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Rotavirus Infections
Guidelines for Treatment and Prevention

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Contents

Abstract

The classification of rotaviruses as well as the pathogenesis and the diagnosis of rotavirus infections are briefly reviewed. Treatment of rotavirus disease consists mainly of oral or intravenous rehydration, using World Health Organization-recommended oral rehydration solutions or lactated Ringer's solutions, respectively. Specific antivirals have been tried in animal models but are not used for human treatment at present. The epidemiology of rotaviruses is complex as at any one time and in any geographical area different types co-circulate. The development of rotavirus candidate vaccines is reviewed, one of which, the tetravalent, rhesus rotavirus-based human reassortant vaccine, was licensed for universal use in the US in 1998. Its implementation requires careful surveillance of co-circulating rotavirus types (molecular epidemiology) as well as of any potential adverse effects not previously detected.

Rotaviruses are the major cause of infantile gastroenteritis worldwide and also the causative agents of acute diarrhoea in the young of many mammalian species, e.g. cows, pigs and sheep; they have also been isolated from birds, e.g fowl, pigeon.

Rotaviruses are a genus of the *Reoviridae* family and possess a genome of 11 segments of double stranded RNA. The wheel-like structure of the double shelled particle as seen by electron microscopy is pathognomonic.[1]

1. Classification of Rotaviruses

A classification scheme for rotaviruses has been derived from the immunological reactivities of their main structural components: viral protein VP6 forms the inner capsid and carries group- and subgroup-specific determinants. So far, 5 groups (A to E) have been confirmed by complete cross-reactivities, groups F and G are likely to be new groups. Within group A, 4 subgroups (I; II; I+II; nonI, nonII) have been differentiated.

Viral proteins VP4 and VP7, both forming the outer capsid, carry serotype-specifying determinants which also elicit the production of neutralising antibodies in the infected host. Accordingly, a dual classification scheme, similar to that developed for influenza viruses, has been established. It differentiates glycoprotein (G) types (VP7-specific) and protease sensitive protein (P) types (VP4-specific). So far, 14 different G types and more than 20 P types have been distinguished, indicating extensive genomic and antigenic diversity within group A rotaviruses.[1] As VP4 and VP7 are coded for by different RNA segments (RNA4, and RNA7, 8 or 9, respectively), various combinations of P and G types can be observed *in vivo* and *in vitro*, both in animals and in humans.[1,2]

2. Pathogenesis

Rotaviruses infect the mature epithelial cells at the tips of the villi of the small intestine. The VP4 molecule of the virus interacts with the cellular receptor which has not been fully characterised but which contains sialic acid. Replication occurs exclusively in the cytoplasm. As a consequence of virus replication and virus shedding, cells are lysed and the villous tips become atrophic and unable to absorb fluid and nutrients. However, the villous atrophy is counteracted by a reactive crypt hyperplasia. Diarrhoea is caused by both: reduction of absorption through the necrotic villous epithelia and secretory hyperactivity of the stimulated crypt cells.[2,3] Recently, the nonstructural rotavirus protein NSP4 (coded for by RNA 10) has been identified as a viral enterotoxin as it affects intracellular Ca^{2+} levels.[4-6] However, the significance of this protein for the development of diarrhoea in some animal models is still under discussion[7] and for pathogenicity in humans remains to be demonstrated.

After primary rotavirus infection a mainly serotype-specific humoral immune response is elicited, but partial protection also develops against subsequent rotavirus infections by other serotypes.[8,9] After 2 or more natural infections, subsequent infections will remain asymptomatic even if they are heterotypic to the previous infections.[9] The exact correlates of protection remain to be determined, but are most likely high levels of virus-specific copro-antibodies of the immunoglobulin (Ig) A subclass.[8-10]

3. Clinical Symptoms and Diagnosis

After a short incubation period of 1 to 2 days the onset of the illness is sudden and characterised by watery diarrhoea lasting from 4 to 7 days, vomiting and rapid dehydration; however, also mild and inapparent infections can occur.

Diagnosis of the infection is relatively easy as high numbers of virus particles are shed in the faeces (up to 10^{11} virus particles/ml at the peak of the diarrhoea). The main diagnostic techniques are enzyme-linked immunosorbent assay (ELISA), passive particle agglutination test and also direct electron microscopy.

4. Treatment

Treatment is by oral, intravenous or subcutaneous rehydration. The formula usually employed for oral rehydration solutions (ORS) has been accepted and is recommended by the World Health Organization (WHO), and consists of an isotonic salt solution supplemented by glucose (see table I).[11] More recently, the use of a reduced osmolarity ORS, known as 'ORS Light' (see table I), has also been shown to be therapeutically effective.[11] Therapy with rice water (obtained after mixing rice powder at 50 g/L in water and boiling) is widely used in developing countries but this has not been shown to have a clinical advantage over application of the WHO ORS formulae.[12,13] 50 to 100 ml/kg of ORS should be given within 4 hours of the patient presenting with diarrhoea, depending on the degree of dehydration.[14]

In patients with very severe vomiting when oral rehydration is not possible, intravenous fluid replacement should be used and this should consist of lactated Ringer's, normal saline or a similar solution (see table II).[14,15] Intravenous fluid replacement should be given at a rate of 20 ml/kg/h until the patient's pulse, perfusion and mental status have returned to normal. This should be followed by 50 to 100 ml/kg of ORS within 4 hours

Table I. Oral rehydration solutions (ORS) for the treatment of rotavirus-related diarrhoea (after International Study Group on reduced-osmolarity ORS solutions,[11] with permission)

	WHO ORS	Reduced osmolarity WHO ORS ('ORS light')
Composition (mmol/L)		
Sodium	90	60
Potassium	20	20
Chloride	80	50
Citrate	10	10
Glucose	111	84
Total osmolarity (mmol/L)	311	224
Prepare by dissolving the following (g/L of water)		
NaCl (Mw58.4)	3.5	1.75
KCl (Mw74.6)	1.5	1.5
$C_6H_5Na_3O_7.2H_2O$ (Mw294.1)	2.9	2.9
Glucose (Mw180.2)	20	15

Mw = molecular weight; **WHO** = World Health Organization.

of the patient presenting. Where intravenous administration is not possible, large volumes of fluid can also be given subcutaneously by hypodermoclysis.[15]

It has been shown that liquid deficits are corrected more rapidly by oral compared with intravenous application.[16,17] In an animal model (piglets) the addition of L-glutamine to the ORS has been shown to improve fluid absorption.[18] Oral immunoglobulin (300 mg/kg of human serum immunoglobulin preparation, administered at 50 mg/ml in 5% glucose solution) seems to reduce the duration of diarrhoea and virus shedding.[19,20] However, use of oral immunoglobulin has not yet become part of a standard procedure. Poor nutrition is a risk factor for the development of severe diarrhoea, and sufficient calorie intake during rehydration aids recovery.[21,22] The addition of 5×10^9 colony forming units of *Lactobacillus* strain GG or of other lactic acid bacteria to ORS or ORS Light (table I) led to significant shortening in the duration of diarrhoea, compared with control patients treated with the corresponding ORS alone.[17,23]

Drug therapy in rotavirus gastroenteritis is generally not advisable. Antibacterials are ineffective. The antimobility drugs codeine phosphate, diphenoxylate and loperamide may reduce fluid loss, but carry the risk of causing ileus or vomiting; they are not recommended for use in young children as severe complications (over dosage, abdominal distention, ileus) have been seen with the use of these drugs.[15] Bismuth salicylate 100 to 150 mg/kg/day was shown to be beneficial in reducing stool frequency and volume, and in improving clinical wellbeing.[24,25] The drug, however, did not affect the clearance of rotaviruses in a significant way.[24]

Antiviral therapy has been tried experimentally. Chelating agents (those capturing calcium ions)

Table II. Composition of solutions used for intravenous rehydration (including normal plasma values)[15]

	Electrolyte concentrations in mmol/L				
	Na^+	K^+	lactate	Cl^-	Ca^{2+}
Intravenous fluids					
Physiological saline[a]	150			50	
Ringer's solution	147	4		156	2.2
Ringer's lactate solution	131	5	29	111	2
Normal plasma values	142	4.5	26	103	2.5

a 0.9% sodium chloride.

are known to destabilise the outer capsid of rotaviruses and, thus, reduce their infectivity. One agent acting in this way, clioquinol, has been shown to decrease diarrhoeal symptoms significantly in a mouse model.[26] As the full viral infectivity requires proteolytic cleavage of the outer capsid protein VP4,[1] protease inhibitors (leupeptin, pentamidine, etc.) decrease the infectivity of rotavirus particle progeny and have been shown to reduce virus replication *in vitro* and *in vivo*.[27,28] Rotavirus IgA antibodies and trypsin inhibitors in breast milk seem to provide some protection in breast-fed children.[28] As *N*-acetyl neuraminic acid (sialic acid) residues form part of the rotavirus receptor, these small molecules can prevent viral adsorption and were found to influence the severity of disease in a mouse model.[29,30] Adenosine analogues have been shown to inhibit rotavirus replication *in vitro*, but do not produce a major effect *in vivo* in animal models.[31,32]

5. Epidemiology and Prevention

Transmission of rotaviruses is primarily faecooral, and viruses are shed in large numbers during acute diarrhoea. Resistance to physical inactivation, particularly on fomites,[33] and the fact that very few particles are needed to initiate infection and disease, explains why rotaviruses spread easily under conditions of overcrowding and poor hygiene, mainly in institutional settings (e.g. hospitals, daycare centres, etc.). Effective disinfection of contaminated materials[34-36] and careful handwashing procedures help to contain infections. The most effective products for surface decontamination are quaternary ammonium compounds in combination with ≥40% alcohol, 10% hydrochloric acid (for use for toilets) or chlorine-based disinfectants with free chlorine at a concentration of >20 000 ppm. The use of pure phenolic disinfectants should be discouraged.[36] People visiting infant and child patients should not visit other patients and visits to hospitalised patients by children should be restricted.[36]

The epidemiology of rotaviruses is very complex as at any one time and in any geographical area co-circulation of rotaviruses of different G and P types has been found.[37-39] Usually, ≥95% of co-circulating rotavirus strains are G1 to G4 types, but other G types may be represented at high frequencies, particularly in tropical regions,[39] e.g. G9 and G10 viruses in India[40] and G5 viruses in Brazil.[39] Recently G9 viruses have also been found to have become epidemic strains in the US[41] and in the UK (Iturriza, Desselberger and Gray, personal communication).

6. Vaccine Development

As rotavirus infections have been recognised worldwide as a major viral infection in childhood associated with more than 800 000 cases of infantile death worldwide, mainly in developing countries,[42] the development of vaccine candidates has been ongoing since the early 1980s (for a review see Desselberger[43]). Recently, a tetravalent, rhesus rotavirus (RRV)-based, human reassortant vaccine, carrying the VP7 molecules of the human G types G1, G2 and G4 in RRV monoreassortants and G3 in the RRV parent strain, has been shown to provide ≥80% protection from severe disease including dehydration.[44-46] The adverse effects of vaccination are minimal. The tetravalent RRV preparation was licensed as a universal vaccine by the US Food and Drug Administration in August 1998 and licensure for Europe is pending. Recommendations on the use of the new vaccine have been made by the US Advisory Committee on Immunization Practices (ACIP) and were published in March 1999.[47] Recently, the US Federal Centre for Disease Control and Prevention has called for a temporary halt of the universal use of the vaccine, because of a suggestive link between the application of the vaccine and small intestinal intussusception. The agency's recommendation has no enforcement power but doctors are likely to follow such warnings. The suspension has been requested until November 1999 when a new study on implementation surveillance will be completed.[48]

Once this vaccine begins to be widely used, its effectiveness will need to be carefully monitored in large implementation studies. It is possible that

the antigenicity of the vaccine strains does not fully match the antigen composition of locally circulating wild type strains, and such a constellation may affect vaccine efficacy. For example, human rotavirus isolates have been obtained in India which are very similar to isolates found in cattle, but unusual in humans.[40] Therefore, epidemiological surveillance including G and P typing will be crucial in the monitoring process. It is planned to include rotavirus vaccination into the Extended Programme of Immunisation promoted by the WHO.

Clearly there is a long way to go from licensure to achieving disease reduction: the vaccine must be recommended by major immunisation advisory committees; it has to be cost effective and financially viable (carried by both the public and private sectors); it has to be integrated into existing vaccination schedules; it requires promotion; it has to find widespread parental acceptance and has to achieve a high level of overall coverage.[49] The long term efficacy and effectiveness of these novel vaccines remains to be evaluated. Alternative approaches to vaccine development, like parenteral application of virus-like particles,[50,51] microencapsulation of virus particles,[52] addition of lactic acid bacteria to the vaccine[53] and DNA-based vaccine formulae[54-56] are still in their experimental stages.

7. Conclusions

Treatment of rotavirus infections is mainly by oral or intravenous rehydration using ORS or lactated Ringer's or similar solutions, respectively. The use of antimotility drugs in children is not recommended. Specific antiviral treatment has been studied in animal models, but so far no such treatment has been accepted for use in infants and children.

A tetravalent, RRV-based human reassortant rotavirus vaccine covering G1 to G4 rotavirus types has recently been licensed in the US. It's implementation requires careful surveillance of co-circulation rotavirus G and P types and has met some difficulties with possible, previously undetected adverse effects.

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