Rotavirus Overview

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Abstract: Rotaviral gastroenteritis is a serious public health problem in both developed and developing countries. The disease is ubiquitous, affecting nearly all children by the age of 5 years. It is the most common cause of hospitalizations for gastroenteritis among children in the United States (30%–70% depending on the season) and is associated with direct and indirect costs of approximately $1 billion per year. Symptoms of rotaviral gastroenteritis are nonspecific (ie, diarrhea, vomiting, and fever), with disease severity varying considerably. Diagnostic confirmation of rotaviral gastroenteritis requires laboratory tests (most commonly enzyme immunoassay or latex agglutination); however, because specific diagnosis is costly and does not affect treatment, laboratory tests are generally not performed. Because no antiviral therapies are currently available, treatment of rotavirus infection is supportive and primarily aimed at the replacement of fluid and electrolyte losses. Based on the observations that improved sanitation does not decrease disease prevalence and that hospitalizations remain high despite the availability and use of oral rehydrating solutions, the primary public health intervention for rotavirus infection is vaccination. Current vaccines (ie, RotaTeq, Merck and Company; Rotarix, GlaxoSmithKline) are effective for reducing rotaviral gastroenteritis (particularly severe disease), emergency department visits, and hospitalizations. Rotavirus vaccination is now included as part of the routine vaccination schedule for all infants in the United States.

Key Words: rotavirus, gastroenteritis, rotavirus vaccine, diagnosis, treatment, epidemiology

Rotavirus is the most common cause of severe diarrhea in infants and young children in both the United States and around the world. Rotavirus infection is nearly universal, with approximately 95% of children experiencing rotavirus gastroenteritis by age 5 years. There is no difference in the incidence of rotavirus infection between developed and developing countries, indicating that improved sanitation does not decrease disease prevalence and that hospitalizations are nonspecific (ie, diarrhea, vomiting, and fever), with disease severity varying considerably. Diagnostic confirmation of rotaviral gastroenteritis requires laboratory tests (most commonly enzyme immunoassay or latex agglutination); however, because specific diagnosis is costly and does not affect treatment, laboratory tests are generally not performed. Because no antiviral therapies are currently available, treatment of rotavirus infection is supportive and primarily aimed at the replacement of fluid and electrolyte losses. Based on the observations that improved sanitation does not decrease disease prevalence and that hospitalizations remain high despite the availability and use of oral rehydrating solutions, the primary public health intervention for rotavirus infection is vaccination. Current vaccines (ie, RotaTeq, Merck and Company; Rotarix, GlaxoSmithKline) are effective for reducing rotaviral gastroenteritis (particularly severe disease), emergency department visits, and hospitalizations. Rotavirus vaccination is now included as part of the routine vaccination schedule for all infants in the United States.

DISEASE BURDEN

Rotavirus gastroenteritis inflicts a devastating impact on infants and young children, particularly in developing countries. It is estimated that the disease is associated with the deaths of more than 600,000 children per year worldwide, with the majority of deaths occurring in Africa and Asia. Yearly death tolls are high in India (146,000), Nigeria (47,500), China (41,000), Pakistan (36,500), Congo (29,000), and Ethiopia (29,000). Bangladesh has the highest per capita death rate from the disease. Although mortality rates in the United States are much lower (20–60 deaths/yr), the disease is still associated with substantial disease burden. It is estimated that rotavirus gastroenteritis is associated with 410,000 physician visits, 205,000 to 272,000 emergency department visits, and 55,000 to 70,000 hospitalizations each year in the United States. Thus, between 1 in 67 and 1 in 85 children in the United States will be hospitalized with rotavirus by the age of 5 years. Risk factors for rotavirus-induced hospitalization include no breastfeeding, low birth weight, being in child care, no insurance or having Medicaid, and the presence of another child <24 months in the house.

The direct and indirect costs associated with the disease are estimated to be approximately $1 billion in the United States. A study in 1993 calculated that the average total cost per episode of diarrhea presenting to a primary care physician was $289, with time missed from work by the parent/caretaker responsible for half of the total cost. The majority of parents missed at least 1 day of work (average 1.3 days). As expected, costs are much higher when hospitalization is required. A study analyzing medical claims between 1993 and 1996 found that the cost of hospitalization (in 1998 dollars) was in excess of $2300, with a range of $648 to $79,886. Other studies of rotavirus-related hospitalizations have estimated median charges per hospitalization of $2999 to $3399. Notably, because these analyses included only charges for medical services, these values did not include indirect costs (eg, lost time from work).

One large prospective study examined these indirect costs between November 1997 and December 1999 at 3 pediatric medical centers. The average nonmedical cost per case of severe rotavirus disease that required hospitalization was approximately $450–80% of which ($359) was attributed to missed work and...
EPIDEMIOLOGY

The severity of rotavirus infection is age dependent. Although the disease can occur at any age, the disease most commonly causes clinically significant disease in young infants and children.\(^\text{14,15}\) The first infection after 3 months of age is generally the most significant, with severe, dehydrating rotaviral gastroenteritis primarily occurring among infants and children aged 3 to 35 months.\(^\text{1,2}\) The reasons for the reduced severity of disease in neonates are not completely understood, but because the onset of rotavirus disease corresponds with the decline of maternal antibody levels, early protection may be related to transplacental antibodies that persist for the first months of life.\(^\text{14,15}\)

Transmission of rotavirus is primarily via fecal-to-oral spread, both through close person-to-person contact and contact with contaminated environmental surfaces.\(^\text{2,16}\) The virus is also probably transmitted via fecally contaminated food and water and/or respiratory droplets.\(^\text{2,16}\) Once established within the small intestine, the virus replicates in the villous epithelium, resulting in decreased intestinal absorption of sodium, glucose, and water, and decreased levels of intestinal lactase, alkaline phosphatase, and sucrase activity that may result in isotonic diarrhea.\(^\text{2}\)

Rotavirus outbreaks exhibit a seasonal pattern. In temperate climates, rotavirus infections peak in winter months.\(^\text{1,2,11}\) In 1 study,\(^\text{18}\) the proportion of patients hospitalized with gastroenteritis who had confirmed rotavirus infection ranged from 25% during the off season to more than 70% during peak season. In the United States, annual epidemics begin in the Southwest during November and December, progressing north and east and reaching the Northeast by April or May.\(^\text{14}\) A similar pattern has been identified in Europe, with the seasonal peak beginning in Spain in January, spreading to northern countries by March.\(^\text{14}\) Seasonality is less marked closer to the equator but the disease is more pronounced during drier and cooler months. The reason for this seasonality remains unknown.\(^\text{14,15}\) Recent data from the Centers for Disease Control and Prevention suggest that the seasonality of rotavirus could be changed by the introduction of rotavirus vaccines. According to a recent interim report rotavirus activity in the 2007 to 2008 season began in February, 3 months later than the previous 15 years.\(^\text{19}\)

Rotavirus is characterized by substantial genetic diversity, as evidenced by the presence of multiple serotypes. The most common circulating strains associated with rotaviral gastroenteritis worldwide are serotype G1 through G4 and G9. These strains are responsible for 95% of pediatric rotavirus diarrhea worldwide.\(^\text{2}\) G1 is particularly prevalent in North America, Australia, and Europe (70% of infections) but less so in South America, Asia, and Africa (20%–30%).\(^\text{10,21}\) In addition, G9 has emerged in recent years as an important strain, with the highest rates in South America and Australia.\(^\text{20}\) Other serotypes continue to emerge including G5, G8, and G12 strains.\(^\text{20}\)

COURSE OF THE DISEASE

After an incubation period of 1 to 3 days, the illness can begin abruptly with a variable presentation.\(^\text{1}\) The clinical features of rotavirus illness are nonspecific and similar to those caused by other gastrointestinal pathogens, although they tend to be more severe.\(^\text{2}\) Fever, diarrhea, and vomiting are the most common symptoms, which can occur either alone or in combination.\(^\text{18}\) In a study of children admitted with diarrhea, vomiting, and unexplained fever, the most common presentation was diarrhea, vomiting, and fever in combination (63%) (Fig. 3).\(^\text{18}\) Ninety-seven percent presented with diarrhea and/or vomiting and 91% had diarrhea (with or without vomiting and/or fever).\(^\text{18}\)
The severity of presenting symptoms is variable with the spectrum of illness, ranging from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever. Clinical presentation can vary by age group. In general, the first infection after 3 months of age is the most severe. Infants may be asymptomatic or only have mild symptoms with a lower likelihood of diarrhea and vomiting compared with older children. However, infants can experience a wide range of symptoms, including frank necrotizing enterocolitis. Indeed, it has been proposed that 30% to 40% of cases of necrotizing enterocolitis may be related to rotavirus infection. Adults with rotavirus infection are usually asymptomatic or have mild disease—presumably because of protection from previous infections—although 3% to 5% of admissions for gastroenteritis in adults are due to rotavirus.

Rotaviral gastroenteritis is more severe than other causes of gastroenteritis and more often results in dehydration, hospitalization, and if not treated, shock, electrolyte imbalance, and death. Temperature of >102°F can occur in up to a third of patients. Gastrointestinal symptoms typically resolve within 3 to 7 days.

**DIAGNOSIS**

Rotavirus cannot be diagnosed solely on clinical grounds; however, findings suggestive of rotavirus infection include a mildly febrile illness accompanied by vomiting and watery diarrhea. Although there are differences between rotaviral gastroenteritis and other forms of acute gastroenteritis, it is not possible to distinguish rotavirus-induced disease solely on clinical presentation. Nevertheless, fever, acid-reducing substance-positve stool, and low serum bicarbonate are more likely in rotaviral gastroenteritis, whereas the presence of gross bloody diarrhea is more common in acute gastroenteritis caused by other organisms. Disease occurrence during peak rotavirus season in temperate climates in appropriate age groups can also suggest the presence of rotavirus.

Although laboratory testing is generally performed, it is the only way to confirm the diagnosis. The most widely available methods for disease confirmation are enzyme immunoassay (eg, Rotaclone) and latex agglutination. These tests are easy to perform, provide rapid results, and are highly sensitive (70%–98%) and specific (71%–100%). Other techniques include electron microscopy, culture, and polymerase chain reaction.

**TREATMENT**

Treatment of rotavirus is supportive and primarily aimed at the replacement of fluid and electrolyte losses. Rehydration can be accomplished using the World Health Organization formulation or any of a number of commercial formulations. Studies have shown that these formulations are effective for children who are mildly to moderately dehydrated. Intravenous fluids should be used for those with severe diarrhea, intractable vomiting, altered consciousness, or if the child cannot or will not drink. Nutritional therapy is also important and can reduce the morbidity and mortality of rotaviral gastroenteritis. Early initiation of refeeding is important because oral rehydration therapy is low in calories. There are no antiviral agents available for the treatment of rotavirus infection.

**PREVENTION**

The goal of rotavirus vaccine development is to duplicate the protection produced by natural infection. At present, 2 vaccines are licensed for use in the United States: RotaTeq and Rotarix. These vaccines use somewhat different principles to achieve immunity against a broad range of diverse strains of rotavirus. RotaTeq, approved in February 2006 by the US Food and Drug Administration, is a live, oral vaccine that contains a combination of 5 human/bovine reassortant rotavirus strains that replicate poorly in the gut. Three doses at 2, 4, and 6 months of age are recommended. In contrast, Rotarix is a live-attenuated human rotavirus vaccine prepared from a single human strain (P1A[8]G1) that replicates well in the gut. Two doses, administered at 2 and 4 months are recommended.

In clinical trials, the 3-dose regimen of RotaTeq was associated with 74% efficacy against rotaviral gastroenteritis of any severity and 98% efficacy against severe disease. RotaTeq was associated with substantial reductions in office visits (86%), emergency department visits (94%), and hospitalizations (96%). Similarly, in a clinical study conducted in Europe, the 2-dose regimen of Rotarix was associated with 79% efficacy against rotavirus of any severity and 96% efficacy against severe disease in the first season. Efficacy was sustained through 2 rotavirus seasons. Rotarix reduced hospitalizations for rotaviral gastroenteritis by 100% and medically attended visits by 92% in the first rotavirus season, and reduced hospitalizations by 96% through 2 seasons. It seems that vaccination against rotavirus disease may already have had an effect on disease rates. An interim report on the 2007 to 2008 rotavirus season in the United States, when only RotaTeq was available, suggests that rotavirus vaccination may have contributed to a decreased magnitude of rotavirus activity during this season. Reductions were greater than expected based on the protective effects of the vaccine alone, suggesting that a herd effect may also be contributing to these reduced rates.

**SUMMARY AND CONCLUSIONS**

Rotaviral gastroenteritis is associated with a substantial clinical and economic burden in both developed and developing countries. The disease burden is particularly considerable in infants and young children, producing infections that range from mild diarrhea to severe diarrhea, vomiting, and fever that result in hospitalization and death. The prevalence of the disease may be under-reported because laboratory confirmation is not typically performed. Because there are currently no specific treatments for rotaviral infection, vaccination is the primary public health intervention for rotavirus infection. At present, approved vaccines (RotaTeq and Rotarix) produce effective protection against disease (particularly severe disease), and decrease emergency room visits...
and hospitalizations. Rotaviral vaccination is included in the routine vaccination schedule of all infants in the United States.

REFERENCES


