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REVIEW OF ROTAVIRUS INFECTION

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ABSTRACT Rotaviruses are a major cause of diarrheal illness in human infants and young animals, including calves and piglets. "Reo" stands for respiratory-enteric orphan, from the source of virus isolates and the lack of association with clinical disease. Infections in adult humans and animals are also common. Among the rotaviruses are the agents of human infantile diarrhea, Nebraska calf diarrhea, epizootic diarrhea of infant mice, and SA11 virus of monkeys. Gastroenteritis is a leading cause of infant death and stunting. Rotaviruses have a worldwide distribution and cause an estimated 611,000 deaths annually. Rotaviruses is a genus within the Reoviridae, family of non-enveloped. Rotaviruses are fastidious agents to culture. Most group A human rotaviruses can be cultivated if pretreated with the proteolytic enzyme trypsin and if low levels of trypsin are included in the tissue culture medium.

KEYWORDS : Rotaviruses, Gastroenteritis, diarrhea, Virus

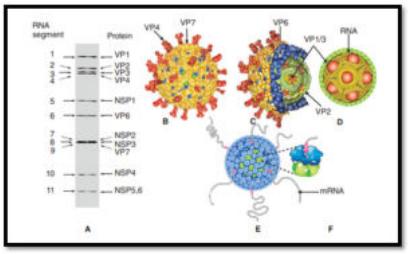
INTRODUCTION

Rotaviruses are the most important cause of severe dehydrating gastroenteritis in children younger than 5 years in all socioeconomic groups and in all regions of the world.1 Gastroenteritis is a leading cause of infant death and stunting. Rotaviruses were discovered in 1973 as being associated with diarrheal disease in children (Bishop et al. 1973; Flewett et al. 1973).2 Rotaviruses have a worldwide distribution and cause an estimated 611,000 deaths annually.3 Higher latitude and higher income correlate with a seasonal pattern of disease in cold and dry months; lower latitude and income correlate with less distinct seasonality, although neither location nor income can fully explain observed annual patterns.[4]

Rotaviruses is a genus within the Reoviridae, family of nonenveloped, have a genome of 11 segments of double-stranded RNA (dsRNA) which can be easily separated by polyacrylamide gel electrophoresis, which were approximately 70 nm in diameter.5 The RNA segments code for six structural (VP1, VP2, VP3, VP4, VP6, VP7) and six nonstructural proteins (NSP1–NSP6) (Estes 2001). The structural proteins make up a triple-layered particle and are located in the core (inner layer; VP1–VP3), inner shell (intermediate layer; VP6) and outer shell (outer layer; VP4, VP7).3 Rotavirus got its name from the wheel-like appearance of the virion in electron micrographs.[6]

The proteins in the mature virus particle determine host specificity, cell entry and enzymatic functions necessary for the production of viral transcripts, and contain epitopes that generate immune responses (FIG. 1). Non-structural proteins, which include the viral enterotoxin NSP4, are involved in genome replication and innate immune response antagonism (a role for NSP1).[7]

Rotavirus is a very stable virus that can survive in the environment for weeks or months if it is not disinfected.



EPIDEMIOLOGY

Rotavirus infection is universal, and almost all children acquire serum antibody against the virus in the first 2 or 3 years of life.[8] Severe gastroenteritis caused by rotavirus most commonly affects infants and children between 6 months and 2 years of age,[9] although in lower socioeconomic populations the peak of illness may be somewhat earlier.[9-10]

As of 2016 rotavirus remained the most common cause of severe dehydrating diarrhea in infants and children younger than 5 years in low-, middle-, and high-income countries, responsible for approximately 28.8% of deaths due to diarrhea in this age group.[2] The estimated 128,500 childhood deaths in 2016 is a substantial decrease from the estimated 453,000 childhood deaths in 2008.[2,11]

The physical hardiness of the rotavirus particle, the high particle concentration in stool (up to 1011 particles/mL),[12] and the small minimum infectious dose (ID50 = 10 focus-forming units).[13]

PATHOGENESIS

Cell death and desquamation reduce digestion and adsorption of nutrients (primary malabsorption) and lead to villous atrophy. This is followed by a reactive crypt-cell hyperplasia accompanied by increased secretion, which is thought to contribute to the severity of diarrhea.

The effect of rotavirus infection on the enteric nervous system also may play a role in pathogenesis (Lundgren et al. 2000).

Through the mouth, the virus enters the body. Rotaviruses infect cells in the small intestine's villi (gastric and colonic mucosa are spared). They multiply in enterocyte cytoplasm and disrupt their transport systems. NSP4, a viral enterotoxin expressed by the rotavirus, promotes secretion via activating a calcium-dependent signal transduction pathway. Damaged cells may slough into the intestine's lumen, releasing huge quantities of virus into the stool (up to 1012 particles per gram of feces).Viral excretion usually lasts from 2 to 12 days in otherwise healthy patients but may be prolonged in those with poor nutrition and immunocompromised patients.[14]

Infection can cause decreased sodium, glucose, and water absorption, as well as lower levels of intestinal lactase, alkaline phosphatase, and sucrase activity, which can contribute to isotonic diarrhoea.

CLINICAL FEATURES

Rotaviruses are responsible for the majority of diarrheal illnesses in infants and children around the world, but not in adults. There is an incubation period is about 1–3 days. Watery diarrhoea, fever, abdominal pain, and vomiting are common symptoms, which can lead to dehydration.[14] The combination of vomiting and a seasonal occurrence in the winter months has led investigators to name the condition "winter vomiting disease."[6] Severe electrolyte and fluid loss in infants and children can be dangerous if not treated. Patients with milder cases have symptoms for 3–8 days and then recover completely.[14]

Uhnoo and Svensson studied the comparative features of group A, subgroups 1 and 2 in Swedish infants. 459 Patients with subgroup 1 strains developed fever up to 39°C significantly more often than those with subgroup 2, but infants who had subgroup 2 infections were sicker, hospitalized more frequently, and more likely to have respiratory symptoms. The frequency of diarrhea and vomiting in the two groups was similar.[6] Genotyping of rotavirus nucleic acid from stool specimens by the polymerase chain reaction (PCR) is the most sensitive detection method.

INACTIVATION

The rotavirus particle is physically resistant to inactivation by

fluorocarbons, ether, and chlorine concentrations often employed to treat sewage effluent and drinking water.[15] However, the particle is inactivated by calcium chelators and by antiseptic agents that contain relatively high concentrations of alcohols (>40%), free chlorine (>20,000 ppm), or iodophors (>10,000 ppm iodine).[16] A commonly used hand-sanitizing agent (Purell), which contains 62% ethanol, substantially reduces viable rotavirus carriage on fingertips,[17] and a disinfectant spray (Lysol), which contains 79% ethanol and 0.1% o-phenylphenol, prevents the experimental transmission of rotavirus from fomites to human volunteers.[18] At high relative humidity, rotavirus survival is severely decreased in the environment.[15]

DIAGNOSIS

The presence of virus in stool collected early in the illness, as well as an increase in antibody titer, are used to make a laboratory diagnosis.[14]
Various commercial antigenic assays, RT-PCR, electron microscopy, immunological electron microscopy, polyacrylamide gel electrophoresis (PAGE) for viral genomic RNA, and viral culture can all be used to identify rotavirus. The detection of viral antigen in faeces or rectal swabs, which is most typically done using enzyme-linked immunosorbent assay (ELISA) or latex agglutination formats, is the foundation for practical, commercially available, and widely used diagnostic kits.[19] Latex agglutination is particularly suitable for use in areas with limited resources, although a confirmatory technique is desirable to evaluate indeterminate results because of the limited sensitivity of the test.[19,20]

Although there are various techniques for measuring serum, fecal, and salivary antibodies against rotavirus, the acute and generally self-limited nature of rotavirus infections limits the usefulness of these techniques for clinical decision making.[1]

Genotyping of rotavirus nucleic acid from stool specimens by the polymerase chain reaction (PCR) is the most sensitive detection method.[14]

Electron microscopy of stool specimens negatively stained with phosphotungstic acid is rapid and, despite only moderate sensitivity, has high specificity because of the distinctive appearance of rotavirus particles.[21]

THERAPY

No specific antiviral therapy is recommended for rotavirus gastroenteritis. Because rotavirus gastroenteritis is generally self-limited, and dehydration is the primary cause of morbidity and mortality, rehydration and restoration of electrolyte balance are the primary therapies.

World Health Organization (WHO) has published guidance on the treatment of acute diarrhea and dehydration in both well-nourished and malnourished children.[22,23]

Even in the face of moderate vomiting, oral rehydration solution (ORS) is effective in treating dehydration caused by rotavirus gastroenteritis, and it is favoured over intravenous (IV) rehydration in situations of mild or moderate dehydration. The effectiveness of ORS is based on the solute-coupled cotransport of sodium by enterocytes, which continues to operate even in the damaged gut.[24]

Randomized controlled trials in developing countries have demonstrated that, for children older than 6 months, zinc supplementation during and for a short time after an episode of diarrhea can decrease the duration of diarrhea by approximately half a day on average and decrease the probability that diarrhea will last more than 7 days, but the treatment is associated with a small increase in the incidence of vomiting.[25,26]

Racecadotril (no commercial preparations available in the United States) is an enkephalinase inhibitor that reduces intestinal hypersecretion and has been evaluated as an adjunct to oral rehydration solutions. Although some randomized clinical trials demonstrate that adding racecadotril to the mix can reduce mean stool production in inpatients and mean diarrheic stools in outpatients, two randomized, double-blind, placebo-controlled clinical trials in India found no such impact.[27,28]

Most antiemetic's are not considered to have a favorable risk-benefit profile for self-limiting vomiting in acute pediatric gastroenteritis, although a single dose of the selective serotonin 5-hydroxytryptophan 3 receptor antagonist ondansetron may be considered in the emergency room context to enable oral rehydration (taking into account a warning for QT prolongation and cardiac arrhythmias).[27]

Oral immunoglobulins are not recommended for normal usage, although they may be useful in treating chronic rotavirus diarrhoea and worth additional research for prophylaxis in high-risk situations where immunization is unlikely to be effective, such as immunodeficiency or extreme prematurity. In case reports, feeding human serum immune globulin to children with chronic rotavirus diarrhea has been followed by resolution of diarrhea and viral shedding.[29]

VACCINES IN DEVELOPMENT

Because of the great global burden of childhood rotavirus gastroenteritis, significant multinational efforts have been directed toward the development of a safe and effective rotavirus vaccine.[1]

In 1998, a tetravalent, rhesus-human reassortant rotavirus vaccine (RRV-TV) was licensed and recommended for routine childhood immunization in the United States (Centers for Disease Control and Prevention 1999a). Both are oral live-attenuated virus vaccines.

In January 2005, a new vaccine for prevention of rotavirus infections was licensed in Mexico. This monovalent live-attenuated human rotavirus vaccine (G1) produced by GlaxoSmithKline (derived from strain 89–12 which was isolated from a rotavirus-infected child in Cincinnati, Ohio, USA) is administered to infants using a two-dose schedule six to ten weeks apart. The first dose is administered between 6 and 14 weeks of age and the second dose between 14 and 24 weeks of age.

Vaccine efficacy data from Finland and Latin America show 70–73 percent protection against rotavirus gastroenteritis, 85–86 percent protection against severe rotavirus gastroenteritis and 93 percent protection against rotavirus illness requiring hospitalization (Bernstein et al. 2002, De Vos et al. 2004, Vesikari et al, 2004).

Vaccines for three GI infections have been shown to be effective and are licensed for use. A pentavalent rotavirus vaccine was recommended for routine use in infants in the United States in 2006, with three doses given at 2, 4, and 6 months, respectively.[30] In 2008, a monovalent rotavirus vaccine with two doses at 2 and 4 months was proposed as an alternative. As described earlier, this vaccine has had a substantial impact on the morbidity associated with rotavirus infection in children in the United States.[31]

Rotavirus vaccine is now available in more than 90 countries; however, vaccine efficacy varies geographically and is lower in resource-limited countries where the bulk of rotavirus infections still occur.[32]

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