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Rotaviral gastroenteritis in infants and small children

Ioan GHERGHINA, Professor of Pediatrics, MD, PhD[a,b];
Dumitru MATEI, Professor of Family Medicine, MD, PhD[a,c];
Eliza CINTEZA, Assistant Professor, MD, PhD[a,b]; Mihai CRAIU, Lecturer, MD, PhD[a,b];
Alexis COCHINO, Assistant Professor, MD[a,b]; Mirela COVACESCU, Lecturer, MD[a,b];
Diana DAMIAN, Resident, Neonatology[a]; Doina CANA, Biologist[a];
Denisa LEU, Microbiologist[a]

[a]Institute for Mother and Child Health "Alfred Rusescu"
[b]2nd Pediatrics Department, "Carol Davila" University of Medicine and Pharmacy
[c]Family Medicine Department, "Carol Davila" University of Medicine and Pharmacy

ABSTRACT

The Rotavirus is one of the most important etiological agents in infectious gastroenteritis in infants and small children. The authors present recently published data regarding the rotavirus gastroenteritis and clinical aspects from their practice. The article is concluding with discussion upon particular therapeutic strategies regarding the rotavirus prophylaxis using the licensed vaccines.

Key words: Rotavirus, gastroenteritis, infants

INTRODUCTION

Rotavirus is the most important pathogen in gastroenteritis in infants and small children, worldwide. This regards both severity and frequency of infection: rotavirus is generating more than 111 million episodes of acute gastroenteritis annually. Almost all children will be infected with rotavirus during the first 5 years of life, irrespective social and economical of a given family. More than 600,000 children die annually worldwide as result of infection with rotavirus, most cases occurring in developing countries (80%). Many others require hospitalization generating direct and indirect costs over 1 billion dollars a year. As a result, the infection with this virus represents a public health issue. Optimal approach is represented by rapid and efficient treatment, in sick children and prophylaxis in healthy infants (1-3).

Address for correspondence:
Eliza Cinteza, MD, PhD, "Alfred Rusescu" Institute for Mother and Child Health, 120 Lacul Tei Blvd., District 2, Bucharest, Romania
email address: elizacinteza@yahoo.com

In developed countries, with moderate climate, rotavirus infection has significant seasonality, most cases being documented during cold season. In developing countries, rotavirus infection seems to have the same frequency all year long.

Rotavirus transmission is mainly by fecal-oral route (1,2,4,5). Rotaviruses are resistant in the environment and also to common disinfectants recommended for bacteria and enteropathogenetic protozoa. At room temperature they preserve infective abilities for several months. They also retain infectivity at low temperatures (even below freezing point), being able to remain a long time on surfaces, in drinkable or residual water, which partly explains the occurrence of infections, including nosocomial ones. Excretion period after the clinical recovery can be prolonged as long as 7-14 days and may be a source of infection. Another explanation for these frequent infections resides in the infecting capacity of rotavirus even in an extreme small innoculus. The minimal infecting amount is estimated to be fewer than 10 particles (1). Once ingested, the virus, that is resistant to acid gastric environment, colonizes epithelial cells in the upper two-thirds of the small intestine. During incubation, which lasts from 18 to 36 hours, rotaviruses present a rapid multiplication rate. The initial innoculus of 10 viral particles generates millions of viruses that invade and destroy the microvillar enterocytes (6). This process is also influenced by simultaneous toxin production. This aggressive toxin, NSP 4, along with destruction of the epithelial cells contributes to genesis of entherotoxic diarrhea, a condition that has a complex mechanism and leads to massive fluid loss. Extreme depletion of water and electrolytes, can result in hypovolemic shock. Without appropriate fluid replacement this severe condition can be lethal in 2-3 days.

Through frequent stools a massive excretion is generated. It is estimated at 1012 viral particles per gram of feces (1).

The rotavirus produces diarrhea through several mechanisms:

- malabsorption, secondary to destruction of the microvillar enterocytes;
- microvillus ischemia with the activation of the enteric nervous system;
- the fosterage of intestinal secretion by the nonstructural protein NSP4 that has extremely potent enterotoxin properties (5).

After 5 to 7 days, the diarrheic syndrome subsides; stools are regaining normal aspects, as result of intestinal epithelium recovery. The natural immune response triggered by first infection is efficient against subsequent rotavirus enteritis episodes, mainly against severe form of disease. ❑

THE STRUCTURE OF THE ROTAVIRUS

The rotavirus has been identified, for the first time, as the cause of an illness in humans, in 1973, by Ruth Bishop a young microbiologist that was working at the gastro-intestinal department at the Royal Children's Hospital in Melbourne, Australia. The identification has been made on a fragment of intestinal mucous membrane, examined at the microscope. The rotaviruses belong to Reoviridae family and are RNA viruses, spherical, no tire, with the appearance of a wheel in section, 70 μm in diameter.

The viral capsule is made up of 3 concentrically placed protein layers, that go around the genome formed from 11 RNA segments, each containing only one gene, that codes the synthesis for two types of protein: structural (that makes up the virus) and non-structural (that are being synthesized in infected cells). Structural proteins are called VP, and are numbered as such: VP1, VP 2, VP3, VP4, VP6, and VP7. Non-structural proteins are called NSP, there are also 6 numbered as such: NSP1,….NSP6.

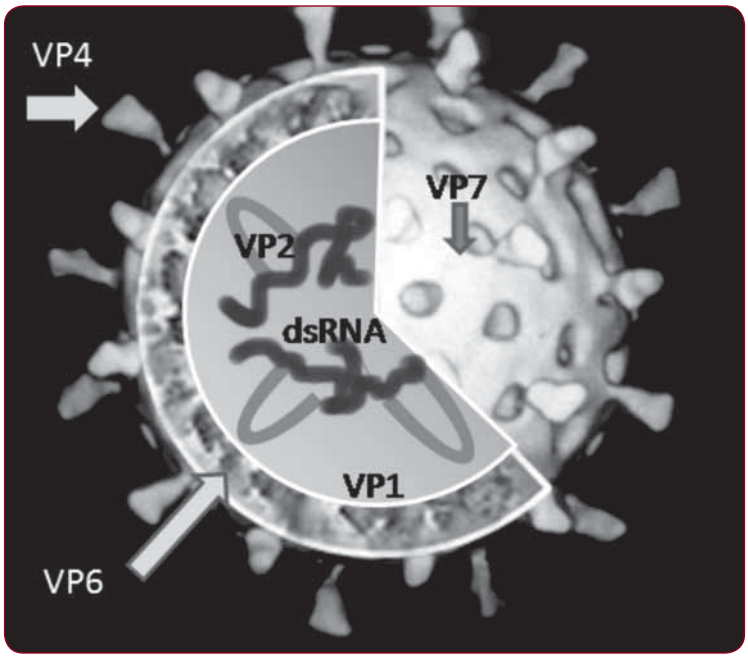

FIGURE 1. Structure of Rotavirus (from Wikipedia, with permission of Graham Colm)

These are synthesized after the virus has entered the cell. The external layer of the capsule is formed from VP4 and VP7. The intermediate layer is structured from VP6 and the viral core from VP2, VP1 and VP3 enzymes. The viral core contains all the enzymatic activity necessary so that the messenger RNA may rewrite the information from all 11 segments of the viral genome (1,6), that leads to the copying of the viral genes.

The VP7 protein, that forms the external layer, is covered by "tops", formed from VP4. These proteins play a very important role in the immune answer of the host and, as well, in the production of the vaccine.

VP4 facilitates the penetration of the virus in the cell, as well as VP5 and VP8 that result from the cleavage of VP4 into the host body (6).

Out of the 42 types of identified rotavirus following VP4 and VP7 combinations, only 4 or 5 are responsible for over 90% of the rotaviral diarrhea, respectively G1-4 and G9 types (for human diarrhea), cumulated with other 3 types, more recently discovered: G12, G8 and G5.

Year	Total number of hospitalizations	Total number of diarrheic diseases	%
2007	8,975	1,556	17.33
2008 (8 months)	5,796	1,068	18.42
Total	14,771	2,624	17.76

TABLE 1. Gastroenteritis episodes in IMCH "A. Rusescu"

Viral genotype G1 is the most spread worldwide.

A study was made in a Brazilian village, on 648 children with diarrhea, under the age of 5, during a 3 year period of time. 32% had rotavirus enteritis. 78% of these children had genotype G9, predominantly associated with genotype P. Genotype G1 has as a dominant biological trait the maintaining of this strain dominantly throughout several consecutive seasons (7).

In this study it has been shown for the first time that genotype G9 has epidemiological characteristics similar to G1. G2 and G3 rotaviruses or P have not been detected during this study and there are not clearly known mechanisms of re-emerging disease (8). In conclusion, antiviral vaccine for rotavirus should provide protection against genotype G9.

There are at least 25 types of VP4, three of which may be present in humans: P8, P4 and P6. The most common association between VP7 and VP4 is G1P8, G3P8, G4P8, G9P8, G9P6 and G2P4.

In Institute for Mother and Child Health (IMCH) "Alfred Rusescu" Bucharest, in 1990, was conducted a clinical trial on etiology of diarrhea in hospitalized infants. These data are estimating a frequency of rotavirus infections of 39% (5). Other studies were performed later (9) in IMCH, with similar results.

Since 2005, the quick rotavirus tests tend to become a routine medical procedure, Tabel 1, Tabel 2, Tabel 3. ❑

	Viral		Bacterial	Other causes	Neutrophils (stools)	Unknown
	Rotavirus	Adenovirus				
Total	305	20	164	10	980	1145
2,624	11.62%	0.76%	6.25%	0.38%	37.34%	43.63%

TABEL 2. Etiology of enteritis in admitted patients IMCH "A. Rusescu"

Presented Oct 2008-March 2009	Admitted	Specific evaluation	Stool cultures	Viral etiology eval	R and A eval	R eval	N eval
13,726	3,432	2,976	2,204	1,078	982	90	6
Positive			335 EC 195 (8.84%) 15.19% ShF 4(0.18%) Sal DO 6 (0.27%) Sal BO 5(0.26%) Citro 37(1.67%) Yers 2(0.09%) Candida 81(3.67%)	450 41.74% R 380 (35.25%); A 34 (3.15%); concomitant R&A10 (0.9%); N 2 (0.18%%)			

TABEL 3. Etiology of enteritis in presented patients to the Emergency Room IMCH "A. Rusescu"

Legend: R – Rotavirus; A – Adenovirus; N – Norovirus; eval – evaluation; EC – Escherichia Coli, ShF – Shigella Flexneri, Sal DO – Salmonella DO; Sal BO – Salmonella BO, Citro – Citrobacter; Yers – Yersinia

CLINICAL ASPECTS IN ROTAVIRAL GASTROENTEROCOLITIS

Diarrhea episodes with proven viral etiology (rotavirus, adenovirus) had an entero-toxic clinical appearance (5,10):

- Vomiting and frequent watery stools in 90% of children;
- Moderate or high fever;
- Abdominal meteorism;
- Acute dehydration syndrome (ADS) (mild or moderate with an estimated fluid deficit of 3-10% of body weight) in 50% of cases;
- Severe ADS (with an estimated fluid deficit of more than 10% of body weight) in 2% of the cases;
- alteration of the general status. ❑

SEVERAL TREATMENT GUIDELINES IN ROTAVIRUS GASTROENTERITIS WERE PUBLISHED UNTIL NOW (11-15)

Treatment goals can be achieved by targeting various mechanisms:

1. Pathogenical

a. Restoration of hydro-electrolytic and acid-base status

– Orally in 80% of the cases

– Endovenous fluid replacement

b. Antisecretory treatment: racecadotril

2. Dietary: Early breast or formula feeding – after 4 hours

3. Etiological: usually no antibiotics; in documented bacterial enteric infections antibiotic treatment according to sensitivity testing.

4. Symptomatic: diosmectite

5. Intravenous Immune Globulin (IVIG): in selected severe cases ❑

EVOLUTION

In our data

- Rapid favorable outcome in 88% of cases, with hospitalization period of 3 to 5 days.
- Slowly favorable evolution in 6% of cases
- Recurrence : 2%
- Post-enteritis syndrome: 4%
- Deaths: none occurred ❑

CLINICAL CASE

PVA, 22 months old toddler, was admitted for high fever (39.5°C), relative frequent (4-5 times a day) diarrheic stools, with large amounts of mucus, severe alteration of the patient's general status, lack of appetite, moderate ADS with an estimated fluid deficit of 7-8%.

Clinical picture: enterocolitis associated with herpangina and interstitial pneumonia.

Laboratory findings: cultures from stools - negative, stools cytology: neutrophils >10/field, rotavirus and adenovirus negative, hyponatremia.

Treatment was started with oral rehydration (with ORS), low-lactose diet, trimetoprim sulphametoxazole 240 mg twice a day, mannitol and intravenous ampicillin and gentamicin.

Favorable outcome. Within the 3rd day: no fever, well hydrated, good appetite, two "transition" stools. He was discharged from hospital in the 4th day.

In the same day he started vomiting, passed very frequent watery stools (10-15/day), fever recurred (for 36 hours) and presented weight loss. Rotavirus test, repeated, was positive. It was considered a nosocomial infection. He started again the rehydration therapy, mannitol, acetaminophen, aminoacids solution. After 12 hours of severe disease course he received also IVIG (Humaglobin 400mg/kg two consecutive days). Within 12 hours, the fever started to fade and in 24 hours he had no fever. After 3 days he presented 5-6 stools a day, and the appetite normalized.

Conclusion: The case presented is a severe type of nosocomial rotavirus enteritis in a 22 months old child with adequate nutritional status, high socio-economical standard, without daycare attendance. Apparently, the severe evolution has been stopped by IVIG.

The **antiviral immunity,** after three decades of research, it remains uncertain. Recurrent infections seem to bring about resistance to the virus; nevertheless, following a natural infection with rotavirus, immune resistance is incomplete. This immune resistance depends on the length of time between two exposures, on the properties of the rotavirus involved in infection and also, on the immune status of the host at the time of infection. The best protection has been encountered in developed countries, especially when the re-infection has been made by a similar serotype as the initial one.

In developing countries, where there are several G types of rotavirus moving around in the same time, many children have several infections with rotavirus in the first year of life. The

antibodies that appear following the natural infection are of different types. The presence of IgAs (secretor) seems to have crucial importance for local protection. The levels of IgAs in the stool are correlated with the degree of protection. In case of patients with a low IgA, the resistance to rotaviral infection is counterbalanced by a high level of IgG in the serum. Other non characteristic means of immune defense are Nk Ltc cells, citokins and other chemical mediators.

VP6 is the most important immunomodulating protein within the virus capsid. Nevertheless, the antibodies for VP4 and VP7 are crucial, so that the protection can be possible as far as the intestinal mucosa is concerned. It has been proven that anti VP4 antibodies prevent the sticking of the virus to the target cell. Anti VP6 antibodies neutralize the intracellular virus during the transcytosis process from the basolateral surface to the apical one, thus inhibiting the replicative cycle of the rotavirus.

The current prophylactic treatment is the result of the active immunization.

There have been several types of antirotavirus vaccines used:

- Vaccine based on an attenuated bovine rotavirus strain, that offers protection against severe infections is inefficient
- Multicomponent vaccine, with both human and animal strains, to which one of the animal genes that encodes a neutralizing protein has been replaced with the human rotavirus gene – Rotashield (quadrivalent vaccine). Intussusception has been noted.
- RotaTeq vaccine – pentavalent vaccine from bovine rotavirus was not associated with intussusception. It proved to be efficient, 98.3% for severe gastroenterocolitis and 68.0% in all rotavirus gastroenterocolitis (16).
- Riix 4414 vaccine (Rotarix) uses attenuated human virus strains (89-12). It must be administered orally in 2-dose series. It has proven its efficacy in 89% out of the total number of cases and 100% in severe forms of the disease. It was not associated with intussusception (17, 18).
- The anti rotavirus human vaccine is efficient in 42% of gastroenteritis cases.

The routine immunization with Rotavirus vaccine is routinely recommended by the American Academy of Pediatrics. Two vaccines were approved for this purpose: Rotateq (first introduced) and Rotarix. There is no preference for one of them. Both are administered orally, first in a 3-dose series with doses administered at 2, 4, and 6 months of age. The second must be administrated in a 2-dose series, at 2 and 4 months of age. "The first dose of rotavirus vaccine should be administered from 6 weeks through 14 weeks, 6 days of age. The minimum interval between doses of rotavirus vaccine is 4 weeks. All doses should be administered by 8 months, 0 days of age" (19). ❑

THE PASSIVE ANTIROTAVIRAL IMMUNITY

The passive transfer of IgAs through breast milk ensures the protection of the infant against a wide range of infections, including the one caused by the rotavirus (20,21). The decline of the antiviral antibodies during the immunologic gap and mostly after the age of 6 months increases the risk of a rotavirus infection.

The colostrums (8 ml/kg) may be used as a source of human immunoglobulins in oral administration (1).

Probiotics have proven to have a positive effect in viral diarrhea, especially the rotaviral ones, reducing the evolution with 24 hours. They demonstrate the rapid therapeutic effect and the cost efficiency (22) in children more than in adults (23). ❑

CONCLUSIONS

1. Rotavirus gastroenteritis represents a public health issue because of high prevalence, frequent severe episodes and huge costs.
2. An efficient prophylactic strategy is represented by vaccination of infants under the age of 6 months.
3. Passive immunotherapy (including IVIG) may be used in severe, potentially lethal cases. ❑

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