done on fresh, entire feces samples or rectal swabs from individuals who are experiencing diarrhea. Electron microscopy (EM), a precise and sensitive technique, is used for direct rotavirus detection. Magnetic microparticles functionalized with monoclonal antibodies have recently enhanced the capture, concentration, segregation, and characterization of infectious rotavirus particles in clinical samples [4].

However, in order to regularly detect the rotavirus in a large number of specimens, the EM approach is costly, necessitates highly skilled workers, and is labor-intensive. The majority of rotavirus cases are diagnosed using commercially available antigen detection methods (ELISA, immunochromatography, or latex agglutination). The latex agglutination method, which can be used without additional tools to quickly and easily detect disease outbreaks, especially in resource-poor nations where rotavirus detection techniques are hard to come by [1].

Because of its outstanding sensitivity, specificity, and adaptation to a large sample volume of samples in the 96-well plate, the ELISA-based technique is the antigen screening platform that has been the subject of the most research. Rotavirus growth in cell culture aids in the verification of viral vitality and enhances the virus's molecular identification, which may be done in clinical or environmental samples at extremely low quantities. Although cell-culture-based techniques are highly sensitive, they are laborious and expensive. It is time-consuming, highly prone to contamination, and is often not requested for clinical diagnosis [5].

Although more sensitive than antigen detection platforms, techniques based on the polymerase chain reaction (PCR), such as reverse transcription (RT)-PCR, qPCR, and real-time PCR that detect RNA in clinical samples are still predominantly used as research tools. To genotype circulating rotavirus strains, VP7, VP4, and other genomic parts must be sequenced. The drawbacks of conventional sequencing methods are their high cost, labor-intensive nature, and low throughput [9].

The RV classification working groups recently pushed for whole genome research to fully characterize the RV genome and find unusual genotype constellations. The technique hasn't been applied much, though, because additional resources are required [11].

Prevention & Rotavirus vaccines

Treatment / Management:

Relief of symptoms, as well as the management and avoidance of related dehydration, are the goals of treatment for rotavirus infection. Salt solutions for oral rehydration should be tried first. To aid in symptom alleviation and control the amount of diarrhea Codeine, loperamide, and diphenoxylate can all be given to adults.

Bismuth salicylate should only be administered following the exclusion of other infectious agents, despite the fact that it has been shown to be beneficial in treating rotavirus symptoms. Hospitalization and intravenous fluids may be required if the patient is dehydrated and the symptoms do not respond to oral medications [4].

According to numerous specialists, oral injection of human serum immunoglobulins may be beneficial in the treatment of hospitalized kids with rotavirus infection. Other studies suggest that probiotics, zinc, and ondansetron are potential therapeutics for acute gastroenteritis [17, 19].

Most patients who visit an outpatient clinic or the emergency room can be sent safely home after treatment. Antiemetic drugs may be advantageous for adults, but young children should not take them. Patients who exhibit symptoms of dehydration, persistent vomiting, electrolyte imbalances, abdominal discomfort, ileus, renal failure, or pregnancy may benefit from admission to the hospital [1].

Prevention:

Antibiotics and other medications cannot treat rotaviruses, which are extremely contagious. The key public health strategy is vaccination because better cleanliness does not reduce the prevalence of rotaviral disease and the risk of hospitalizations remains high despite the use of oral rehydrating medications. In nations that have followed this advice, rotavirus infections have considerably decreased in frequency and severity [2].

Vaccines:

In 92 countries worldwide as of the end of 2018, government vaccination regimens included the rotavirus vaccine, with another 6 countries having done so gradually or regionally. Gavi, The vaccination Alliance, supports the introduction of the rotavirus vaccination in several lower-income nations. As of 2019, 46 of the initial 73 Gavi-eligible countries have obtained Gavi funding for the introduction of rotavirus vaccines, while 8 of those countries had Gavi approval already and were preparing to do so soon [20].

Rotarix (GlaxoSmithKline Biologicals; prequalified in 2009), RotaTeq (Merck & Co., Inc.; prequalified in 2008), Rotavac (Bharat Biotech, Hyderabad, India; prequalified in 2018), RotaTeq (Merck & Co., Inc.; prequalified in 2008), and ROTASIIL (Serum Institute of India PVT. The WHO has prequalified the following four rotavirus vaccines: (Ltd., Pune, India; prequalified in 2018) [20].

Lanzhou Lamb Rotavirus (LLR) vaccine [Lanzhou Institute of Biological Products Co., Ltd., Lanzhou, China] and Rotavin-M1 [Center for Research and Production of Vaccines and Biologicals (POLYVAC), Hanoi, Vietnam], both accessible on the private market in Vietnam, are two additional rotavirus vaccines that are provided on a national level. Each vaccination has a distinct profile and presentation, necessitating diverse introduction concerns [21].

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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