

# The management of Rotavirus disease in children

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## Abstract

Rotavirus disease is known to be the most important cause of severe gastroenteritis in children worldwide. It affects nearly all children by the age of five years. Transmission of the virus occurs mainly through the faecal-oral route. Complications that are associated with rotavirus infection include malnutrition and dehydration. These may have a fatal outcome. Vaccination against rotavirus disease is the most efficient way to protect children against rotavirus infection and can save many lives. Primarily, treatment is aimed at rehydration to replace fluid and electrolyte losses.

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## Introduction

Rotavirus is the leading cause of gastroenteritis in children under the age of five. By the age of five, worldwide, nearly all children will have been infected with the virus at least once. This was especially true during the “pre-vaccine” era.<sup>1,2</sup> Diarrhoea is one of the leading causes of mortality and morbidity in children, especially those in low- and middle-income countries (LMICs).<sup>3</sup> In 2013, 6.3 million children worldwide died before they reached their fifth birthday. Approximately half (3.2 million), of the children died due to infectious diseases and diarrhoea killed more than 500,000 children. In South Africa (SA), diarrhoea is one of the diseases accounting for the highest levels of morbidity and mortality in children less than five years of age. The mortality rate is reported to be between 8% and 20%.<sup>4,5</sup> Researchers have alluded to the fact that the occurrence of diarrhoea in children is commonly seen in poor informal settlements characterised by an unclean, non-hygienic environment that lacks sanitation, as well as over-congestion, insufficient clean water provision, poverty, undernourishment and the overall poor health status of these children.<sup>6,7</sup> All these factors may contribute to an increase in major disease burden and negative economic effects, as a result of low quality of life, loss of work, medical costs, and high mortality rate. Rotavirus disease may be more prevalent in resource-limited settings, although there is no real difference in the incidence of rotavirus infection when a comparison is made between developed and developing countries.<sup>8,9</sup> This may indicate that improved sanitation does not necessarily decrease transmission of the virus.<sup>8,9</sup>

The major difference in the nature of infection caused by the rotavirus in developed and developing countries lies in the peak

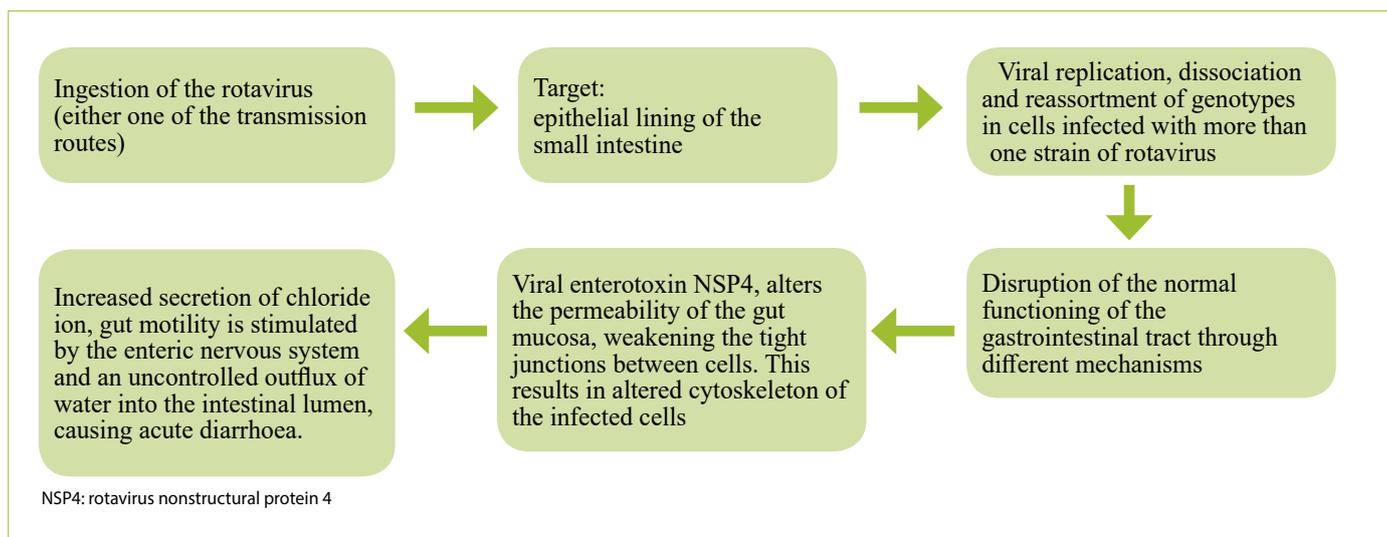
age of serious infection.<sup>5</sup> In developing countries, the mean age of onset of symptomatic rotavirus infection is between the ages of six and nine months, while in developed countries, the mean age of onset is between nine and 15 months.<sup>5</sup>

Symptoms of rotavirus infection include an acute onset of diarrhoea with subsequent dehydration that may have a fatal outcome.<sup>2</sup> Rotavirus vaccination programmes protect against the development of severe diarrhoea because they mimic a mild, asymptomatic infection.<sup>4,10</sup> The inclusion of the rotavirus vaccine in typical vaccination programmes has notably reduced the burden of rotavirus-induced gastroenteritis in many countries.<sup>10</sup> For example, in Mexico, the diarrhoea-related mortality rate was reduced by 46% following the introduction of the rotavirus vaccine.<sup>11</sup> In South Africa the number of reported deaths due to diarrhoea in children under five years of age has declined by over 50% in the past eight years, from 3 228 in 2007/2008 to 1 513 in 2014/2015.<sup>12</sup>

## Transmission and pathogenesis

The human rotavirus was first identified and isolated in epithelial cells taken from children suffering from acute diarrhoea in 1973.<sup>13</sup>

Rotavirus is a nonenveloped virus of the genotype, *Reoviridae* and is characterised by a double-stranded RNA genome comprising 11 segments that encode for six structural and six nonstructural segments.<sup>10</sup> Rotavirus has a strong seasonal variation, and it presents mostly during the winter in areas with a temperate climate. Children belonging to so-called high-income social classes are mostly affected.<sup>10</sup>



**Figure 1.** Pathophysiology of rotavirus disease in humans<sup>10</sup>

Transmission of the rotavirus occurs via the following routes:<sup>10</sup>

- Faecal-oral route
- Close personal contact
- Contaminated environmental sources

The prevalence of rotavirus in countries with a high income suggests that non-faecal routes and transmission of the rotavirus may also play a role.<sup>10</sup> The virus may be shed from the oropharynx in children suffering from upper respiratory tract diseases, with or without gastrointestinal tract involvement. This suggests that respiratory droplets are an added source of transmission.<sup>10</sup>

The pathophysiology of rotavirus disease is depicted in Figure 1.

The role that antibodies play in the protection of young children from naturally-occurring rotavirus infection has been documented, especially in the case of immunoglobulin G antibodies.<sup>13</sup> Antibodies also seem to be a key factor associated with protection from many vaccine-preventable diseases.<sup>13</sup>

### Risk factors and clinical presentation

Typical risk factors and the clinical presentation of rotavirus disease include the different grades of severity, associated signs and symptoms, and significant complications.

#### • Risk factors<sup>10</sup>

There is a very high incidence in infants and children.

#### **Subclinical-to-mild disease**

- Older children and adults.
- Up to 30–50% of an infected child's family members may become co-infected.

#### **Mild disease**

- Full-term neonates (may have some protection from maternal antibodies).

#### **Moderate disease**

- Premature infants (do not have full maternal antibody protection yet).

#### **Severe disease**

- Usually seen in children between the ages of four months and two years of age. (Maternal antibody protection begins to decrease beyond four months of age, and from two years onwards the risk of dehydration decreases in likelihood).

#### • Clinical presentation<sup>1,10</sup>

#### **Incubation period**

- In the range of 1–4 days.

#### **Duration**

- The infection lasts between 3–7 days.

### Rotavirus gastroenteritis

- Peak incidence is during the winter months.
- It ranges from watery diarrhoea that only lasts a few days in mild cases, to more severe cases that are characterised by a sudden onset and diarrhoea that may be preceded by fever, abdominal pain and vomiting.
- Risk of dehydration which may be severe enough to result in hypovolaemic shock.
- Rotavirus infection is noninvasive, but accounts for a high percentage of diarrhoea-related cases that require hospitalisation.

Warning: Outbreaks of rotavirus disease are common in childcare facilities such as daycare and preschool facilities, as well as children's wards or healthcare units. Severe dehydration and hypovolaemia can result in death.<sup>1</sup>

### Diagnosis

Rotavirus is mostly diagnosed based on the clinical presentation. It is not always possible to distinguish between rotavirus-induced

gastroenteritis and other forms of gastroenteritis.<sup>1,9</sup> However, in rotavirus-induced gastroenteritis, fever with an acid-reducing, substance-positive stool and low serum bicarbonate is more likely. It may present with watery diarrhoea. Other types of acute gastroenteritis may present with bloody diarrhoea.<sup>1,9</sup>

Disease confirmation may only be possible with laboratory testing. The most widely used mechanism may include enzyme immunoassay and latex agglutination.<sup>9</sup> These tests are easy to perform and provide rapid, sensitive and specific results.<sup>9</sup>

## Complications

Complications that are associated with rotavirus disease include dehydration and malnutrition. Dehydration, and its associated symptoms, is the most common complication.<sup>9,10</sup>

The severity of dehydration can be assessed in children according to the presenting symptoms in Table I (not specific to rotavirus).<sup>10</sup>

Mild-to-moderate dehydration	Severe dehydration
Restlessness	Reduced or altered consciousness
Irritability	Lack of urine output
Decreased fontanels (in infants)	Low blood pressure
Sunken eyes	Weak and/or quickened pulse
Thirst	Cool moist extremities
	Peripheral cyanosis

Malnutrition can predispose children to further susceptibility to gastrointestinal infections. The rotavirus plays a significant role in this destructive cycle since the diarrhoea disrupts the gut's ability to absorb nutrients, leading to further malnutrition.<sup>10</sup> The hydration status of children who are suffering from rotavirus should be assessed. The patient should be supported with proper nutrition.<sup>10</sup>

## Prevention

Improved sanitation, hygiene and access to clean water have not had a significant impact on the reduction of the incidence of rotavirus disease.<sup>8,9</sup> Vaccines were developed as a first-line prevention against rotavirus disease, and have been shown to dramatically reduce the incidence of the disease and the burden of hospitalisation.<sup>1,9,14</sup>

Children may be re-infected with rotavirus numerous times during their childhood, but it is often the first infection that results in severe rotavirus diarrhoea and dehydration. This can necessitate hospitalisation.<sup>14</sup> The rotavirus vaccine protects children against the first infection.

In 2009, the World Health Organization recommended the inclusion of a rotavirus vaccine in the national immunisation programmes of all countries.<sup>15</sup> South Africa was the first country in Africa to introduce the rotavirus vaccine via its Expanded Programme on Immunisation (EPI) in the public sector.<sup>16</sup> The vaccine has been available free of charge at public healthcare clinics in South Africa since 2009.<sup>16</sup> Since March 2015, 28 African

countries have included the rotavirus vaccine in their national immunisation programme.<sup>12</sup> Since the introduction of the vaccine in South Africa in 2009, there has been a sustained reduction in both rotavirus and all-cause diarrhoeal disease in children under the age of five years.<sup>17</sup>

At present, two effective rotavirus vaccines [RV1 (Rotarix<sup>®</sup>) and RV5 (RotaTeq<sup>®</sup>)] are available and registered for use in infants in South Africa to protect against the disease. RV1 is a live-attenuated monovalent (single-strain) human rotavirus vaccine and is available via the EPI to all infants in South Africa.<sup>9,14,18</sup> Conversely, RV5 is a live pentavalent, oral vaccine that contains a combination of five human-bovine reassortant rotaviruses.<sup>1,14</sup> Both vaccines have proved to be effective in clinical trials in preventing rotavirus diarrhoea.<sup>19</sup>

The rotavirus vaccination is administered orally as a liquid, inside the cheek, and may be given at the same time as other childhood vaccines. Babies who receive the vaccine may be fed normally afterwards. Repeat dosing is not indicated if an infant spits out, vomits or regurgitates the vaccine.<sup>20</sup> Recommendations for the use and administration of RV1 and RV5 vaccines are summarised in Table II.

## Reasons for missed vaccines

Parents cite concerns about vaccine safety as a reason for not vaccinating children. These include the vaccines' potential to overstrain or overburden the child's immune system.<sup>12</sup>

The overall benefits of using the rotavirus vaccines far exceeds any risks with regard to preventing mortality and hospitalisation.<sup>21</sup>

## Treatment

At present, no specific antiviral medicines are available to treat rotavirus infection.<sup>1,15</sup> Diarrhoea, resulting from the rotavirus infection, can quickly lead to dehydration and hospitalisation or even death in children who do not receive treatment soon enough.

The primary therapeutic focus of rotavirus diarrhoea is on rehydration to replace the loss of fluids to prevent metabolic acidosis and electrolyte disturbances, and on nutritional support therapy.<sup>1,15,16</sup> How to assess dehydration in children with diarrhoea is illustrated in Figure 2.

The most important factors in treating paediatric patients with rotavirus-associated diarrhoea is rehydration (water and electrolytes), zinc supplementation, continued feeding and counselling and education to caregivers for prevention.<sup>22</sup>

Diosmectite is used as an adjunct to hydration therapy for the treatment of acute infectious diarrhoea in children. It is an adsorbent agent and is an activated natural aluminosilicate clay consisting of a double aluminium and magnesium silicate. Diosmectite binds to the digestive mucus and has the ability to adsorb toxins, bacteria and rotavirus.<sup>25</sup> It interacts with the mucosa to increase its quantity, quality and lifespan. This accelerates the recovery of the infected mucosa.<sup>26</sup> It has been proven to be clinically effective, specifically for the treatment of rotavirus as a

**Table II.** Recommendations for the use and administration of the rotavirus 1 and rotavirus 5 vaccines<sup>1,18,20</sup>

Vaccine	Dose	Dosage interval
<b>RV1</b>	First dose: 6 weeks (1 ml)	Should not be given after 24 weeks of age. A minimum interval of four weeks should be kept between the two vaccine doses. The first dose should be given at six weeks, but not later than 14 weeks. The second dose should be given at 14 weeks, but not later than 24 weeks. If a child missed the first dose at six weeks and is < 20 weeks old, the first dose should be given, followed by the second dose four weeks later.
	Second dose: 14 weeks (1 ml)	If a child missed the first dose at six weeks and is > 20 weeks but < 24 weeks of age, one dose of the vaccine should be given.
<b>RV5</b>	First dose: 2 months (2 ml)	Should not be given after 32 weeks of age.
	Second dose: 4 months (2 ml)	A minimum interval of four weeks should be kept between the two vaccine doses.
	Third dose: 6 months (2 ml)	The first dose can be given from 6–12 weeks of age, at intervals of 4–10 weeks.
<b>Precautions and contraindications</b>	<p>A child cannot receive the second dose if the first dose has not been administered.</p> <p>The vaccine should not be given if a child has a history of chronic gastrointestinal disease or severe diarrhoea. The child should be referred for a medical opinion.</p> <p>Asymptomatic HIV children should be vaccinated, but symptomatic HIV-infected children should not.</p> <p>Any child with a severe (life-threatening) allergy to any component of rotavirus vaccine or who has had a severe (life-threatening) allergic reaction to a previous dose of rotavirus vaccine should not receive another dose.</p> <p>The oral applicator of RV1 contains latex rubber and should not be used in infants with a severe (anaphylactic) allergy to latex. The RV5 dosing tube is latex-free.</p> <p>The rotavirus vaccine is contraindicated in infants who have been diagnosed with severe combined immune deficiency, a rare genetic disorder.</p> <p>Although there is no evidence of increased risk with intussusception, as a precaution, the risks for and the benefits of vaccination in infants with a previous episode of intussusception should be considered.</p> <p>Children who are moderately or severely ill at the time of vaccination should probably wait until they have recovered. This includes children who have diarrhoea or are vomiting.</p> <p>A decision should be made, on a case-by-case basis, whether to vaccinate a child with an ongoing digestive problem, a weakened immune system due to HIV/AIDS or another disease that affects the immune system, or who is being treated with drugs, such as long-term steroids or those for cancer.</p>	
<b>Adverse effects</b>	<p>Vaccinated infants are slightly (1–3%) more likely to be irritable or to have mild, temporary diarrhoea or vomiting after vaccination than infants who did not receive the vaccine.</p> <p>Moderate or severe reactions have not been associated with the vaccine.</p>	
<b>Storage and handling</b>	<p>All vaccines should be kept in the refrigerator at a temperature between 2–8 °C and should not be frozen. If there is any uncertainty, the shake test should be carried out to determine whether the vaccines have frozen.</p> <p>The diluent for RV1 can be stored at a room temperature of 20–25 °C.</p> <p>The vaccines should be protected from light by storing them in their original box.</p> <p>The RV1 vaccine is supplied in two vials that must be mixed together before administration. Only the diluent that is supplied by the manufacturer should be used to reconstitute the vaccine. It should be administered promptly after reconstitution or stored at 2–8 °C for a maximum of 24 hours.</p>	

AIDS: acquired immune deficiency syndrome, HIV: human immunodeficiency virus, RV1: rotavirus vaccine 1, RV5: rotavirus vaccine 5

result of its ability to inhibit viral replication and the expression of NSP4. Ion secretion and cell damage induced by rotavirus are strongly inhibited, particularly in the early events of rotavirus infection. It cannot however, restore already-established cell damage.<sup>27</sup> Diosmectite has a good safety profile and has proved to significantly reduce the duration of diarrhoea and decrease stool output in children with acute watery diarrhoea.<sup>25,28</sup>

Diosmectite is administered for a period of three days. The dose should be reduced thereafter. It can be mixed with water or a semi-liquid, e.g. baby food or purée. Other medication should not be administered concurrently with diosmectite to avoid any interactions. It should be given an hour after the diosmectite dose.<sup>26</sup>

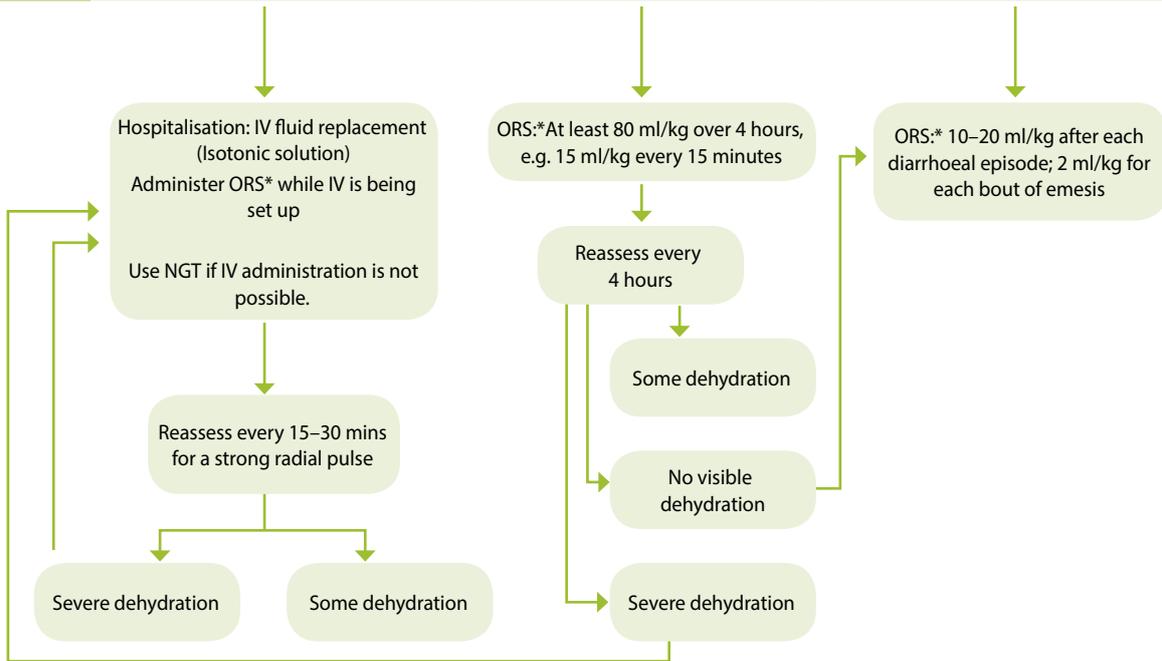
Minor adverse effects include constipation (which usually resolves with a reduction in the dose), flatulence and vomiting. Allergic reactions are rare and include urticaria, rashes, pruritis and angio-oedema.<sup>26</sup>

Probiotics such as *Lactobacillus acidophilus* or *Bifidobacterium longum* are useful as adjuncts to rehydration in the treatment of rotavirus diarrhoea in mild-to-moderately ill patients.<sup>1</sup> When compared to the administration of oral rehydration solution alone, probiotics have been shown to decrease the duration of diarrhoea, vomiting and fever.<sup>1,29</sup> Further studies are necessary to investigate the use of probiotics in severely ill patients.<sup>1</sup> Table III summarises supportive treatment for rotavirus gastroenteritis.

## Conclusion

Rotavirus is one of the leading causes of severe gastroenteritis and mortality in children under five. Vaccination against rotavirus has considerable health benefits and significantly reduces the burden of rotavirus disease. Diarrhoea resulting from rotavirus can quickly lead to severe, and often fatal, dehydration. The pharmacist has an important educational and supportive role to play in the prevention, identification and treatment of rotavirus diarrhoea.

	Classification C: severe dehydration	Classification B: some dehydration	Classification A: no visible dehydration
Signs of classification	Two of the signs	Two of the signs, but not severe dehydration	None of the signs
Level of consciousness	Lethargic or unconscious	Restless or irritable	Well alert
Sunken eyes	Sunken eyes	Sunken eyes	Eyes are not sunken
Ability to drink	Drinks poorly, or is not able to drink	Thirsty, drinks eagerly	Drinks normally. There is not excessive thirst
Skin pinch (turgor)	There is a severe decrease in skin turgor. Skin pinch returns > 2 seconds	There is a moderate decrease in skin turgor. Skin pinch returns in < 2 seconds	Skin pinch returns immediately



Administration of IV fluids to a severely dehydrated child <sup>20</sup>		
Age (Months)	First, give 30ml/kg in:	Then, give 70ml/kg in:
< 12 months	1 hour <sup>a</sup>	5 hours <sup>a</sup>
> 12 months	30 minutes <sup>a</sup>	2.5 hours <sup>a</sup>

<sup>a</sup> Repeat if the radial pulse is still very weak or not detectable

\*A homemade sugar and salt solution may be used if an oral rehydration solution is not available<sup>14</sup>:



**Homemade sugar and salt solution**

½ level teaspoon of table salt plus  
8 level teaspoons of sugar dissolved in 1 litre boiled and then cooled water  
(1 level teaspoon = 5 ml)

**Supplemental zinc**

**The WHO<sup>15</sup> recommends an oral zinc intake for 10-14 days for all episodes of diarrhoea:**

**≤ 6 months: 10 mg/day**  
**> 6 months: 20 mg/day**

IV: intravenously, NGT: Nasogastric Tube, ORS: oral rehydration solution, WHO: World Health Organization

Figure 2. Assessment of dehydration and fluid therapy in patients with diarrhoea<sup>9,22,23,24</sup>

**Table III.** Supportive treatment for rotavirus gastroenteritis<sup>1</sup>

	Use	Avoid
<b>Primary treatment: rehydration therapy</b> (Refer to Figure 2)	<ul style="list-style-type: none"> <li>• ORS, IV and nasogastric tubes</li> <li>• Recommend frequent small doses of ORS, even if the patient is vomiting</li> <li>• Continue breastfeeding during rehydration treatment</li> <li>• Rotavirus can cause temporary lactase deficiency in some non-breastfeeding infants. Lactose-free formulas may help</li> </ul>	<ul style="list-style-type: none"> <li>• Avoid juices and other liquids that are high in complex or simple sugars, as the osmotic overload may worsen the diarrhoea</li> </ul>
<b>Nutritional supplementation</b>	<ul style="list-style-type: none"> <li>• Supplemental zinc</li> <li>• Electrolytes</li> <li>• Introduce refeeding as early as possible, as rehydration fluids are low in kilojoules<sup>4</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Avoid fluids that contain mostly sugar and that lack significant electrolyte supplementation, e.g. cola</li> <li>• Raw vegetables, fruit, green vegetables, spicy food and frozen foods and drinks</li> </ul>
<b>Adjuncts to rehydration</b>	<ul style="list-style-type: none"> <li>• Diosmectite</li> <li>• Probiotics</li> </ul>	<ul style="list-style-type: none"> <li>• Do not use any anti-diarrhoeal agents</li> </ul>

IV: intravenous, ORS: oral rehydration solution

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