

Rotavirus

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Rotaviruses

History :

Rotaviruses (RVs) were recognized as a major cause of acute

Gas-TroentEritis (AGE) in infants and young children in 1973.

Before that year RVs had already been discovered during the last 40 years an enormous amount of basic research on RV structure, replication, pathogenesis and immune responses has accumulated.

Due to modern diagnostic techniques the molecular epidemiology of RVs has been extensively explored. Recently, two live attenuated RV vaccines have been licensed in many countries and are increasingly being applied in universal vaccination programs.

Epidemic :

Rotavirus infection causes severe gastroenteritis in infants and young children worldwide. Globally, there are at least 600,000 children < 5 years old who die from diarrhea with severe dehydration and electrolyte and acid-base disturbances each year . The majority of rotavirus-related deaths (> 80%) are found in resource-limited countries, such as those found in southern Asia and sub-Saharan Africa . Most childhood rotavirus infections occur by 5 years of age and are unrelated to community sanitary conditions, home location of the infected children, or the greater socioeconomic status of the affected countries . Therefore, the overall incidence of rotavirus infection would not change even if improvements in water supplies, sanitation, personal nutrition, housing, and public health education were made, suggesting that viral transmission might occur *via* non-fecal routes . Vaccines are an effective and available measure for combating rotavirus disease and for preventing rotavirus infection .

Acute gastroenteritis is one of the leading causes of childhood mortality worldwide and accounts for 15% of all deaths in younger children. Most of these deaths occur in malnourished infants from countries of lower socioeconomic status and from the disadvantaged rural regions of Africa and Asia .

Whereas the mortality from rotavirus in young children is rare in industrialized countries with higher socioeconomic status, rotavirus disease incidence is similar in countries from both higher and lower socioeconomic levels. Before the rotavirus vaccine was licensed, it had been estimated that rotavirus infection and disease resulted in 220,000 hospitalizations, 1.8 million outpatient visits, and more than 7.1 million children who had episodes of rotavirus-related gastroenteritis annually in industrialized countries .

The introduction of virus :

The Rotavirus genome is composed of 11 double-stranded RNA (dsRNA) segments .

By the electron microscopy , the Rotavirus is observed to have a 70 nm, non-enveloped, icosahedral structure that surrounds a double-stranded RNA genome . The genomic RNA of rotavirus is enclosed in a triple-layered capsid . The virus particle comprises three layers , an inner core ,an intermediate layer ,and an outer later . from the insiae towards the outside , the core is composed of the structural protein vp2 and vp1 (RNA-dependent RNA polymerase).the inner icosahedral capsid have a specific antigen vp6, whereas the outer icosahedral capsid is vp7 .Sixty spikes of VP4 project outward .The VP6 protein forms the middle capsid layer and the VP7 and VP4 proteins are the major outer capsid surface proteins (Fig. 1)

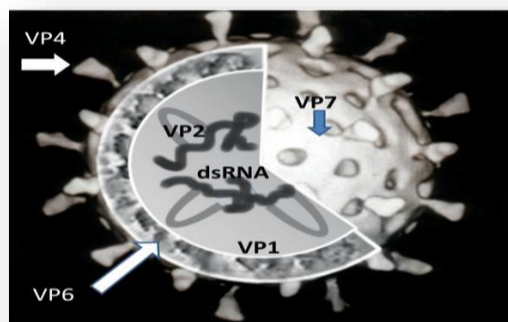


Fig.1 Carton Structure for Rotavirus

Classification :

Rotaviruses constitute the genus *Rotavirus*, and according to the Baltimore classification Rotaviruses one of the 15 genera of *Reoviridae* family, which is subdivided into the sub-families of the *Spinareovirinae* , and *Sedoreovirinae* which the Rotavirus belong to.

Structure and genome :

The RVA genome is approximately 18,500 bp in size and consists of 11 segments of dsRNA which encode 6 structural and 6 non-structural proteins. The genes are monocistronic, except for genome segment 1, which encodes two proteins. The gene segments are between 667 and 3302 bp in length(Fig.2)

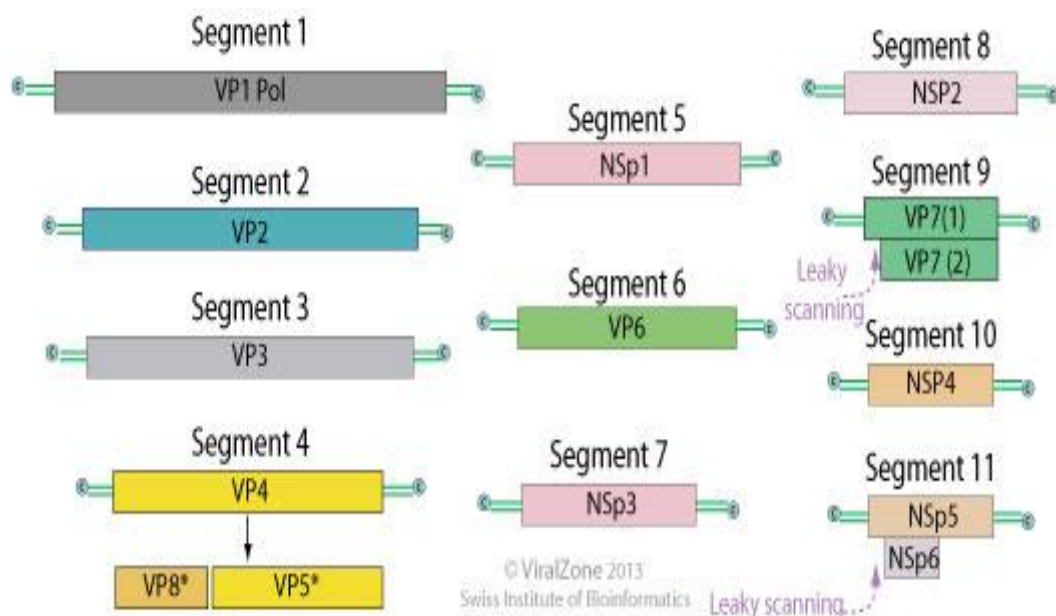


Fig.2 The Rotavirus genome

The RNA is surrounded by a three layered icosahedral protein capsid. Viral particles are up to 76.5 nm in diameter and are not enveloped.

The fully infectious RV particle (=virion) consists of 3 protein layers and is also termed triple-layered particle (TLP). By electron microscopy, TLPs resemble wheels, and this appearance has led to the name of Rotavirus for the genus. Based on cryo-electron microscopy and image reconstruction data the following structure of icosahedral symmetry has been recognized: the single layered particle (SLP = core shell) is formed by 120 molecules of the viral protein 2 (VP2), arranged as 60 dimers in a T = 1 symmetry.

The viral core is surrounded by 260 trimers of VP6, which form the middle layer and constitute double-layered particles (DLPs). VP6 trimers make contact with both the underlying core (VP2) as well as VP7 and VP4 trimers on the outside. The DLPs in turn are covered by 260 trimers of VP7 and 60 spikes of VP4 trimers (=180 molecules) to form the TLPs.

The core shell encloses the viral genome of 11 segments of dsRNA as well as the viral RNA dependent RNA polymerase (RdRp), VP1 and the capping enzyme, VP3. The genomic RNA segments have been proposed to form conical cylinders around the replication complexes. Thus, in actively transcribing double-layered particles (DLPs), a decreased order of the middle (VP6) layer was found to be accompanied by increased order of the core content. The 11 RNA segments have very short completely conserved 5' and 3' terminal nucleotide (nt) sequences, 5'-GGC • • • ACC-3'. The untranslated regions (UTR) of the RNA segments (+ sense) are small: 9–48 nt at the 5' end, and 17–182 nt at the 3' end. The 5' and 3' ends are of partial inverted complementarity and are subject to long range.

Rotavirus genes can be 'rearranged', due to partial nt duplications or deletions of RNA segments generated by special forms of intragenic recombination. Rotaviruses with rearrangements in 3 genes were found to package approximately 1800 additional bp of RNA, i.e. about 10% of the genome, to be replication competent and to be physically and genetically stable. (Fig. 3)

The 11 segment of rotaviruses can reassort their genomes .when two genetically distinct rotaviruses infect one cell and the resulting 22 genome segments end up in different 11 segment combinations in new virions .

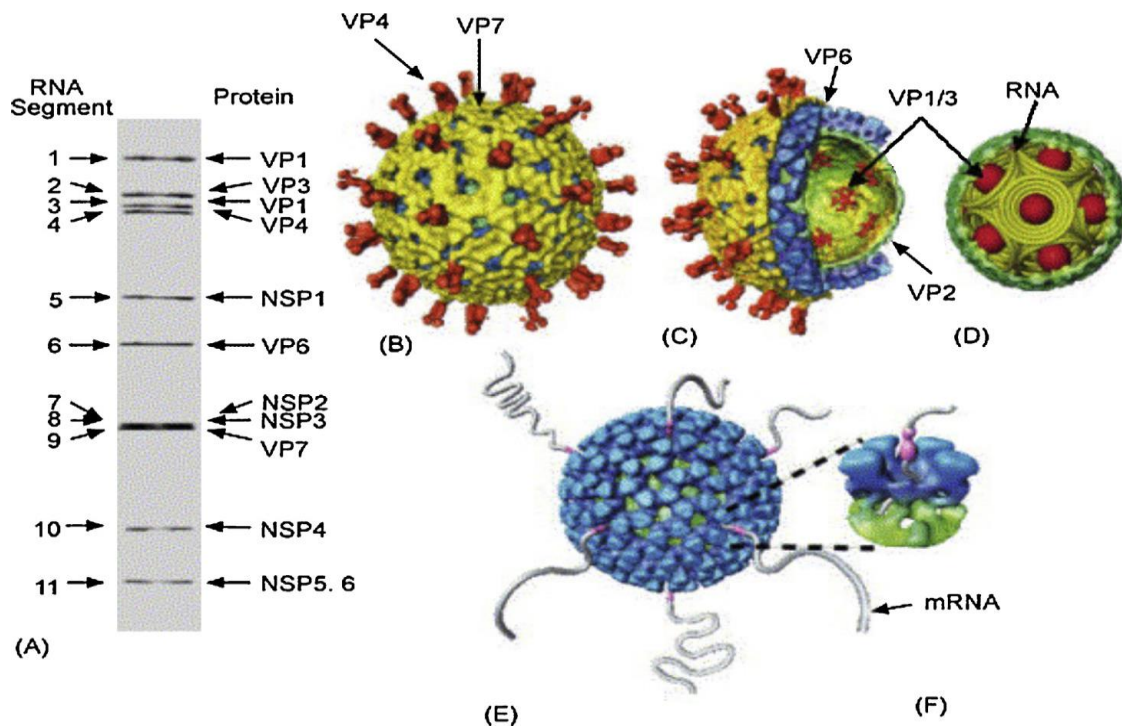


Fig.3 aspects of rotavirus structure

Proteins:

The gene-protein and protein-function assignments have been determined for several RVA strains. Besides the 6 structural proteins (VP1, VP2, VP3, VP4, VP6, VP7), 5–6 non-structural proteins (NSP1–NSP5/6). RVCs do not encode an NSP6.

Table 1:**Gene-protein assignments, protein localization and protein-function**

Genome segment	Size (bp)	Encoded protein	Size (kDa)	Location in virion	Molecules/virion	Functions
1	3302	VP1	125	Core	12	RNA-dependent RNA polymerase
2	2687	VP2	94	Core	120	Stimulates viral RNA replicase
3	2592	VP3	88	Core	12	Guanylyl transferase mRNA capping enzyme
4	2362	VP4	86	Outer layer	180	Cell attachment, virulence
5	1581	NSP1	58	Nonstructural	780	5'RNA binding
6	1356	VP6	44	Middle layer	780	Structural and species-specific antigen
7	1062	VP7	37	Outer layer	Very few	Enhances viral mRNA activity and shut-offs cellular protein synthesis
8	1059	NSP2	36	Nonstructural		NTPase involved in RNA packaging
9	1074	NSP3	34	Nonstructural		Structural and neutralisation antigen
10	751	NSP4	20	Mainly nonstructural		Enterotoxin
11	666	NSP5 NSP6	21	Nonstructural		ssRNA and dsRNA binding modulator of NSP2

Transmission :

Rotaviruses are transmitted primarily by the fecal-oral route, although contaminated surfaces, hands or food may also serve to transmit infection in some cases. Attendance of day childcare centers is a risk factor to get a rotavirus infection. Rotavirus spreads easily among infants and young children. They can also pass rotavirus to family members and other people with whom they have close contact. Children can spread the virus both before and after they become sick with diarrhea. The incubation period is short (1–2 days). Control and prevention measures for the rotavirus include isolating infected children from others, thoroughly cleaning and disinfecting environmental surfaces with effective agents and handwashing before and after contact with infected persons or contaminated surfaces. It is especially affect the small bowel cells as the target organ.

Penetration and Replication Cycle:

The infectious rotavirus particle is made up of three concentric layers of protein, and contains a genome consisting of eleven segments of double-stranded (ds)RNA. The initial cell attachment of rotaviruses is mediated by interactions with specific cellular glycans receptors which contain sialic acid. Such interactions mediates by the VP8* domain of the rotavirus spike protein VP4.

The mechanism of cell penetration of RV particles remains unclear; it may occur by receptor-mediated endocytosis or direct membrane penetration, with solubilization of the outer capsid proteins due to low Ca^{2+} concentrations in endosomes to yield DLPs. Upon infection, the viral RNA-dependent RNA polymerases are activated, resulting in genome transcription and extrusion of the eleven viral mRNAs into the host cytoplasm. The mRNAs direct viral protein synthesis and serve as templates for minus-strand synthesis to yield dsRNAs in the viroplasm.

Viroplasm is function as sites of genome packaging and replication in the infected cell. It is produce progeny cores with replicase activity which the transcription occurs in. These cores are coated with VP6, forming immature DLPs that bud across the membrane of the endoplasmic reticulum, acquiring a transient lipid

membrane which is modified with the ER resident viral glycoproteins NSP4 and VP7. As the particles move towards the interior of the ER cisternae, the transient lipid membrane and the nonstructural protein NSP4 are lost, while the virus surface proteins VP4 and VP7 rearrange to form the outermost virus protein layer, yielding mature infectious triple-layered particles.

Mature virions are released following cell death and associated breakdown of the host plasma membrane. Figure 4 summarized the replication cycle.

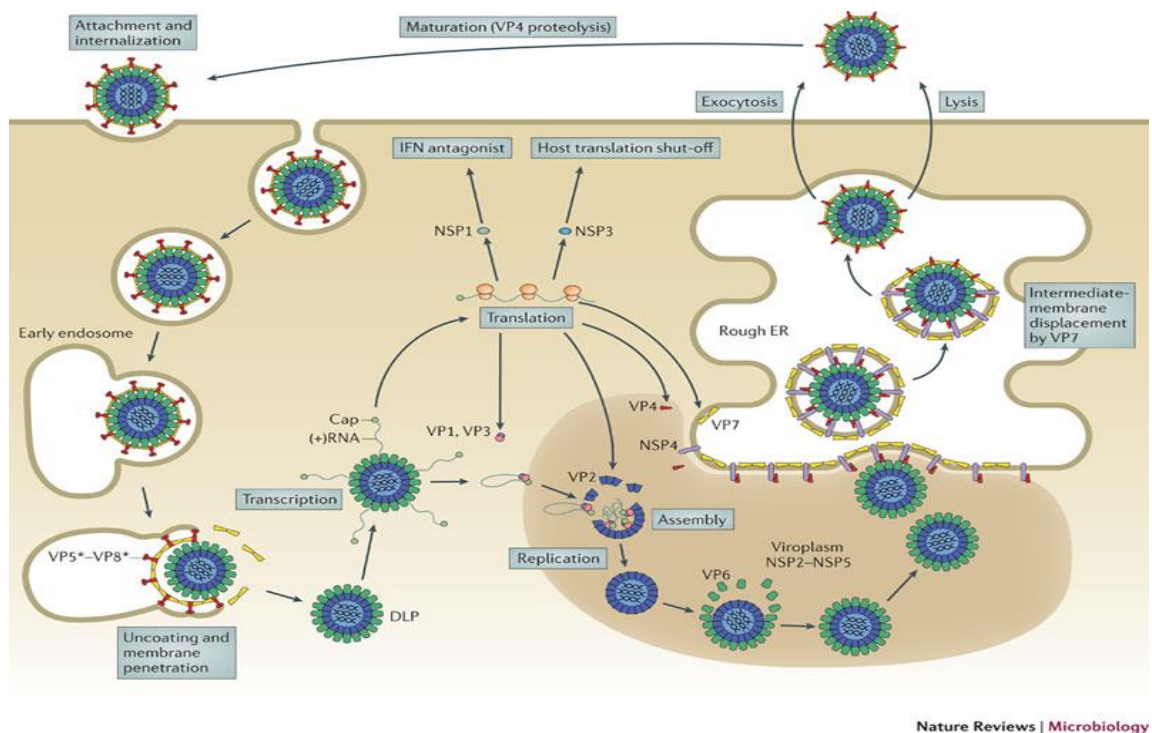


Fig.4 : Penetration and Replication Cycle of the Rotavirus.

Symptoms:

Rotaviruses are a leading cause of severe diarrheal disease and dehydration in infants and young children throughout the world. The virus spreads rapidly, presumably through person-to-person contact, airborne droplets, or possibly contact with contaminated toys. Symptoms usually appear approximately two to three days after infection, and include projectile vomiting and very watery diarrhea, often with fever and abdominal pain.

Diagnosis :

The diagnosis of RV infection is by electron microscopy or ELISA, and more recently by RT-PCR. Of those procedures, ELISA is applied most frequently in the routine diagnostic laboratory (due to the ease of use and speed of obtaining a result). However, RT-PCR, which is highly sensitive and specific and also suitable.

Control the virus and Prevention:

There is no specific drug treatment for rotavirus infection, although oral rehydration therapy is recommended. There are now two new rotavirus vaccines to prevent severe rotavirus disease.

Treatment :

Rotaviruses are a leading cause of severe diarrheal disease and dehydration in infants and young children throughout the world. Most symptomatic episodes occur in young children between the ages of 3 months and 2 years. The virus spreads rapidly, presumably through person-to-person contact, airborne droplets, or possibly contact with contaminated toys. Symptoms usually appear approximately two to three days after infection, and include projectile vomiting and very watery diarrhea, often with fever and abdominal pain. The first infection is usually the worst one.

There is no specific drug treatment for rotavirus infection, although oral rehydration therapy is recommended. There are now two new rotavirus vaccines to prevent severe rotavirus disease. Two rotavirus vaccines, Rotarix and RotaTeq, are in widespread use globally for the prevention of rotavirus gastroenteritis in young infants. Their use has resulted in reductions of infant diarrheal deaths, hospitalizations and incidence of rotavirus gastroenteritis. Thus even in countries where mortality rates for rotavirus gastroenteritis are low, there is a substantial health benefit associated with vaccination.

Deference between RotaTaq and Rotarix vaccine:

	RotaTaq	Rotarix
Type	Pentavalent bovine-human reassortants G1,G2,G3,G4,P1{8}	Monoovalent human strain GiP {8}
Dosage	3 doses , orally	2 doses , orally
Age of administration	1st dose by 6-12 weeks. Subsequent doses at 4-10 week internals . Last dose not after 32 week	1st doses between 6-14 week .2nd dose 14-24 week . Interval between doses not less than 4 week
Formulation	Liquid	Lypophilized ; reconstituted
Efficacy versus hospitalization	59% againt hospitalization for diarrhea of any cause in 1st year of life	42% against hospitalization for sever gastroenteritis
Efficacy against severe RV gastroenteritis	98%	100%
Intussusceptions	None	None

Genetics:

The RV does not have any genetic mutation. but it can lead to severe dehydration causes intussusceptions.

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