



Rotavirus infection: Optimal treatment and prevention

Which fluids should you avoid when treating patients' gastroenteritis? Should nursing mothers continue to breastfeed? And what about the timing of the 2 vaccines and their administration with other vaccines? Read on.

PRACTICE RECOMMENDATIONS

□ Patients with rotavirus infection require oral, enteral, or intravenous fluids to treat dehydration. **(A)**

□ Give the first dose of rotavirus (RV) vaccine between the ages of 6 weeks and 14 weeks 6 days; give subsequent doses at 4- to 10-week intervals, completing by 8 months. **(A)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

Rotavirus is the most common cause of severe gastroenteritis in infants and children younger than 5 years of age, and it accounts for approximately 5% of childhood deaths worldwide.¹ In the United States, rotavirus causes numerous cases of dehydrating diarrhea and vomiting, and is responsible for direct and indirect healthcare costs of approximately \$1 billion per year. Infection during childhood is almost universal.²

Improved personal hygiene and community sanitation have steadily reduced the prevalence of bacterial and parasitic disease. But these measures have had little effect on the spread of rotavirus and its potential complications of severe dehydration, hospitalization, and even death.¹ Importantly, we now have the means to vaccinate against rotavirus infection and dramatically reduce the incidence of disease. In this article, I describe the available vaccines and the vaccination recommendations endorsed by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). I also review supportive treatment for rotavirus infection, which entails both do's and don'ts.

Who is at risk of rotavirus disease?

For most term neonates, rotavirus disease is mild, perhaps because of partial protection from maternal antibodies.³ However, premature infants lacking full maternal antibody protection often suffer from more serious gastroenteritis. The most severe infections usually strike children between the ages of 4 months, when maternally derived antibody protection wanes, and 23 months, when dehydration risk lessens.⁴⁻⁶

The virus spreads from person to person via the fecal-oral route.^{6,7} Thirty percent to 50% of family members of an infected child may also become infected, but disease in older chil-

Donald B. Middleton, MD
Department of Family
Medicine, University of
Pittsburgh School of Medicine

middletondb@upmc.edu

Dr. Middleton is a member of the pediatric advisory board for vaccines for Merck & Co, Inc.

Research assistance for this manuscript was provided by Lori Lush, PharmD, of JK Associates, Inc. and supported by Merck & Co., Inc. The author was not compensated and retained full editorial control over the content of the manuscript.

The Journal of Family Practice no longer accepts articles whose authors have received editorial assistance from commercially sponsored third parties. This article was accepted prior to implementation of this policy.

➤ In severe cases, fever, abdominal pain, and vomiting may precede diarrhea.

dren and adults is usually subclinical or mild.⁶ Outbreaks of rotavirus are common in child-care centers and in children's hospitals.^{7,8}

How the disease presents

Rotavirus gastroenteritis peaks during the winter. With mild cases, a watery diarrhea will last a few days. In severe cases, onset is usually abrupt with fever, abdominal pain, and vomiting, which can precede diarrhea. A third of patients have a temperature higher than 102°F (38.9°C).⁶ There is a risk of dehydration, shock, and even, occasionally, infant death.⁹

Typically, the incubation period is 1 to 4 days, and the infection lasts 3 to 7 days. However, damage to the brush border of the intestinal villi can produce persistent disaccharide malabsorption, resulting in prolonged diarrhea even after resolution of infection.^{10,11} Stools generally do not contain blood or leukocytes. Ultrasound examination during rotavirus infections has shown thickening of the distal ileum and lymphadenopathy, which may predispose to intussusception.¹² Other problems possibly linked to wild-type rotavirus infection are Kawasaki disease and sudden infant death syndrome. Recurrent rotavirus infection with one of the many different serotypes is common during childhood.

More than 25 different assays can detect rotavirus in stool, but the most reliable method is direct electron microscopy. A suitable clinically available alternative is enzyme immunoassay testing of stool samples. In mild cases, testing to detect rotavirus is not necessary. But for bloody, severe, or persistent diarrhea, stool testing for rotavirus and other entities is warranted.

Supportive treatment: Do's and don'ts

No specific antiviral treatment is available for rotavirus infection. That said, the do's and don'ts that follow will help guide your care.

DO administer oral, enteral, or intravenous (IV) fluids to prevent or correct dehydration. Oral rehydration therapy is the standard treatment for dehydration in anyone with

acute gastroenteritis, including that caused by rotavirus. The recommended World Health Organization (WHO) oral rehydration solution contains sodium, chloride, and electrolytes (TABLE 1).¹³ Rice-based oral rehydration solution is an easily metabolized carbohydrate formulation that helps repair damaged tissues and enhances electrolyte absorption.⁹ WHO has endorsed guidelines that base fluid replacement on the patient's age and weight, and that recommend oral zinc intake (10 mg/d for 10-14 days up to age 6 months; 20 mg/d for 10-14 days for older children) for all episodes of diarrhea (<http://hetv.org/pdf/diarrhoea-guidelines.pdf>). Oral glucose electrolyte solutions containing less sodium and chloride are also effective treatments.

DO recommend frequent small doses of oral rehydration solution, even if the patient is vomiting.¹⁴ Rehydration volumes are suggested in TABLE 1. Alternatively, give 10 to 20 mL/kg for each diarrheal episode, and 2 mL/kg for each bout of emesis. Feeding frequent small volumes (30 mL every 5-10 minutes) reduces the risk of emesis.

Although oral rehydration solutions are contraindicated for infants and young children with depressed consciousness, vomiting is not a contraindication to oral intake. About half of the oral intake stays in the stomach, even after vomiting. A single dose of ondansetron may safely reduce vomiting.¹⁵

Patients with mainly diarrhea can take fluids or feed at will. With children who refuse to drink, oral rehydration solutions can be administered via nasogastric tube at approximately 5 mL/min to limit vomiting and maintain hydration.¹⁴ In dehydrated infants and toddlers with collapsed veins, nasogastric intubation has been shown to be less traumatic than repetitive attempts at placing IV catheters.

DO encourage nursing mothers to continue breastfeeding during rehydration treatments. If a mother is bottle feeding, keep this in mind: Rotavirus can cause temporary lactase deficiency for some non-breastfeeding infants; lactose-free formulas may help.

DON'T assume that parents know how to provide proper supplementation. Tell them to avoid fluids containing mostly sugar that

TABLE 1

Prevent or correct dehydration using the WHO-recommended oral rehydration salts solution¹³

With this formulation...	...rehydrate per these specifications...			...at this rate
Component (mmol/L)	Age	Weight (kg)	mL solution/4 h	
Sodium (75); chloride (65); glucose (75); potassium (20); citrate (10)	≤4 mo	<6	200-400	
	4-12 mo	6 to <10	400-700	
	12 mo-2 y	10 to <12	700-900	
	2-5 y	12 to 19	900-1400	

WHO, World Health Organization.

lack significant electrolyte supplementation (eg, cola) unless no other fluid alternative is available. Advise caregivers to avoid juices and other liquids high in complex or simple sugars because the osmotic load may worsen diarrhea.¹⁴

■ DON'T give antidiarrheal agents for acute treatment in infants and young children. Such treatment has resulted in death.¹⁴

KEEP IN MIND

■ Hospitalization may be needed to replace fluids via IV or interosseous supplementation. For the severely dehydrated child, 20 mL/kg isotonic fluid can be administered as a rapid bolus.¹⁴ It may be necessary to repeat a rapid fluid infusion of 10 to 20 mL/kg every 20 to 30 minutes. For less severely ill infants who require IV rehydration, standard references such as the *Harriet Lane Handbook*¹⁶ provide excellent guidance.

■ Probiotics may help. Consider probiotics with *Lactobacillus* or *Bifida bacterium* to reduce the severity of diarrhea in infants and children who are mildly to moderately ill.^{17,18} Their usefulness in the severely ill patient has not been demonstrated.

Available vaccines and clinical recommendations

In February 2006, the US Food and Drug Administration (FDA) licensed a 3-dose, oral pentavalent rotavirus vaccine (RV5, RotaTeq) for use among infants. The vaccine contains live reassortant rotaviruses¹⁹—4 human rotavirus G outer-surface proteins and 1 human

P attachment protein reassorted into a bovine rotavirus not infectious to humans.

In February 2008, the FDA approved a 2-dose, oral monovalent rotavirus vaccine (RV1, Rotarix), an attenuated live human rotavirus containing 1 G protein and 1 P protein. Both vaccines have proven to be clinically effective in rotavirus prevention trials, but effectiveness may depend on which rotavirus serotypes circulate each season.

ACIP, AAP, and AAFP recommend that all infants be routinely vaccinated with either RV5 or RV1.^{6,20-22} Vaccination should be complete by the time infants reach the age of 8 months (TABLE 2). Guidelines for vaccination emphasize the following points:

■ Timing. According to the ACIP, the first dose of either vaccine must be administered between the ages of 6 weeks and 14 weeks 6 days (the RV5 manufacturer [Merck] states a maximum age of 12 weeks). Give subsequent doses at 4- to 10-week intervals, as long as all doses are administered by 8 months of age. The RV1 manufacturer (GlaxoSmithKline) suggests completing the second (final) dose of its vaccine by age 24 weeks.

If an infant 15 weeks of age or older accidentally receives a first dose of RV vaccine, the series should be continued, as long as the last dose can be given by 8 months of age. Either vaccine can be administered concurrently with all other vaccines.

■ Contraindications. The only absolute contraindications to RV5 administration are a demonstrated hypersensitivity to any com-



Administer oral rehydration therapy, but do not give antidiarrheal medications.

TABLE 2

Recommended rotavirus live virus vaccine dosing⁶

Patient age (mo)	RV5 (RotaTeq)	RV1 (Rotarix)
2	2 mL	1 mL
4	2 mL	1 mL*
6	2 mL*	—

*The final dose of either vaccine must be given by no later than 8 months of age.

➤
ACIP, AAP, and AAFP recommend that all infants be vaccinated with the RV5 or RV1 vaccine.

ponent of the vaccine and severe combined immunodeficiency disease (SCID). Contraindications to RV1 vaccine are vaccine component hypersensitivity, SCID, latex-induced allergy (anaphylaxis), and uncorrected malformation of the gastrointestinal (GI) tract that might predispose to intussusception.

Precautions. Precautions for vaccines include other forms of primary or secondary immunocompromised or immunodeficiency states, including cancer and acute or chronic GI disorders such as ongoing gastroenteritis or intussusception. Infants with transient mild illness with or without low-grade fever and infants who are breastfeeding can receive either vaccine. RV5 is shed in 9% of recipients and RV1 in 26% of recipients after Dose 1, but transmission of vaccine virus is not known to occur. Likewise, reversion of vaccine virus to more virulent pathogens is not known to occur. A household member with an immunocompromised condition does not preclude giving either RV vaccine to an infant. The risk of transmitting vaccine virus is much smaller than the risk of acquiring infectious wild-type rotavirus.

Regurgitation of a vaccine dose is uncommon. When it does occur, the RV5 vaccine should *not* be repeated; some of the vaccine dose is retained and the safety of the additional vaccine from a second dose is unknown. Readministration of a dose of RV1 is not recommended, although not contraindicated.

Vaccine efficacy

The safety and efficacy of live rotavirus vaccines were demonstrated in large studies that enrolled 71,725 children in RV5 vaccine trials²³ and 24,163 children in RV1 vaccine tri-

als.²¹ The pivotal RV5 study included a nested substudy to evaluate efficacy against any G1–G4 rotavirus gastroenteritis.

RV5 (RotaTeq) vaccine. In double-blind, placebo-controlled clinical trials, for the first rotavirus season, live RV5 vaccine effectively prevented severe rotavirus infection in 98% of cases, and reduced hospitalization by 95%, emergency department visits by 94%, physician office visits by 86%, and all rotavirus cases by 74% for infants who received all 3 doses of vaccine according to protocol.²³ Hospitalization for any-cause gastroenteritis was reduced by 63%. Second-season data showed persistence of antibody protection. All 3 doses of vaccine are required for maximum protection.²³

Both preterm and term infants received their first dose of vaccine between 6 and 12 weeks of life. For preterm infants who are experiencing medical difficulties, the first dose of vaccine may be delayed until the patient is stable, if it can be given before 15 weeks of age.

RV1 (Rotarix) vaccine. In double-blind, placebo-controlled clinical trials, for the first rotavirus season, live RV1 vaccine was 85% (Latin America) to 96% (Europe) effective in preventing severe rotavirus infection. It reduced hospitalization due to rotavirus by 85% (Latin America) to 100% (Europe), and all rotavirus cases by 87% (Europe) for infants who received both doses of the vaccine according to protocol. For the second season, the vaccine reduced severe rotavirus disease by 70% to 96%, and any rotavirus disease by 73% to 89%, showing persistence of antibody protection.⁶

Adverse events

With both vaccines, common side effects include irritability, flatulence, fever, vomiting, diarrhea, cough, runny nose, and loss of appetite. The RV5 vaccine has been shown not to increase the risk of intussusception compared with placebo.^{24,25} The RV1 vaccine should not be used in children with an uncorrected bowel malformation, due to unproven increased risk of intussusception. Risk of death from complications after administration of either vaccine did not differ from that among children receiving placebo.

Costs of RV vaccines

As of April 11, 2011, RV5 costs \$59.76/\$69.59 per dose in the public/private sectors, respectively (3-dose series: \$179.28/\$208.77); RV1 costs \$89.25/\$102.50 per dose (2-dose series: \$178.50/\$205). Routine vaccination costs about \$138 per case averted and \$3024 per serious case averted. Neither vaccine contains thimerosal. Both vaccines are available in 10-dose packs.

Source: Centers for Disease Control and Prevention. CDC vaccine price list. Prices last reviewed/updated: April 8, 2011. Available at: <http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm>. Accessed April 11, 2011.

Postmarketing surveillance of vaccination outcomes

Even though rotavirus vaccine coverage with RV5 RotaTeq in the 2007-2008 and 2008-2009 seasons was far less than that with other childhood immunizations, the number of rotavirus infections dropped by >60% in both 2008 and 2009.²⁶ The number of stool tests for rotavirus and the percentage of positive results also dropped dramatically.

Additionally, the rotavirus peak incidence was delayed 2 to 4 months until April 2008 and March 2009.²⁶ Incidence was reduced in all age groups, suggesting the possibility of herd immunity despite a low vaccine coverage rate (estimates are 57% for ≥ 1 dose) that would not be expected to provide herd immunity.²⁷ Hospitalizations in the United States for rotavirus gastroenteritis dropped

by as much as 85%,²⁸ markedly reducing costs for gastroenteritis.

In a 2010 report from an emergency department in Houston, a complete RV5 vaccine series conferred 82% protection against acute gastroenteritis, 96% against severe rotavirus disease requiring IV rehydration, and 100% against hospitalization.²⁹ For more on the vaccine, see the report by Yen et al.³⁰

Reports of the effectiveness of Rotarix in postmarketing surveillance are limited, but the vaccine does seem to provide broad coverage.³¹

Incorporating rotavirus vaccine into a family medicine practice

Given inadequately reimbursed costs including the cost of stocking RV vaccine (see "Costs of RV vaccines" above), family physicians who treat relatively few infants must determine whether offering RV vaccine fits within their practices.

For family physicians who do treat infants, offering RV vaccination makes sense. These oral vaccines are highly effective, safe, and easy to administer, and will prevent a great deal of worry and calls regarding infants who have a fever or diarrhea or are vomiting. Due to the costs of stocking all vaccines, private practitioners are wise to purchase vaccine loss insurance. Many insurance agencies provide a rider on office insurance policies to cover vaccine supplies.

JFP

CORRESPONDENCE

Donald B. Middleton, MD, UPMC St. Margaret, 815 Freeport Road, Pittsburgh, PA 15215; middletondb@upmc.edu



The oral rotavirus vaccines can be given concurrently with other vaccines in the immunization schedule.

References

1. Parashar UD, Gibson CJ, Bresee JS, et al. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis*. 2006;12:304-306.
2. Malek MA, Curns AT, Holman RC, et al. Diarrhea- and rotavirus-associated hospitalizations among children less than 5 years of age: United States, 1997 and 2000. *Pediatrics*. 2006;117:1887-1892.
3. Xu J, Dennehy P, Keyserling H, et al. Serum antibody responses in children with rotavirus diarrhea can serve as proxy for protection. *Clin Diagn Lab Immunol*. 2005;12:273-279.
4. World Health Organization. Rotavirus vaccines. *Wkly Epidemiol Rec*. 2007;82:285-295.
5. Ward RL, Bernstein DI, Staat MA. Rotaviruses. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Disease*. Vol 2, 6th ed. New York, NY: Saunders; 2009:2245-2270.
6. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2009;58(RR-2):1-25.
7. Butz AM, Fosarelli P, Dick J, et al. Prevalence of rotavirus on high-risk fomites in day-care facilities. *Pediatrics*. 1993;92:202-205.
8. Fischer TK, Bresee JS, Glass RI. Rotavirus vaccines and the prevention of hospital-acquired diarrhea in children. *Vaccine*. 2004;22(suppl):S49-S54.
9. Kapikian AZ, Hoshino Y, Chanock RM. Rotaviruses. In: Knipe DM, Howley PM, Griffin DE, et al, eds. *Fields Virology*. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:1787-1825.
10. Lorrot M, Vasseur M. How do the rotavirus NSP4 and bacterial enterotoxins lead differently to diarrhea? *Virol J*. 2007;4:31.
11. Ramig RE. Pathogenesis of intestinal and systemic rotavirus infection. *J Virol*. 2004;78:10213-10220.
12. Robinson CG, Hernanz-Schulman M, Zhu Y, et al. Evaluation of anatomic changes in young children with natural rotavirus infection: is intussusception biologically plausible? *J Infect Dis*. 2004;189:1382-1387.

CONTINUED

13. World Health Organization. *Oral Rehydration Salts: Production of the New ORS*. Geneva, Switzerland: WHO Document Production Services; 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_FCH_CAH_06.1.pdf. Accessed April 11, 2011.
14. King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 2003;52(RR-16):1-16.
15. DeCamp LR, Byerley JS, Doshi N, et al. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med*. 2008;162:858-865.
16. The Johns Hopkins Hospital, Custer JW, Rau RE. *Harriet Lane Handbook: A Manual for Pediatric House Officers*. 18th ed. St. Louis, Mo: Mosby/Elsevier; 2008.
17. Canani RB, Cirillo P, Terrin G, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *BMJ*. 2007;335:340.
18. Van Niel CW, Feudtner C, Garrison MM, et al. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics*. 2002;109:678-684.
19. Heaton PM, Goveia MG, Miller JM, et al. Development of a pentavalent rotavirus vaccine against prevalent serotypes of rotavirus gastroenteritis. *J Infect Dis*. 2005;192(suppl 1):S17-S21.
20. Centers for Disease Control and Prevention. Recommended immunization schedules for persons aged 0 through 18 years — United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(5):1-4.
21. American Academy of Pediatrics (AAP) Committee on Infectious Diseases. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics*. 2009;123:1412-1420.
22. Temte JL. Practice guidelines. ACIP releases 2009 child and adolescent immunization schedules. *Am Fam Physician*. 2009;79:56. Available at: <http://www.aafp.org/afp/2009/0101/p56.html>. Accessed January 4, 2010.
23. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354:23-33.
24. Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine: United States, 1998-1999. *MMWR Morb Mortal Wkly Rep*. 1999;48:577-581.
25. Centers for Disease Control and Prevention. Postmarketing monitoring of intussusception after RotaTeq vaccine: United States. February 1, 2006-February 15, 2007. *MMWR Morb Mortal Wkly Rep*. 2007;56:218-222.
26. Centers for Disease Control and Prevention. Reduction in rotavirus after vaccine introduction — United States, 2000-2009. *MMWR Morb Mortal Wkly Rep*. 2009;58:1146-1149.
27. Clark HF, Lawley D, Mallette LA, et al. Decline in cases of rotavirus gastroenteritis presenting to The Children's Hospital of Philadelphia after introduction of a pentavalent rotavirus vaccine. *Clin Vaccine Immunol*. 2009;16:382-386.
28. Chang HG, Smith P, Tserenpuntsag B, et al. Reduction in New York hospitalizations for diarrhea and rotavirus. Presented at: 43rd National Immunization Conference; March 30-April 2, 2009; Dallas, Tex. Abstract 41. Available at: <http://cdc.confex.com/cdc/nic2009/webprogram/Paper18073.html>. Accessed April 15, 2011.
29. Boom JA, Tate JE, Sahni LC, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. *Pediatrics*. 2010;125:e199-e207.
30. Yen C, Tate JE, Wenk JD, et al. Diarrhea-associated hospitalizations among US children over 2 rotavirus seasons after vaccine introduction. *Pediatrics*. 2011;127:e9-e15.
31. Correia JB, Patel MM, Nakagomi O, et al. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. *J Infect Dis*. 2010;201:363-369.