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■ **Rotavirus infections in domestic animals**

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■ **Ροταϊώσεις των κατοικίδιων ζώων**

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ABSTRACT. Rotaviruses are major enteric pathogens of humans and a wide variety of animals. *Rotavirus* infections have a worldwide prevalence. The viral genome is composed of 11 double-stranded RNA segments with six structural and five or six non-structural proteins. Over 35,000 strains have been identified and classified into five main (A, B, C, D, E) and three additional tentative (F, G, H) serotype groups. A binary classification system has been proposed defining ‘G’ or ‘P’ types, with at least 27 G and 35 P genotypes reported thusfar. The virus is transmitted primarily by the faecal-oral and oral routes. After attachment, entry into the host cells occurs through direct entry, fusion or endocytosis. Main mechanisms of *Rotavirus*-induced diarrhoea involve extensive enterocyte losses and nutrient disdigestion and malabsorption. Clinical features of *Rotavirus* infections range from asymptomatic infections to fulminant disease leading to rapid death. In calves, lambs and kids, piglets and foals, salient sign of the disease is diarrhoea; diarrhoeic faeces are white, yellow or, in severe cases, blood-tinted or frank haemorrhagic. In dogs and cats, the infection occurs usually as self-limiting diarrhoea. Avian *Rotavirus* infections are characterized by enteritis, growth depression and/or growth retardation. Definitive diagnosis of the infection can only be achieved by laboratory tests, including electron microscopic examination, immunohistochemical examination, immunofluorescence, ELISA, latex agglutination and molecular techniques. There is no specific treatment against *Rotavirus* infections. Treatment is based in providing supportive care and managing clinical signs and potential complications. Effective vaccines, containing inactivated, recombinant or attenuated strains of the virus, are available. Challenge studies have shown the ease of the virus in cross-infecting various animal species; animal strains of the virus may cross species and infect humans. Due to the ability of the virus to overcome species barriers, animal strains may act as natural source of viral genomes, promoting mutations and creating new viral genotypes, whose virulence cannot be predictable.

Keywords: diarrhoea, gut, host, *Rotavirus*, zoonosis

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ΠΕΡΙΛΗΨΗ. Οι ροταϊοί αποτελούν σημαντικό λοιμογόνο παράγοντα με παγκόσμια διάδοση, ο οποίος προσβάλλει τον άνθρωπο και τα κατοικίδια ζώα. Το γονιδίωμα του ιού αποτελείται από 11 τμήματα διπλών αλυσίδων RNA, τα οποία συνθέτουν έξι δομικές και πέντε ή έξι μη-δομικές πρωτεΐνες. Μέχρι τώρα, έχουν απομονωθεί περισσότερα από 35.000 στελέχη του ιού, τα οποία ταξινομούνται σε πέντε κύριες (A, B, C, D, E) και τρεις επικουρικές (F, G, H) ομάδες. Με βάση ένα δυαδικό σύστημα ταξινόμησης, τα στελέχη του ιού διακρίνονται επίσης σε 'G' ή 'P' τύπο, έχουν δε ταυτοποιηθεί περισσότεροι από 27 'G' και 35 'P' γενότυποι του ιού, με πολλούς μεταξύ τους συνδυασμούς. Ο ιός μεταδίδεται κυρίως από το στόμα. Μετά την προσκόλλησή του στα κύτταρα του εντέρου, εισέρχεται σε αυτά με διείσδυση, με συγχώνευση ή με ενδοκυττάρωση. Οι κύριοι παθογενετικοί μηχανισμοί της διάρροιας που προκαλείται από Ροταϊό, είναι η εκτεταμένη καταστροφή των κυττάρων του εντερικού επιθηλίου και η, ως συνέπεια αυτής, ελλιπής απορρόφηση και πέψη των θρεπτικών συστατικών. Η κλινική εικόνα της μόλυνσης από ροταϊούς ποικίλλει, είναι δε δυνατόν να κυμαίνεται από ασυμπτωματική μόλυνση μέχρι σοβαρή νόσο, η οποία μπορεί να απολήξει σε θάνατο. Σε μοσχάρια, αρνιά, χοιρίδια και πουλάρια, το κύριο σύμπτωμα της λοίμωξης είναι η διάρροια με χαρακτηριστικά λευκά, κίτρινα ή, σε βαριές μορφές, αιμορραγικά διαρροϊκά κόπρανα. Σε σκύλους και γάτες, η λοίμωξη προκαλεί συνήθως ήπια συμπτώματα. Σε πτηνά, η λοίμωξη, συνήθως, προκαλεί μέτρια βαρύτητας εντερίτιδα, αδιαφορία και καθυστέρηση της ανάπτυξης. Η οριστική διάγνωση της νόσου βασίζεται σε εργαστηριακές εξετάσεις, μεταξύ των οποίων η ηλεκτρονική μικροσκοπήση, η ανοσοϊστοχημική εξέταση, ο ανοσοφθορισμός, η ELISA, οι δοκιμές συγκόλλησης και οι μοριακές τεχνικές. Δεν υπάρχει ειδική θεραπευτική αγωγή για την αντιμετώπιση της λοίμωξης από ροταϊούς. Η αγωγή βασίζεται στη γενική υποστήριξη του ασθενούς ζώου και την αντιμετώπιση κλινικών συμπτωμάτων και ενδεχόμενων επιπλοκών της λοίμωξης. Αποτελεσματική πρόληψη της νόσου επιτυγχάνεται με τα διαθέσιμα εμβόλια με αδρανοποιημένα, ανασυνδυασμένα ή μειωμένης λοιμογόνου δύναμης στελέχη του ιού. Με πειραματικές μολύνσεις, έχει αποδειχθεί η δυνατότητα μετάδοσης του ιού μεταξύ διαφορετικών ζωικών ειδών, καθώς και μεταξύ των ζώων και του ανθρώπου. Καθώς ο ιός έχει τεκμηριωμένα τη δυνατότητα να διαπερνά το φραγμό των ζωικών ειδών, στελέχη του ιού από ζώα αποτελούν πηγές ιικού γονιδιώματος, από τις οποίες μπορεί να δημιουργηθούν νέα στελέχη του ιού, η παθογόνος δράση των οποίων δεν μπορεί να προβλεφθεί.

Λέξεις ευρητηρίας: διάρροια, έντερο, ζωνόσος, ξενιστής, ροταϊός

INTRODUCTION

Rotaviruses are major enteric pathogens of humans and a wide variety of animals (Desseberger et al., 2001; Gentsch et al., 2005; Estes and Kapikian, 2007). *Rotavirus* infections have a worldwide prevalence and have been diagnosed in almost every mammalian or avian species on earth (Saif et al., 1994; Parashar et al., 2003; Wani et al., 2003). The pathogenic activity of the virus leads primarily to diarrhoea in young animals. Severity of the disease varies, depending on age, nutritional conditions and immunological status of the individuals affected.

Severity and rate of infection varies among animal species. In livestock, rotaviruses are commonly detected, leading to enzootic enteritis, particularly in young calves, piglets and foals. Their control requires significant resources, as they are a constant threat in intensively farmed animals. In dogs and cats, various studies have shown increased prevalence of the infec-

tion, although this rarely leads to clinical conditions (McNulty et al., 1978; Mochizuki et al., 2001; Tupler et al., 2012). In poultry, rotaviruses are considered as significant agents contributing to the poultry enteritis complex, that way causing significant economic losses (Barnes et al., 2000).

In humans, *Rotavirus* infection is a leading cause of acute dehydrating diarrhoea, primarily affecting infants and young children. It is estimated that *Rotavirus*-associated diarrhoea leads to over 125 million cases of infantile gastroenteritis and to death of approximately 600,000 children every year, mainly in developing countries (Parashar et al., 2009). It is also generally accepted that until the 5th year of age almost every child will have been infected by the virus, irrespective of its state, location or socioeconomic status (Bilcke et al., 2009). In adults, *Rotavirus* infections usually remain subclinical, while moderate, self-limiting clinical signs may occur occasionally (Itturiza-Gomara et al., 2009).

Objectives of this review are to (a) describe the role of rotaviruses in the pathogenicity of neonatal diarrhoeic syndrome in domestic animals, (b) discuss *Rotavirus* infections, which are caused by a poorly understood enteric pathogen, and (c) highlight the zoonotic significance of *Rotavirus* infections.

STRUCTURE AND CLASSIFICATION OF THE VIRUS

Rotavirus is classified in the Reoviridae family of viruses. The name of virus has been officially adopted in 1979 (Matthews, 1979), after a suggestion by T.H. Flewett (Flewett et al., 1974) and is based on the latin word 'rota' indicating the wheel-like shape of virus particles during microscope observation.

The viral genome is composed of 11 double-stranded RNA (dsRNA) segments, ranging from 0.6 to 3.3 kb (Estes and Cohen, 1989). Each genome segment encodes a single viral protein (monocistronic), except segment 11, which encodes two different pro-

teins by an additional overlapping open reading frame (Gonzalez et al., 1998). In total, there are six structural (VP1-VP4, VP6, VP7) and five or six non-structural (NSP1-NSP5/NSP6) proteins (Table 1).

The mature infective *Rotavirus* particle has a non-enveloped symmetric icosahedral capsid and a diameter of about 70-75 nm (Bishop et al., 1973; Estes and Cohen, 1989). The external layer of the virus is discontinuous and looks like a sponge, because of the multiple small extensions of the VP4 spike (Settembre et al., 2011). The structural proteins of the virion are depicted as three concentric circles, forming an equal number of layers around the dsRNA genome (triple layered particle) (McClain et al., 2010). The inner layer is composed mainly of the core lattice protein VP2, which encases a RNA-dependent RNA polymerase (RdRp) VP1 and RNA capping enzyme VP3. The intermediate layer is composed entirely of the VP6, which is considered to be the most stable protein of the virion, while the outer layer is made up by two proteins, the glycoprotein VP4 and the VP7.

Table 1. Rotavirus genes and proteins.

RNA segment	Protein	Copies per particle	Code letter	Genotypes	Location	Function	References(s)
1	VP1	<25	R	1-9	Edges of core	RNA-dependent RNA polymerase	Vasquez del Carpio et al., 2006; Matthijssens et al., 2008b; 2011a
2	VP2	120	C	1-9	Inner shell of core	Stimulator of RNA replication	Matthijssens et al., 2008b; 2011a; McClain et al., 2010
3	VP3	<25	M	1-8	Edges of core	Guananyl-transferase mRNA capping enzyme	Donelli and Superti, 1994; Matthijssens et al., 2008b; 2011a
	VP4				Surface spike	Host cell attachment	Matthijssens et al., 2008b; 2011a; McClain et al., 2010
4	VP5*	120	P	1-35	Body of surface spike	Host cell attachment, modification of host cell membrane permeability	Patton et al., 1993; Denisova et al., 1999; Zarate et al., 2000
	VP8*				Upper edge of surface spike	Host cell attachment, capability for haemagglutination	Fiore et al., 1991; Patton et al., 1993
5	NSP1	-	A	1-16	Non-structural	Antagonism of host antiviral response	Taniguchi et al., 1996; Matthijssens et al., 2008b; 2011a
6	VP6	780	I	1-16	Inner capsid	Intermediate capsid layer -species specific	Matthijssens et al., 2008b; 2011a; McClain et al., 2010
7	NSP3	-	T	1-12	Non-structural	Support viral mRNA transcription	Poncet et al., 1993; Matthijssens et al., 2008b; 2011a
8	NSP2	-	N	1-9	Non-structural	Formation of viroplasm	Taraporewala and Patton; 2004; Matthijssens et al., 2008b; 2011a
9	VP7	780	G	1-27	Surface	Outer protein layer, virus penetration	Matthijssens et al., 2008b; 2011a; Hyser et al., 2010
10	NSP4	-	E	1-14	Non-structural	Enterotoxin	Matthijssens et al., 2008b; 2011a; Aoki et al., 2009
11	NSP5/6	-	H	1-11	Non-structural	Formation of viroplasm	Taraporewala and Patton; 2004; Matthijssens et al., 2008b; 2011a

These two proteins form, respectively, a set of spike-like projections as the VP7 shell partly covers the base of the VP4 spike and appears to lock VP4 onto the virion. The VP4 protein may be further separated into 2 parts, the VP5*, located at the base, and the VP8*, located on top of VP4 3-D architecture (Patton et al., 1993).

The role of the structural and the non-structural viral proteins has been extensively studied. With regard to the structural proteins, the external proteins VP4 and VP7 are remarkable. They are known to be responsible for the attachment of the viral particles to specific intestinal cellular receptors and the penetration of the virion into the cell's cytoplasm. They are also considered to be principal regulators for the pathogenic effects of rotaviruses (Mori et al., 2003). Moreover, VP4 and VP7 act as independent neutralizing antigens constituting the major antigenic determinant for the viral recognition by the host immunity system. On the other hand, the non-structural proteins react with viral RNA and have a multi-functional role in genome replication, encapsidation and composition of new virus particles (Hu et al., 2012). NSP2 and NSP5 proteins have a key role in the formation of viroplasm (Eichwald et al., 2004). NSP3 has been proposed to act in facilitation of translation of viral mRNA and to suppress host protein synthesis, while it has been established to play a role in the extra-intestinal spread of rotaviruses (Mossel and Ramig, 2002). Finally, glycoprotein NSP4 seems to behave as a viral enterotoxin capable of inducing age-dependent diarrhoea by transforming the host cellular membranes and causing a cohesion of reactions, which leads to necrosis and apoptosis of infected cells (Dong et al., 1997; Ciarlet et al., 2000; Zhang et al., 2000; Ball et al., 2005).

Since the first isolation of a *Rotavirus* in 1969 (Mebus et al., 1969) until today, over 35,000 strains of the virus have been identified, originating from animal or human samples. In order to better study these strains, various classification systems have been proposed, which rely, mainly, on their antigenic relationships and genomic characteristics. Nowadays, *Rotavirus* strains are classified into five main (A, B, C, D, E) and two additional tentative (F, G) serotype groups (or serogroups) on the basis of antigenic sites located on the VP6 protein (Ball, 2005; Estes and Kapikian, 2007; Matthijnssens et al., 2012; Otto et al., 2012). Strains classified into serogroup A, B or C have

been found to be pathogenic for various animal species and humans; serogroup E strains have been isolated only from pigs; serogroup D, F or G strains have been isolated only from avian species (Saif and Jiang, 1994; Dhama et al., 2009; Martella et al. 2007; Matthijnssens et al., 2011b). Most virulent and commonly isolated strains belong to serogroup A (GARVs); they are an important cause of acute infectious diarrhoea in children and various domestic mammalian and avian species. Serogroup C strains (GCRVs) also cause diarrhoea in infants and children, while serogroup B strains (GBRVs) have been associated mainly with diarrhoea in neonatal lambs (Fitzgerald et al., 1995) and adult humans (Sen et al., 2001). Recently, a new *Rotavirus* serogroup (H) has been added in the virus' classification, which includes strains that have been identified only in adult humans in Asia (Attoui et al., 2012).

A binary classification system has been proposed for *Rotavirus* strains, which takes into account the configuration of the outer viral layer with glycoprotein VP7, defining 'G' types, or the protease sensitive protein VP4, defining 'P' types. Up today, on worldwide basis, at least 27 G and 35 P genotypes have been reported in strains of animal or human origin, with over 43 G-P combinations. Another classification scheme, specifically for GARVs, has been adopted by the Rotavirus Classification Working Group (Matthijnssens et al., 2008b). The scheme is based on nucleotide sequence identity cut-off values of each of the 11 RNA segments, setting a letter code for each viral protein; thus, VP7-VP4-VP6-VP1-VP2-VP3-NSP1-NSP2-NSP3-NSP4-NSP5/6 are represented by Gx-Px-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx, respectively, with 'x' representing number of corresponding genotype. The widespread use of full genome analysis has been already proved to be essential in the study of genomic relationships between strains and serotype groups of the virus. Additionally, the Rotavirus Classification Working Group has now established a naming manual for study and comparison of viral segments, including (a) the segment's serotype group, (b) the type of the host or its production method, (c) the country where it was detected, (d) the name that was given to the segment by the scientists who have isolated it, (e) the year of isolation and (f) its genotype combination [G] - [P] (Matthijnssens et al., 2011a).

TRANSMISSION OF THE VIRUS AND PATHOGENESIS OF THE INFECTION

Rotavirus strains are remarkably stable on exposure to various environmental conditions (Estes et al., 1979). Under normal conditions (temperature, humidity, sunshine), the viral particles can remain infective for up to seven months, making the soil and various crops a potential source of infection for animals and humans. Similarly, they remain infective in raw foods and water for over 14 days, causing, occasionally, food- or water-borne outbreaks of the disease (Hurst and Gerba, 1980; Hung et al., 1984; Koopmans et al., 2003; Koroglu et al., 2011). In addition, elimination of the virus is also difficult. Rotaviruses may retain their infectivity, even after use of various disinfectants (e.g., chloroform solution, sodium hypochlorite) or ultra-violet irradiation or temperature treatments, as only disinfectants containing $\geq 95\%$ ethanol have been found to be effective against the virus (Steele et al., 2004; Li et al., 2009).

The virus is transmitted primarily by the faecal-oral and oral routes, when faecal traces or other contaminated material enter into the digestive tract of susceptible hosts. Transmission via the respiratory route has also been suggested, but has not been adequately proven (Prince et al., 1986). In avian species, vertical transmission has not been reported (Guy, 1998). After invasion into the host, viral particles pass through the digestive tract and, after a short incubation period (1-2 days), infect the proximal small intestine. Absence of a lipid envelope, as well as presence of a triple-layered protein capsid, allow *Rotavirus* particles to maintain viability during transit through the acid environment of the stomach or duodenum. Target cells of the virus are mature enterocytes on the villus tip of the jejunum and ileum. However, the virus has also been found in goblet cells, epithelial endocrine cells and macrophages in the lamina propria (Kapikian and Chanock, 1996).

Although various studies have presented facets of the pathogenicity of rotaviruses, the entire process is not fully understood (Lundgren and Svensson, 2001; Arias et al., 2002; Jayaram et al., 2004). The initial step in rotaviral infection is virus attachment, performed after several reactions between the viral surface spike protein VP4 and the respective receptors on the cell membrane of host cells, such as integrins (Coulson et al., 1997) and heat shock protein Hsc70 (Isa et al., 2008). Some strains of the virus require the

presence of sialic acid on the cell surface for efficient binding, but the great majority (of animal or human origin) is sialic acid-independent (Ciarlet and Estes, 1999). Following binding, the viral particle is activated by trypsin cleavage of VP4 into two fragments: a viral haemagglutinin (VP8*) and a membrane-penetration protein (VP5*). *Rotavirus* entry into cells takes place through direct entry, fusion or Ca^{2+} -dependent endocytosis (Ciarlet and Estes, 2001; Tsai, 2007; Ruiz et al., 2009). In fact, different *Rotavirus* strains may use different internalization pathways, which can vary according to individual interactions of each strain with the potential host (Lopez and Arias, 2004). Within infected cells, virus replication, morphogenesis of new virions, cell lysis and particle release are Ca^{2+} -dependent processes, which are determined by NSP4 action (Ruiz et al., 2000; Hyser et al., 2010). During cell entry, surface proteins of the virions are destroyed, yielding transcriptionally active double-layered particles (Lawton et al., 2000). Budding of new viral particles generally occurs across the endoplasmic reticulum membrane, while final assembly of infective particles takes place in the endoplasmic reticulum lumen. NSP4, as an endoplasmic reticulum transmembrane glycoprotein, in association with VP7, stimulates viral parts construction and regulates viral morphogenesis (Estes, 2001). Moreover, NSP4, acting as a viral enterotoxin, provokes a significant increase in intracellular Ca^{2+} volume concentration (Diaz et al., 2008), which is essential for stabilization of new virions VP7 protein; finally, it modifies integrity of intestinal epithelial cells, causing significant loss of water and electrolytes and, eventually, leading to the cellular necrosis (Tian et al., 1996; Estes, 2001).

The main mechanisms of *Rotavirus*-induced diarrhoea involve extensive enterocyte losses and nutrient maldigestion and malabsorption, as a consequence of enterocyte death (Ramig, 2004). These processes lead to significant increase of osmotic pressure in the intestinal lumen, which, in turn, induces watery diarrhoea. Moreover, the breakdown barrier of intestinal mucosa allows entrance of opportunistic enteric pathogens, bacterial (*Clostridium*, *Escherichia coli*, *Salmonella*) or viral (*Astrovirus*, *Coronavirus*, *Norovirus*) agents, which often may coexist with *Rotavirus* infections and complicate the course and the necessary treatment (Garcia et al., 2000).

Table 2. Summary of features of rotavirus infection in domestic animals

	Horses	Cattle	Sheep/Goats	Pigs	Dogs	Cats	Chickens	Turkeys	Rabbits
Serogroups causing infection	A	A (B, C)	B (A)	A (C, B)	A (C)	A	A, D (F, G)	A, D (F, G)	A
Usual age	< 90 days	<14 days	<14 days	<60 days	<10 days	< 10 days	<4 weeks	<4 weeks	<3 weeks
Reported seroprevalence	D: 20-40% A: 2-16%	D: 15-46% D: 13%	A: 10-20% D: 27-70%	D: 3-5% 5-46%	A: 10-30%	D: 7-10%	A: 10-40%	D: 10-30%	D: 20%
Typical disease setting	Outbreaks	Endemic	Outbreaks	Endemic	Sporadic cases	Sporadic cases	Endemic	Endemic	Endemic
Availability of rapid diagnostic tests	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Evidence for zoonotic transmission	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

D: animals with clinical diarrhoea, A: animals with no clinical signs.

CLINICAL SIGNS

Clinical features of infections by rotaviruses range from asymptomatic infections to fulminant disease leading to rapid death (Table 2) (Saif and Jiang, 1994; Dhama et al., 2009; Martela et al., 2010). Most infected animals will not develop clinical signs. Clinical severity of the infection depends on age, host, viral strain and immune response (McNulty, 1978; Bridger et al., 1992). After a short incubation period, the disease usually appears suddenly, with an acute course.

In calves, lambs and kids, severe disease develops with diarrhoea, primarily in animals younger than 10 days, with mortality ranging from 1 to 50%. Death can be the consequence of the direct effects of the pathogenic action of the virus, although secondary bacterial infections may also be lethal; this depends upon the virulence determinants of each viral strain and individual factors in each affected animal, e.g., its immunological competence (Torres-Medina et al., 1985; Holland, 1990; Munoz et al., 1996). Sudden death can also be the only finding in hyper-acute cases of the disease (Woode, 1978). In piglets, diarrhoea is the main finding, in a high morbidity-low mortality disease (Bohl et al., 1978). In foals, infections by rotaviruses are the main cause of diarrhoea in animals younger than three months (Conner and Darlington, 1980; Browning and Begg, 1996). In all above species, the salient, but not sole, sign of the disease is diarrhoea; diarrhoeic faeces are white, yellow or, in severe cases, blood-tinted or frank haemorrhagic. Other clinical signs include anorexia, vomiting, depression and acute abdominal pain. Death of an affected animal may occur as a result of extensive dehydration and loss of proteins and electrolytes, caused by the

irrepressible diarrhoea. In most cases (if appropriate supportive treatment is initiated), recovery should be expected within 3-9 days after onset of clinical signs. In all cases, growth retardation of affected animals can follow after subsidence of the clinical signs.

In dogs and cats, infection usually occurs as self-limiting diarrhoea in puppies and kittens, respectively, which often remains undetected. In contrast, in domestic rabbits, young rabbits (1-3 month-old) are particularly susceptible to infections, usually manifesting as acute diarrhoeic syndrome with increased mortality rate (Schoeb et al., 1986; Thouless et al., 1988).

In poultry, severity of infections varies considerably among the different avian species. Survey studies have repeatedly demonstrated the presence of the virus in chicken and turkey flocks. Diarrhoea and appetite abnormalities or inappetence are the most frequently reported clinical signs, which may occur, usually, 48 hours after infection, leading to death due to emaciation or dehydration. In long-standing cases, growth retardation, impaired feed utilization and poor feed conversion efficiency may occur. In chickens, pigeons and turkeys infections usually lead to mild non-fulminant diarrhoea, while in pheasants mortality can be as high as 30-50 %. In addition, infections have been associated in appearance of chronic runting and stunting syndrome (McNulty, 2003; Otto et al., 2006).

Unlike human *Rotavirus* infections, in animals no clinical signs beyond those of the digestive system have been reported. However, as particles of the virus have been identified to several organs of infected animals, possible occurrence and incidence of extra-intestinal signs should be investigated (Azevedo et al., 2005; Crawford et al., 2006).

PATHOLOGICAL FINDINGS

Macroscopic and histological changes that take place in the intestinal mucosa following infections by rotaviruses are similar in all species that can be affected by the virus (Coelho et al., 1981). Even mildly virulent strains can cause intestinal changes, but there is no good correlation between histological lesions and clinical signs.

Initial lesions are usually observed within 48 h after infection and are more pronounced in the proximal small intestine (Mebus and Newman, 1977). Lesions are often located in the mucosa of the duodenum and the ileum, rarely extending to the entire length of the small intestine (Pearson and McNulty, 1977; Snodgrass et al., 1977; Pearson et al., 1978). Macroscopically, the salient changes consist of discolouration of the intestinal mucosa, thinning of the intestinal wall and loss of the absorptive surface in the upper half of intestinal villi (Snodgrass et al., 1979; Narita et al., 1982). Gross inflammatory signs are virtually absent. In severe cases, focal necrosis on intestinal villi may be observed. Histopathological findings include villus atrophy and blunting, whereas infected enterocytes are presented in the oedematous and swollen cytoplasmic vacuoles (Torres-Medina and Underdahl, 1980; Johnson et al., 1986; Varshney et al., 1995; Ciarlet et al., 1998a; Boshuizen et al., 2003). During the acute phase of the infection, histological changes can be observed in several organs beyond the intestine. In fact, viral antigen has recently been detected in the stomach, the liver, the lungs, the spleen, the pancreas, the kidneys and the bladder of infected hosts, leading to local infiltration of lymphocytes and macrophages (Kim et al., 2011).

As infection progresses (36-72 h after exposure), the infected intestinal cells become degenerated, destroyed and replaced by epithelial cells of the intestinal crypts. These new cells, which are shorter, squamous and cuboidal, can be relatively refractory to virus attachment, as they are devoid of specific *Rotavirus* receptors. This may explain the self-limiting feature of clinical disease.

DIAGNOSIS

Detection of acute watery diarrhoea in neonates in a farm or of wet litter in poultry flocks often provides initial suspicion of infection by rotaviruses. However, as none of the clinical signs may lead to diagnosis with certainty, definitive diagnosis of the infection can only be achieved by laboratory tests.

The various laboratory tests aim to identify viral antigens in faecal samples or to detect specific anti-antibodies of rotaviruses in blood serum. Electron microscopic examination, immunohistochemical examination, immunofluorescence, ELISA, latex agglutination, molecular techniques (e.g., polymerase chain reaction and protein electrophoresis) are frequently employed techniques (Grauballe et al., 1981; Gouvea et al., 1990; 1994a). Samples useful for laboratory diagnosis are faeces and blood serum from sick animals. Preferably, these should be collected within 24 h after onset of clinical signs (Kapikian et al., 2001) and must be sent to the laboratory as soon as possible.

Direct detection of the virus in faecal samples from affected hosts was initially carried out by using electron microscopic examination (Bishop et al., 1974). Nowadays, ELISA and latex agglutination can be used as first-line diagnostic tools, as both methods are quick, relatively accurate and inexpensive for diagnosis of the infection. ELISA assays can be used to detect viral antigens, using mouse monoclonal antibodies, which bind to the structural protein VP6, or specific antibodies against the virus. Latex agglutination can also be used to detect viral antigens. In recent years, the molecular techniques have replaced other methods (Elschner et al., 2002; Schwarz et al., 2002; Fukuda et al., 2012), as they provide increased diagnostic accuracy and allow detection of viral genome, as well as some nucleotide sequences for segment detection (Gouvea et al., 1994b); however, a disadvantage of the techniques is the high cost, hence, at the moment, they are used mainly for research purposes.

In practice, one can use the many commercially available test kits, which are available for detection of serogroup A rotaviruses. These may be performed in a farm, when early diagnosis of the infection will help to initiate early control the disease. In companion animal practice, laboratory confirmation of clinical diagnosis of potential *Rotavirus* infection is rarely pursued, as the approach to the case would not be modified anyway. Nevertheless, due to the zoonotic potential of the virus, laboratory confirmation is recommended and

can be effected by means of a rapid, commercially available test kit. Due to similar antigenic epitopes of GARVs strains, kits used for diagnosis of the disease in humans may also be used in animals (Maes et al., 2003; Fushuku and Fukuda, 2006; Nemoto et al., 2010).

TREATMENT

There is no specific treatment for rotaviral infections. Treatment is based in providing supportive care and managing clinical signs and potential complications. In livestock and companion animals, fluid administration is essential to replace losses from diarrhoea or vomiting, to correct acidosis and to restore electrolytes imbalance. Adequate sodium concentration and appropriate glucose to sodium ratios are the most important components of an efficient rehydration solution (Zijlstra et al., 1997; Lorenz et al., 2011). In young animals, administration of fluids can be performed by means of oesophageal catheter; in older animals, intravenous administration is preferable. In affected piglets, administration of a plasma protein mixture, consisting of immunoglobulins, growth factors and other biologically active peptides, has been advocated to enhance small intestine recovery (Corl et al., 2007).

Alternatively, passive immunisation of individuals affected by the virus can be performed. Oral administration of prepared virus-neutralizing antibodies can support recovery and contribute to decreased severity of clinical signs (Besser et al., 1988; Hurley and Theil, 2011; Vega et al., 2011). Additional administration of probiotics has also been shown to support quick recovery, although potential mechanisms of action are not clear (Munoz et al., 2011; Azevedo et al., 2012). In case of secondary bacterial infections, antimicrobial agents should be administered. Specifically in companion animals or in high-value calves, anti-viral drugs (e.g., cyclophilin A, dipyrromole) can be possibly administered (Gu et al., 2000; He et al., 2012), although their specific therapeutic role in animals has not been evaluated.

PREVENTION

Vaccines for prevention of infections by rotaviruses have been available for some time now (Clark et al., 1996; Saif and Fernandez, 1996). Available

vaccines contain inactivated, recombinant or attenuated strains of the virus, in various combinations. In general, vaccinations should be performed in pregnant animals during the final stage of pregnancy. Nowadays, several vaccine formulations and vaccination schedules are available.

As a general rule, unvaccinated cows should receive two vaccinations, at intervals of three weeks; the second vaccination needs to be performed three weeks before the expected calving date; subsequently, an annual booster dose at the 8th month of pregnancy should be given. Unvaccinated sows should receive two vaccinations, six and three weeks before the expected farrowing date; subsequently, an annual booster dose should be administered. Mares should be vaccinated at the 9th, 10th and 11th month of pregnancy. Nevertheless, vaccination schedules different to the above may be used, taking into account specific production programs in a farm, as well as other vaccinations that need to be performed. No vaccines are yet licenced for dogs, cats, rabbits and poultry.

New, improved vaccines are currently in various stages of development (O'Neal et al., 1997; Ciarlet et al., 1998a; McNeal et al., 1999; Bertolotti-Ciarlet et al., 2003; Ward and McNeal, 2010). Future vaccines may contain only oligopeptides or macropeptides of the viral molecule or even synthetically prepared parts of that ('viral-like' units), which will increase safety and efficacy of future products.

Besides vaccination, oral administration of virus-neutralizing antibodies during the period of peak susceptibility to the infection can lead to efficient protection of treated animals (Saif et al., 1983; Fernandez et al., 1998; LeRousic et al., 2000; Parreno et al., 2004). Administration of colostrum preparations or milk replacers containing specific antibodies produced in hyperimmunized female animals has been shown to be beneficial; such products are now commercially available for use in calves (Parreno et al., 2010).

In any case, the general principles of high hygiene farm status and correct management of neonates should be applied, as essential approaches to limiting the infection.

ZOONOTIC SIGNIFICANCE

Experimental infection of dogs or pigs with human rotaviruses has for long been known to result in replication and propagation of the strains in the ani-

mal host (Bridger et al., 1975; Tzipori, 1976; Tzipori and Makin, 1978; Tzipori et al., 1980). Cross-species challenge studies in a large number of animal species have shown the ease of the virus in cross-infecting various animal species (Schwers et al., 1983; El-Attar et al., 2001; Mori et al., 2001; Chege et al., 2005). These studies have also demonstrated that challenged animals excreted the virus for a long period, thus acting as potential reservoirs of infection for other animals and humans.

More recently, results of serological assays and nucleotide chain recognition methods (Nakagomi et al., 1990; Vonsover et al., 1993; Palombo, 2002) have shown that many strains of the virus isolated from mammalian species can infect humans. Additionally, there has been strong evidence on the zoonotic transmission of avian strains (Gusmao et al., 1994; Mori et al., 2001; Schuman et al., 2009). The findings contributed to understanding the role of animals in controlling *Rotavirus* infection in humans and were taken into account for respective vaccine development (Vesikari et al., 1984; 2006; Clark et al., 1996).

Establishment of the binary recognition system of *Rotavirus* segments [G, P] and use of more accurate methods for analysis of the viral genome have led to the conclusion that viral segments present in animal species possess human tropism (homologous segments). However, this tropism is not absolute, as exemplified by isolation of heterologous segments from various animal species or humans. Isolation of such segments can be the result of identical transfer of a viral particle from one species to another or, more often, the result of a sequence of mutations after two or more viral segments 'meet' into the same host (Muller and Johne, 2007; Matthijnsens, 2008a; 2009a;b; Midgley et al., 2012a).

Many examples of identical or almost identical transfer of animal segments of the virus to humans are now available (De Grazia et al., 2007; Simoes et al., 2008; Martella et al., 2011; Ghosh et al., 2012; Luchs et al., 2012; Midgley et al., 2012b). Most refer to segments isolated from cattle or pigs and have been detected mainly in developing countries, where humans and animals live closely, often sharing a domicile. Some segments of human origin, e.g. Ro1845 or HCR3A, are now considered to be typical examples of such transfer. These were found to be identical to viral segments CU-1, K9 or A79-10 from dogs or Cat97 from cats during nucleotide analysis (Tsugawa

and Hoshino, 2008; Martella et al., 2010). In most cases, infection of humans by segments of animal origin would lead to a mild clinical disease (De Leener et al., 2004). So far, transfer of viral segments of animal origin among humans has not been reported.

Rotavirus mutations among different animal species (mammalian and avian) are the main and more common reason of detection of heterologous segments and creation of new antigen epitopes (Khamrin et al., 2006; Banyai et al., 2009; Grant et al., 2011; Martella et al., 2011; Mukherjee et al., 2011; Park et al., 2011; Jere et al., 2012). According to statistics of the European Rotavirus Network, 1.4% of segments of animal origin seem to have originated from mutations between human and animal strains of the virus (Iturriza-Gomara et al., 2010). The majority of these new recombinant strains are highly infective and can cause severe (even fatal) disease. Moreover, as a consequence of the ability of between-species transmission, these strains are often associated with extensive *Rotavirus* outbreaks, involving a large number of animals and humans.

CONCLUDING REMARKS

The multiplex relationships and interactions between humans and animals considering *Rotavirus*, as well as the zoonotic implications of infection by the virus are now widely accepted (Nakagomi and Nakagomi, 2002; Cook et al., 2004; Gentsch et al., 2005; Martella et al., 2010). Most domestic animal species, especially those with direct contact to humans, can play a role in the spread of the virus, by acting as natural reservoirs of the virus or as intermediate or end hosts. It is also clear that, due to the ability of the virus to overcome the between species barriers, animal strains may act as natural source of viral genomes, promoting mutations and creating new viral genotypes, whose virulence cannot be predictable.

During the past years, specific working groups and genetic information banks have been developed in order to monitor *Rotavirus* segments of human origin all over the world (Tamura et al., 2007; Maes et al., 2009). Main objectives of these groups are the exchange of data, the detection of new segments of the virus and, if possible, the creation of a prediction method about future outbreaks (Iturriza-Gomara et al., 2009; 2010; Esona et al., 2011). However, as the algorithm for creation of new viral epitopes relates

animals and humans, it is obvious that the study of *Rotavirus* does not concern segments of only human or only animal origin. Absence of systematic monitoring of infections by rotaviruses in domestic animals appears to setback understanding of epidemiologic behaviour of the virus. Creation of a surveillance system able to detect and identify animal rotaviruses, collect genetic and antigenic data and assess their zoonotic potential will contribute significantly to the control and prevention of *Rotavirus* infections in both humans and domestic animals.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest. ■

REFERENCES

- Aoki ST, Settembre EC, Trask SD, Greenberg HB, Harrison SC, Dormitzer PR (2009) Structure of rotavirus outer-layer protein VP7 bound with a neutralizing Fab. *Science* 324:1444-1447.
- Arias CF, Isa P, Guerrero CA, Méndez E, Zarate S, López T, Espinosa R, Romero P, López S (2002) Molecular biology of rotavirus cell entry. *Arch Med Res* 33:356-361.
- Attoui H, Mertens PPC, Becnel J, Belaganahalli S, Bergoin M, Brussaard CP, Chappell JD, Ciarlet M, del Vas M, Dermody TS, Dormitzer PR, Duncan R, Fang Q, Graham R, Guglielmi KM, Harding RM, Hillman B, Makkay A, Marzachi C, Matthijnssens J, Milne RG, Jaafar FM, Mori H, Noordeloos AA, Omura T, Patton JT, Rao S, Maan M, Stoltz D, Suzuki N, Upadhyaya NM, Wei C, Zhou H (2012) Family: Reoviridae. In: (eds: King AMQ, Adams MJ, Carstens EB, Lefkowitz EJ) *Virus Taxonomy*. 9th Report of the International Committee for Taxonomy of Viruses. Elsevier, Amsterdam, pp. 541-637.
- Azevedo MS, Yuan L, Jeong KI, Gonzalez A, Nguyen TV, Pouly S, Gochner M, Zhang W, Azevedo A, Saif LJ (2005) Viremia and nasal and rectal shedding of rotavirus in gnotobiotic pigs inoculated with Wa human rotavirus. *J Virol* 79:5428-5436.
- Azevedo MS, Zhang W, Wen K, Gonzalez AM, Saif LJ, Yousef AE, Yuan L (2012) *Lactobacillus acidophilus* and *Lactobacillus reuteri* modulate cytokine responses in gnotobiotic pigs infected with human rotavirus. *Benef Microb* 3:33-42.
- Ball LA (2005) The universal taxonomy of viruses in theory and practice. In: (ed.: Fauquet CM) *Virus Taxonomy: Classification and Nomenclature of Viruses*. 8th Report of the International Committee for Taxonomy of Viruses, Elsevier, San Diego, pp 11-16.
- Ball JM, Mitchell DM, Gibbons TF, Parr RD (2005) Rotavirus NSP4: a multifunctional viral enterotoxin. *Viral Immunol* 18:27-40.
- Banyai K, Esona MD, Mijatovic S, Kerin TK, Pedreira C, Mercado J, Balmaseda A, Perez MC, Patel MM, Gentsch JR (2009) Zoonotic bovine rotavirus strain in a diarrheic child, Nicaragua. *J Clin Virol* 46:391-393.
- Barnes HJ, Guy JS, Vaillancourt JP (2000) Poulter enteritis complex. *Rev Scientif Techn Off Intnatl Epiz* 19:565-588.
- Bertolotti-Ciarlet A, Ciarlet M, Crawford SE, Conner ME, Estes MK (2003) Immunogenicity and protective efficacy of rotavirus 2/6-viruslike particles produced by a dual baculovirus expression vector and administered intramuscularly, intranasally, or orally to mice. *Vaccine* 21:3885-3900.
- Besser TE, Gay CC, McGuire TC, Evermann, JF (1988) Passive immunity to bovine rotavirus infection associated with transfer of serum antibody into the intestinal lumen. *J Virol* 62:2238-2242.
- Bilcke J, Van Damme P, Van Ranst M, Hens N, Aerts M, Beutels P (2009) Estimating the incidence of symptomatic rotaviruses infections: a systemic review and meta analysis. *Plos One* 4:e6060.
- Bishop RF, Davidson GP, Holmes IK, Ruck BJ (1973) Virus particles in epithelial cells of duodenal mucosa from children with acute nonbacterial gastroenteritis. *Lancet* 302:1281-1283.
- Bishop RF, Davidson GP, Holmes LH, Ruck BJ (1974) Detection of a new virus by electron microscopy of faecal extracts from children with acute gastroenteritis. *Lancet* 303:149-151.
- Bohl EH, Kohler EM, Saif LJ, Cross RF, Agnes AG, Theil KW (1978) Rotavirus as a cause of diarrhea in pigs. *J Am Vet Med Assoc* 172:458-463.
- Boshuizen JA, Reimerink JH, Korteland-van Male AM, Van Ham VJ, Koopmans MP, Büller HA, Dekker J, Einerhand AW (2003) Changes in small intestinal homeostasis, morphology, and gene expression during rotavirus infection of infant mice. *J Virol* 77:13005-13016.
- Bridger JC, Hall GA, Parsons KR (1992) A study of the basis of virulence variation of bovine rotaviruses. *Vet Microbiol* 33:169-174.
- Bridger JC, Woode GN, Jones JM, Flewett TH, Bryden AS, Davies H (1975) Transmission of human rotaviruses to gnotobiotic piglets. *J Med Microbiol* 8:565-569.
- Browning GF, Begg AP (1996) Prevalence of G and P serotypes among equine rotaviruses in the faeces of diarrhoeic foals. *Arch Virol* 141:1077-1089.
- Chege GK, Steele AD, Hart CA, Snodgrass DR, Omolo EO, Mwenda JM (2005) Experimental infection of non-human primates with a human rotavirus isolate. *Vaccine* 23:1522-1528.
- Ciarlet M, Crawford SE, Barone C, Bertolotti-Ciarlet A, Estes MK, Conner ME (1998b) Subunit rotavirus vaccine administered parenterally to rabbits induces active protective immunity. *J Virol* 72:9233-9246.
- Ciarlet M, Gilger MA, Barone C, McArthur M, Estes MK, Conner ME (1998a) Rotavirus disease, but not infection and development of intestinal histopathological lesions, is age restricted in rabbits. *Virology*. 251:343-360.
- Ciarlet M, Estes MK (1999) Human and most animal rotavirus strains do not require the presence of sialic acid on the cell surface for efficient infectivity. *J Gen Virol* 80:943-948.
- Ciarlet M, Estes MK (2001) Interactions between rotavirus and gastrointestinal cells. *Curr Opin Microbiol* 4:435-441.
- Ciarlet M, Liprandi F, Conner ME, Estes MK (2000) Species specificity and interspecies relatedness of NSP4 genetic groups by comparative NSP4 and sequence analysis of animal rotaviruses. *Arch Virol* 145:371-383.
- Clark HF, Offit PA, Ellis RW, Eiden JJ, Krah D, Shaw AR, Pichichero M, Treanor JJ, Borian FE, Bell LM, Plotkin SA (1996) The development of multivalent bovine rotavirus (strain WC3) reassortant vaccine for infants. *J Infect Dis* 174:73-80.
- Coelho KIR, Bryan AS, Hall C, Flewett TH (1981) Pathology of rotavirus infection in suckling mice: A study by conventional histology, immunofluorescence, ultrathin sections, and scanning electron microscopy. *Ultrastruc Pathol* 2:59-80.
- Conner ME, Darlington RW (1980) Rotavirus infection of foals. *Am J Vet Res* 41:1699-1703.
- Cook N, Bridger J, Kendall K, Gomara MI, El-Attar L, Gray J (2004) The zoonotic potential of rotavirus. *J Infect* 48:289-302.
- Corl BA, Harrell RJ, Moon HK, Phillips O, Weaver EM, Campbell JM, Arthington JD, Odle J (2007) Effect of animal plasma proteins on intestinal damage and recovery of neonatal pigs infected with rotavirus. *J Nutr Biochem* 12:778-784.
- Coulson BS, Londrigan S, Lee D (1997) Rotavirus contains integrin ligand sequences and a disintegrin-like domain that are implicated in virus entry into cells. *Proc Natl Acad Sci USA* 94:5389-5394.
- Crawford SE, Patel GD, Cheng E, Berkova Z, Hyser JM, Ciarlet M, Finegold JM, Conner ME, Estes MK (2006) Rotavirus viremia and extraintestinal viral infection in the neonatal rat model. *J Virol* 80:4820-4832.
- De Grazia S, Martella V, Giammanco GM, Gòmara MI, Ramirez S, Cascio A, Colomba C, Arista S (2007) Canine-origin G3P[3] rotavirus strain in child with acute gastroenteritis. *Emerg Infect Dis* 13:1091-1093.

- De Leener K, Rahman M, Matthijnsens J, Van Hoovels L, Goegebuer T, Van der Donck I, Van Ranst M (2004) Human infection with a P[14]G3 lapine rotavirus. *Virology* 325:11-17.
- Denisova E, Dowling W, LaMonica R, Shaw R, Scarlata S, Ruggeri F, Mackow ER (1999) Rotavirus capsid protein VP5* permeabilizes membranes. *J Virol* 73:3147-3153.
- Desselberger U, Iturriza-Gomara M, Gray JJ (2001) Rotavirus epidemiology and surveillance. *Proc Novartis Found Sympos* 238:125-147.
- Dhama K, Chauhan RS, Mahendran M, Malik SV (2009) Rotavirus diarrhea in bovines and other domestic animals. *Vet Res Commun* 33:1-23.
- Diaz Y, Chemello ME, Pena F, Aristimuno OC, Zambrano JL, Rojas H, Bartoli F, Salazar L, Chwetoff S, Sapin C, Trugnan G, Michelangeli F, Ruiz MC (2008) Expression of nonstructural rotavirus protein NSP4 mimics Ca²⁺ homeostasis changes induced by rotavirus infection in cultured cells. *J Virol* 82:11331-11343.
- Donelli G, Superti F (1994) The rotavirus genus. *Comp Immunol Microbiol Infect Dis* 17:305-320.
- Dong Y, Zeng CQ, Ball JM, Estes MK, Morris AP (1997) The rotavirus enterotoxin NSP4 mobilizes intracellular calcium in human intestinal cells by stimulating phospholipase C-mediated inositol 1,4,5-trisphosphate production. *Proc Natl Acad Sci USA* 94:3960-3965.
- Eichwald C, Rodriguez JF, Burrone OR, (2004) Characterization of rotavirus NSP2/NSP5 interactions and the dynamics of viroplasm formation. *J Gen Virol* 85:625-634.
- El-Attar L, Dhaliwal W, Howard CR, Bridger JC (2001) Rotavirus cross-species pathogenicity: molecular characterization of a bovine rotavirus pathogenic for pigs. *Virology* 291:172-82.
- Elschner M, Prudlo J, Hotzel H, Otto P, Sachse K (2002) Nested reverse transcriptase-polymerase chain reaction for the detection of group A rotaviruses. *J Vet Med B* 49:77-81.
- Esona MD, Banyai K, Foytich K, Freeman M, Mijatovic-Rustempasic S, Hull J, Kerin T, Steele AD, Armah GE, Geyer A, Page N, Agbaya VA, Forbi JC, Aminu M, Gautam R, Seheri LM, Nyangao J, Glass R, Bowen MD, Gentsch JR (2011) Genomic characterization of human rotavirus G10 strains from the African Rotavirus Network: relationship to animal rotaviruses. *Infect Genet Evol* 11:237-241.
- Estes MK (2001) Rotaviruses and their replication. In: (eds: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE) *Fields' Virology*, 4th edn. Lipincott, Philadelphia, pp. 1747-1785.
- Estes MK, Cohen J (1989) Rotavirus gene structure and function. *Microbiol Rev* 53:410-449.
- Estes MK, Graham DY, Smith EM, Gerba CP (1979) Rotavirus stability and inactivation. *J Gen Virol* 43:403-409.
- Estes MK, Kapikian AZ (2007) Rotaviruses. In: (eds: Knipe DM, Howley PM) *Fields' Virology*, 5th edn. Kluwer, Philadelphia, pp. 1917-1974.
- Fernandez FM, Conner ME, Hodgins DC, Parwani AV, Nielsen PR, Crawford SE, Estes MK, Saif LJ (1998) Passive immunity to bovine rotavirus in newborn calves fed colostrum supplements from cows immunized with recombinant SA11 rotavirus core-like particle (CLP) or virus-like particle (VLP) vaccines. *Vaccine* 16:507-516.
- Fiore L, Greenberg HB, Mackow ER (1991) The VP8 fragment of VP4 is the rhesus rotavirus hemagglutinin. *Virology* 181:553-563.
- Fitzgerald TA, Munoz M, Wood A, Snodgrass DR (1995) Serological and genomic characterization of group A rotavirus from lamb. *Arch Virol* 140:1541-1548.
- Flewett TH, Bryden AS, Davies H, Woode GN, Bridger JC, Derrick JM (1974) Relation between viruses from acute gastroenteritis of children and newborn calves. *Lancet* 304:61-63.
- Fukuda M, Kuga K, Miyazaki A, Suzuki T, Tasei K, Aita T, Mase M, Sugiyama M, Tsunemitsu H (2012) Development and application of one-step multiplex reverse transcription PCR for simultaneous detection of five diarrheal viruses in adult cattle. *Arch Virol* 157:1063-1069.
- Fushuku S, Fukuda K (2006) Examination of the applicability of a commercial human rotavirus antigen detection kit for use in laboratory rabbits. *Exp Anim* 55:71-74.
- García A, Ruiz-Santa-Quiteria JA, Orden JA, Cid D, Sanz R, Gómez-Bautista M, de la Fuente R (2000) Rotavirus and concurrent infections with other enteropathogens in neonatal diarrheic dairy calves in Spain. *Comp Immunol Microbiol Infect Dis* 23:175-183.
- Gentsch JR, Laird AR, Bielfelt B, Griffin DD, Banyai K, Ramachandran M, Jain V, Cunliffe NA, Nakagomi O, Kirkwood CD, Fischer TK, Parashar UD, Bresee JS, Jiang B, Glass RI (2005) Serotype diversity and reassortment between human and animal rotavirus strains: implications for rotavirus vaccine programs. *J Infect Dis* 192:146-159.
- Ghosh S, Urushibara N, Taniguchi K, Kobayashi N (2012) Whole genomic analysis reveals the porcine origin of human G9P[19] rotavirus strains Mc323 and Mc345. *Infect Genet Evol* 12:471-477.
- Gonzalez RA, Torres-Vega MA, Lopez S, Arias CF (1998) In vivo interactions among rotavirus nonstructural proteins. *Arch Virol* 143:981-996.
- Gouvea V, Glass RI, Woods P, Taniguchi K, Clark HF, Forrester B, Fang ZY (1990) Polymerase chain reaction amplification and typing of rotavirus nucleic acid from stool specimens. *J Clin Microbiol* 28:276-282.
- Gouvea V, Santos N, Timenetsky MC (1994a) Identification of bovine and porcine G types by PCR. *J Clin Microbiol* 32:1338-1340.
- Gouvea V, Santos N, Timenetsky MC (1994b) VP4 typing of bovine and porcine group A rotaviruses by PCR. *J Clin Microbiol* 32:1333-1337.
- Grant L, Esona M, Gentsch J, Watt J, Reid R, Weatherholtz R, Santosham M, Parashar U, O'Brien K (2011) Detection of G3P[3] and G3P[9] rotavirus strains in American Indian children with evidence of gene reassortment between human and animal rotaviruses. *J Med Virol* 83:1288-1299.
- Grauballe PC, Vestergaard BF, Meyling A, Genner J (1981) Optimized enzyme-linked immunosorbent assay for detection of human and bovine rotavirus in stools: comparison with electron-microscopy, immunoelectrophoresis, and fluorescent antibody techniques. *Med Virol* 7:29-40.
- Gu Y, Gu Q, Kodama H, Mueller WE, Ushijima H (2000) Development of antirotavirus agents in Asia. *Pediatr Int* 42:440-447.
- Gusmao RH, Mascarenhas JD, Gabbay YB, Linhares AC (1994) Nosocomial transmission of an avian-like rotavirus strain among children in Belem. *Brazil J Diarrhoeal Dis Res* 12:129-132.
- Guy JS (1998) Virus infections of the gastrointestinal tract of poultry. *Poult Sci* 77:1166-1175.
- He H, Zhou D, Fan W, Fu X, Zhang J, Shen Z, Li J, Wu Y (2012) Cyclophilin A inhibits rotavirus replication by facilitating host IFN-I production. *Biochem Biophys Res Commun* 422:664-669.
- Holland RE (1990) Some infectious causes of diarrhea in young farm animals. *Clin Microbiol Rev* 3:345-375.
- Hu L, Crawford SE, Hyser JM, Estes MK, Prasad BV (2012) Rotavirus non-structural proteins: structure and function. *Curr Opin Virol*

- 2:380-388.
- Hung T, Chen G, Wang C, Yao H, Fang Z, Chao T, Chou Z, Ye W, Chang W, Den S, Liong X, Chang W (1984) Waterborne outbreak of rotavirus diarrhea in adults in China caused by a novel rotavirus. *Lancet* 323:1139-1142.
- Hurley WL, Theil PK (2011) Perspectives on immunoglobulins in colostrum and milk. *Nutrients* 3:442-474.
- Hurst CJ, Gerba CP (1980) Stability of simian rotavirus in fresh and estuarine water. *Appl Environ Microbiol* 39:1-5.
- Hyser JM, Collinson-Pautz MR, Utama B, Estes MK (2010) Rotavirus disrupts calcium homeostasis by NSP4 viroporin activity. *mBio* 1:265.
- Isa P, Gutierrez M, Arias CF, Lopez S (2008) Rotavirus cell entry. *Future Virol* 3:135-146.
- Iturriza-Gomara M, Dallman T, Banyai K, Bottiger B, Buesa J, Die-drich S, Fiore L, Johansen K, Koopmans M, Korsun N, Koukou D, Kroneman A, Laszlo B, Lappalainen M, Maunula L, Mas Marques A, Matthijnsens J, Midgley S, Mladenova Z, Nawaz S, Poljsak-Prijatelj M, Pothier P, Ruggeri FM, Sanchez-Fauquier A, Steyer A, Sidaraviciute-Ivaskeviciene I, Syriopoulou V, Tran AN, Usonis V, Van Ranst M, De Rougemont A, Gray J (2010) Rotavirus genotypes co-circulating in Europe between 2006 and 2009 as determined by EuroRotaNet, a pan-European collaborative strain surveillance network. *Epidemiol Infect* 16:1-15.
- Iturriza-Gomara M, Dallman T, Banyai K, Bottiger B, Buesa J, Die-drich S, Fiore L, Johansen K, Korsun N, Kroneman A, Lappalainen M, Laszlo B, Maunula L, Matthijnsens J, Midgley S, Mladenova Z, Nawaz S, Poljsak-Prijatelj M, Pothier P, Ruggeri FM, Sanchez-Fauquier A, Schreier E, Steyer A, Sidaraviciute I, Tran AN, Usonis V, Van Ranst M, De Rougemont A, Gray J (2009) Rotavirus surveillance in Europe: Web-enabled reporting and real-time analysis of genotyping and epidemiological data. *J Infect Dis* 200:215-221.
- Jayaram H, Estes MK, Prasad BV (2004) Emerging themes in rotavirus cell entry, genome organization, transcription and replication. *Virus Res* 101:67-81.
- Jere KC, Mlera L, O'Neill HG, Peenze I, van Dijk AA (2012) Whole genome sequence analyses of three African bovine rotaviruses reveal that they emerged through multiple reassortment events between rotaviruses from different mammalian species. *Vet Microbiol* 159:245-250.
- Johnson CA, Snider TG, Henk WG, Fulton RW (1986) A scanning and transmission electron microscopic study of rotavirus-induced intestinal lesions in neonatal gnotobiotic dogs. *Vet Pathol* 23:443-453.
- Kapikian AZ, Chanock RM (1996) Rotaviruses. In: (eds: Fields BN, Knipe DM, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman B, Straus SE) *Fields' Virology*, 3rd edn. Lippincott, Philadelphia, pp. 1657-1708.
- Kapikian AZ, Hoshino Y, Chanock RM (2001) Rotaviruses. In: (eds: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE) *Fields' Virology*, 4th edn. Lippincott, Philadelphia, pp. 1787-833.
- Khamrin P, Maneekarn N, Peerakome S, Yagyu F, Okitsu S, Ushijima H (2006) Molecular characterization of a rare G3P[3] human rotavirus reassortant strain reveals evidence for multiple human-animal interspecies transmissions. *J Med Virol* 78:986-994.
- Kim HJ, Park JG, Matthijnsens J, Lee JH, Bae YC, Alfajaro MM, Park SI, Kang MI, Cho KO (2011) Intestinal and extra-intestinal pathogenicity of a bovine reassortant rotavirus in calves and piglets. *Vet Microbiol* 152:291-303.
- Koopmans M, Vennema H, Heersma H, van Strien E, van Duynhoven Y, Brown D, Reacher M, Lopman B (2003) European consortium on foodborne viruses early identification of common-source foodborne virus outbreaks in Europe. *Emerg Infect Dis* 9:1136-1142.
- Koroglu M, Yakupogullari Y, Otlu B, Ozturk S, Ozden M, Ozer A, Sener K, Durmaz R (2011) A waterborne outbreak of epidemic diarrhoea due to group A rotavirus in Malatya, Turkey. *New Microbiol* 34:17-24.
- Lawton JA, Estes MK, Prasad BV (2000) Mechanism of genome transcription in segmented dsRNA viruses. *Adv Virus Res* 55:185-229.
- Le Rousic S, Klein N, Houghton S, Charleston B (2000) Use of colostrum from rotavirus-immunised cows as a single feed to prevent rotavirus-induced diarrhoea in calves. *Vet Rec* 147:160-161.
- Li D, Gu AZ, He M, Shi HC, Yang W (2009) UV inactivation and resistance of rotavirus evaluated by integrated cell culture and real-time RT-PCR assay. *Water Res* 43:3261-3269.
- Lopez S, Arias CF (2004) Multistep entry of rotavirus into cells: a Versaillesque dance. *Trends Microbiol* 12:271-278.
- Lorenz I, Fagan J, More SJ (2011) Calf health from birth to weaning II. Management of diarrhoea in pre-weaned calves. *Ir Vet J* 64:9.
- Luchs A, Cilli A, Morillo SG, Carmona C, Timenetsky C (2012) Rare G3P[3] rotavirus strain detected in Brazil: possible human-canine interspecies transmission. *J Clin Virol* 54:89-92.
- Lundgren O, Svensson L (2001) Pathogenesis of rotavirus diarrhea. *Microbes Infect* 13:1145-1156.
- Maes P, Matthijnsens J, Rahman M, Van Ranst M (2009) RotaC: a web based tool for the complete genome classification of group A rotaviruses. *BMC Microbiol* 9:238.
- Maes RK, Grooms DL, Wise AG, Han C, Ciesicki V, Hanson L, Vickers ML, Kanitz C, Holland R (2003) Evaluation of a human group A rotavirus assay for on-site detection of bovine rotavirus. *J Clin Microbiol* 41:290-294.
- Martella V, Banyai K, Lorusso E, Bellacicco AL, Decaro N, Camero M, Bozzo G, Moschidou P, Arista S, Pezzotti G, Lavazza A, Buonavoglia C (2007) Prevalence of group C rotaviruses in weaning and post-weaning pigs with enteritis. *Vet Microbiol* 123:26-33.
- Martella V, Banyai K, Matthijnsens J, Buonavoglia C, Ciarlet M (2010) Zoonotic aspects of rotaviruses. *Vet Microbiol* 140:246-255.
- Martella V, Potgieter AC, Lorusso E, De Grazia S, Giammanco GM, Matthijnsens J, Banyai K, Ciarlet M, Lavazza A, Decaro N, Buonavoglia C (2011) A feline rotavirus G3P[9] carries traces of multiple reassortment events and resembles rare human G3P[9] rotaviruses. *J Gen Virol* 92:1214-1221.
- Matthews RE (1979) Third report of the International Committee on Taxonomy of Viruses. Classification and nomenclature of viruses. *Intervirology* 12:129-296
- Matthijnsens J, Bilcke J, Ciarlet M, Martella V, Banyai K, Rahman M, Zeller M, Beutels P, Van Damme P, Van Ranst M (2009a) Rotavirus disease and vaccination: impact on genotype diversity. *Future Microbiol* 4:1303-1316.
- Matthijnsens J, Ciarlet M, Heiman E, Arijs I, Delbeke T, McDonald SM, Palombo AE, Iturriza-Gomara M, Maes P, Patton JT, Rahman M, Van Ranst M (2008a) Full genome-based classification of rotaviruses reveals a common origin between human Wa-like and porcine rotavirus strains and human DS-1-like and bovine rotavirus strains. *J Virol* 82:3204-3219.
- Matthijnsens J, Ciarlet M, McDonald SM, Attoui H, Banyai K, Brister JR, Buesa J, Esona MD, Estes MK, Gentsch JR, Iturriza-Gómara M, Johne R, Kirkwood CD, Martella V, Mertens PP, Nakagomi O, Parreno V, Rahman M, Ruggeri FM, Saif LJ, Santos N, Ste-

- yer A, Taniguchi K, Patton JT, Desselberger U, Van Ranst M (2011a) Uniformity of rotavirus strain nomenclature proposed by the Rotavirus Classification Working Group (RCWG). *Arch Virol* 156:1397-1413.
- Matthijnssens J, Ciarlet M, Parreno V, Martella V, Banyai K, Garai-cochea L, Palombo E, Arista S, Gerna G, Novo L, Rahman M, Van Ranst M (2009b) Are human P[14] rotavirus strains the result of interspecies transmissions from sheep or other ungulates belonging to the mammalian order of Artiodactyla? *J Virol* 83:2917-2929.
- Matthijnssens J, Ciarlet M, Rahman M, Attoui H, Banyai K, Estes MK, Gentsch JR, Iturriza-Gomara M, Kirkwood CD, Martella V, Mertens PP, Nakagomi O, Patton JT, Ruggeri FM, Saif LJ, Santos N, Steyer A, Taniguchi K, Desselberger U, Van Ranst M (2008b) Recommendations for the classification of group A rotaviruses using all 11 genomic RNA segments. *Arch Virol* 153:1621-1629.
- Matthijnssens J, De Grazia S, Piessens J, Heylen E, Zeller M, Giammanco GM, Banyai K, Buonavoglia C, Ciarlet M, Martella V, Van Ranst M (2011b) Multiple reassortment and interspecies transmission events contribute to the diversity of feline, canine and feline/canine-like human group A rotavirus strains. *Infect Genet Evol* 11:1396-1406.
- Matthijnssens J, Otto P, Ciarlet M, Desselberger U, Van Ranst M, Johne R (2012) VP6 sequence-based cut-off values as a criterion for rotavirus species demarcation. *Arch Virol* 157:1177-1182.
- McClain B, Settembre E, Temple BR, Bellamy AR, Harrison SC (2010) X-ray crystal structure of the rotavirus inner capsid particle at 3.8 Å resolution. *J Mol Biol* 397:587-599.
- McNeal MM, Rae MN, Bean JA, Ward RL (1999) Antibody-dependent and -independent protection following intranasal immunization of mice with rotavirus particles. *J Virol* 73:7565-7573.
- McNulty MS (1978) Rotaviruses. *J Gen Virol* 40:1-18.
- McNulty MS (2003) Rotavirus infections. In: (ed.: Saif YM) *Diseases of Poultry*. Iowa State University Press, Ames, pp. 308-320.
- McNulty MS, Allan GM, Thompson DJ, O'Boyle JD (1978) Antibody to rotavirus in dogs and cats. *Vet Rec* 102:534-535.
- Mebus CA, Newman LE (1977) Scanning electron, light, and immunofluorescent microscopy of intestine of gnotobiotic calf infected with reovirus-like agent. *Am J Vet Res* 38:553-558.
- Mebus CA, Underdahl NR, Rhodes MB, Twiehaus MJ (1969) Calf diarrhea (Scours): reproduced with a virus from a field outbreak. *Univ Nebraska Res Bull* 233:1-16.
- Midgley SE, Banyai K, Buesa J, Halaihel N, Hjulsgager CK, Jakab F, Kaplon J, Larsen LE, Monini M, Poljsak-Prijatelj M, Pothier P, Ruggeri FM, Steyer A, Koopmans M, Bottiger B (2012a) Diversity and zoonotic potential of rotaviruses in swine and cattle across Europe. *Vet Microbiol* 156:238-245.
- Midgley SE, Hjulsgager CK, Larsen LE, Falkenhorst G, Böttiger B (2012b) Suspected zoonotic transmission of rotavirus group A in Danish adults. *Epidemiol Infect* 140:1013-1017.
- Mochizuki M, Hashimoto M, Ishida T (2001) Recent epidemiological status of canine viral enteric infections and Giardia infection in Japan. *J Vet Med Sci* 63:573-575.
- Mori Y, Borgan MA, Takayama M, Ito N, Sugiyama M, Minamoto N (2003) Roles of outer capsid proteins as determinants of pathogenicity and host range restriction of avian rotaviruses in a suckling mouse model. *Virology* 316:126-134.
- Mori Y, Sugiyama M, Takayama M, Atoji Y, Masegi T, Minamoto N (2001) Avian-to-mammal transmission of an avian rotavirus: analysis of its pathogenicity in a heterologous mouse model. *Virology* 288:63-70.
- Mossel EC, Ramig RF (2002) Rotavirus genome segment 7 (NSP3) is a determinant of extraintestinal spread in the neonatal mouse. *J Virol* 76:6502-6509.
- Mukherjee A, Ghosh S, Bagchi P, Dutta D, Chattopadhyay S, Kobayashi N, Chawla-Sarkar M (2011) Full genomic analyses of human G4P[4], G4P[6], G9P[19] and G10P[6] strains from North-eastern India: evidence for interspecies transmission and complex reassortment events. *Clin Microbiol Infect* 17:1343-1346.
- Muller H, Johne R (2007) Rotaviruses: diversity and zoonotic potential--a brief review. *Berl Munch Tierarztl Wochenschr* 120:108-112.
- Munoz M, Alvarez M, Lanza I, Cármenes P (1996) Role of enteric pathogens in the aetiology of neonatal diarrhoea in lambs and goat kids in Spain. *Epidemiol Infect* 117:203-211.
- Munoz JA, Chenoll E, Casinos B, Bataller E, Ramon D, Genoves S, Montava R, Ribes JM, Buesa J, Fabrega J, Rivero M (2011). Novel probiotic *Bifidobacterium longum* subsp. *infantis* CECT 7210 strain active against rotavirus infections. *Appl Environ Microbiol* 77:8775-8783.
- Nakagomi O, Nakagomi T (2002) Genomic relationships among rotaviruses recovered from various animal species as revealed by RNA-RNA hybridization assays. *Res Vet Sci* 73:207-214.
- Nakagomi O, Ohshima A, Aboudy Y, Shif I, Mochizuki M, Nakagomi T, Gotlieb-Stematsky T (1990) Molecular identification by RNA-RNA hybridization of a human rotavirus that is closely related to rotaviruses of feline and canine origin. *J Clin Microbiol* 28:1198-1203.
- Narita M, Fukusho A, Konno S, Shimizu Y (1982) Intestinal changes in gnotobiotic piglets experimentally inoculated with porcine rotavirus. *Natl Inst Anim Health Q* 22:54-60.
- Nemoto M, Hata H, Higuchi T, Imagawa H, Yamanaka T, Niwa H, Bannai H, Tsujimura K, Kondo T, Matsumura T (2010) Evaluation of rapid antigen detection kits for diagnosis of equine rotavirus infection. *J Vet Med Sci* 72:1247-1250.
- O'Neal CM, Crawford SE, Estes MK, Conner ME (1997) Rotavirus virus-like particles administered mucosally induce protective immunity. *J Virol* 71:8707-8717.
- Otto PH, Ahmed MU, Hotzel H, Machnowska P, Reetz J, Roth B, Trojnar E, Johne R (2012) Detection of avian rotaviruses of groups A, D, F and G in diseased chickens and turkeys from Europe and Bangladesh. *Vet Microbiol* 156:8-15.
- Otto P, Liebler-Tenorio EM, Elschner M, Reetz J, Löhren U, Diller R (2006) Detection of rotaviruses and intestinal lesions in broiler chicks from flocks with runting and stunting syndrome (RSS). *Avian Dis* 50:411-418.
- Palombo EA (2002) Genetic analysis of Group A rotaviruses: evidence for interspecies transmission of rotavirus genes. *Virus Genes* 24:11-20.
- Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, Birmingham M, Glass RI (2009) Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis* 200:9-15.
- Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI (2003) Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 9:565-572.
- Park SI, Matthijnssens J, Saif LJ, Kim HJ, Park JG, Alfajaro MM, Kim DS, Son KY, Yang DK, Hyun BH, Kang MI, Cho KO (2011) Reassortment among bovine, porcine and human rotavirus strains results in G8P[7] and G6P[7] strains isolated from cattle in South Korea. *Vet Microbiol* 152:55-66.
- Parreno V, Bejar C, Vagnozzi A, Barrandeguy M, Costantini V, Craig MI, Yuan L, Hodgins D, Saif L, Fernandez F (2004) Modulation

- by colostrum-acquired maternal antibodies of systemic and mucosal antibody responses to rotavirus in calves experimentally challenged with bovine rotavirus. *Vet Immunol Immunopathol* 100:7-24.
- Parreno V, Marcoppido G, Vega C, Garaicoechea L, Rodriguez D, Saif L, Fernández F (2010) Milk supplemented with immune colostrum: Protection against rotavirus diarrhea and modulatory effect on the systemic and mucosal antibody responses in calves experimentally challenged with bovine rotavirus. *Vet Immunol Immunopathol* 136:12-27.
- Patton JT, Hua J, Mansell EA (1993) Location of intrachain disulfide bonds in the VP5** and VP8** trypsin cleavage fragments of the rhesus rotavirus spike protein VP4. *J Virol* 67:4848-4855.
- Pearson GR, McNulty MS (1977) Pathological changes in the small intestine of neonatal pigs infected with a pig reovirus-like agent (rotavirus). *J Comp Pathol* 87:363-375.
- Pearson GR, McNulty MS, Logan EF (1978) Pathological changes in the small intestine of neonatal calves naturally infected with reovirus (rotavirus). *Vet Rec* 102:464-458.
- Poncet D, Aponte C, Cohen J (1993) Rotavirus protein NSP3 (NS34) is bound to the 3' end consensus sequence of viral mRNAs in infected cells. *J Virol* 67:3159-3165.
- Prince DS, Astry C, Vonderfecht S, Jakab G, Shen FM, Yolken RH (1986) Aerosol transmission of experimental rotavirus infection. *Pediatr Infect Dis J* 5:218-222.
- Ramig RF (2004) Pathogenesis of intestinal and systemic rotavirus infection. *J Virol* 78:10213-10220.
- Ruiz MC, Cohen J, Michelangeli F (2000) Role of Ca²⁺ in the replication and pathogenesis of rotavirus and other viral infections. *Cell Calcium* 28:137-149.
- Ruiz MC, Leon T, Diaz Y, Michelangeli F (2009) Molecular biology of rotavirus entry and replication. *Scientif World J* 16:1476-1497.
- Saif LJ, Fernandez FM (1996) Group A rotavirus veterinary vaccines. *J Infect Dis* 174:98-106.
- Saif LJ, Jiang B (1994) Non group A rotaviruses of humans and animals. *Curr Top Microbiol Immunol* 185:339-371.
- Saif LJ, Redman D, Smith L, Theil KW (1983) Passive immunity to bovine rotavirus in newborn calves fed colostrum supplements from immunized or nonimmunized cows. *Infect Immun* 41:1118-1131.
- Saif LJ, Rosen B, Parwani A (1994) Animal rotaviruses. In: (ed.: Kapikian A) *Viral Infections of the Gastrointestinal Tract*. Marcel Dekker, New York, pp. 279-367.
- Schoeb TR, Casebolt DB, Walker VE, Potgieter LND, Thouless ME, DiGiacomo, RF (1986) Rotavirus-associated diarrhea in a commercial rabbitry. *Lab Anim Sci* 36:149-152.
- Schumann T, Hotzel H, Otto P, Johne R (2009) Evidence of interspecies transmission and reassortment among avian group A rotaviruses. *Virology* 386:334-343.
- Schwarz BA, Bange R, Vahlenkamp TW, Johne R, Muller H (2002) Detection and quantitation of group A rotaviruses by competitive and real-time reverse transcription-polymerase chain reaction. *J Virol Methods* 105:277-285.
- Schwens A, Dagenais L, Chappuis G, Pastoret PP, Calberg-Bacq CM (1983) Propagation of bovine rotavirus by young dogs. *J Comp Pathol* 93:135-41.
- Sen A, Kobayashi N, Das S, Krishnan T, Bhattacharya SK, Naik TN (2001) The evolution of human group B rotaviruses. *Lancet* 357:198-199.
- Settembre EC, Chen JZ, Dormitzer PR, Grigorieff N, Harrison SC (2011) Atomic model of an infectious rotavirus particle. *EMBO J* 30:408-416.
- Simoes CM, Wang Y, Glass RI, Jiang B (2008) Evidence for zoonotic transmission of group C rotaviruses among children in Belem. *Braz J Med Virol* 80:1666-1674.
- Snodgrass DR, Angus KW, Gray EW (1977) Rotavirus infection in lambs: pathogenesis and pathology. *Arch Virol* 55:263-274.
- Snodgrass DR, Ferguson A, Allan F, Angus KW, Mitchell B (1979) Small intestinal morphology and epithelial cell kinetics in lamb rotavirus infections. *Gastroenterology* 76:477-481.
- Steele AD, Geyer A, Gerdes GH (2004). Rotavirus infections. In: (eds: Coetzer JAW, Tustin RC) *Infectious Diseases of Livestock*, Oxford University Press, Johannesburg, pp. 1256-1264.
- Tamura K, Dudley J, Nei M, Kumar S (2007) MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) software version 4.0. *Mol Biol Evol* 24:1596-1599.
- Taniguchi K, Kojima K, Kobayashi N, Urasawa T, Urasawa S (1996) Structure and function of rotavirus NSP1. *Arch Virol* 12:53-58.
- Taraporewala ZF, Patton JT (2004) Nonstructural proteins involved in genome packaging and replication of rotaviruses and other members of the Reoviridae. *Virus Res* 101:57-66.
- Thouless ME, DiGiacomo RF, Deeb BJ, Howard H (1988) Pathogenicity of rotavirus in rabbits. *J Clin Microbiol* 26:943-947.
- Tian P, Ball JM, Zeng CQ, Estes MK (1996) The rotavirus nonstructural glycoprotein NSP4 possesses membrane destabilization activity. *J Virol* 70:6973-6981.
- Torres-Medina A, Schlafer DH, Mebus CA (1985) Rotaviral and coronavirus diarrhea. *Vet Clin North Am Food Anim Pract* 1:471-493.
- Torres-Medina A, Underdahl NR (1980) Scanning electron microscopy of intestine of gnotobiotic piglets infected with porcine rotavirus. *Can J Comp Med* 44:403-411.
- Tsai B (2007) Penetration of non-enveloped viruses into the cytoplasm. *Annu Rev Cell Dev Biol* 23:23-43.
- Tsugawa T, Hoshino Y (2008) Whole genome sequence and phylogenetic analyses reveal human rotavirus G3P[3] strains Ro1845 and HCR3A are examples of direct virion transmission of canine/feline rotaviruses to humans. *Virology* 380:344-353.
- Tupler T, Levy JK, Sabshin SJ, Tucker SJ, Greiner EC, Leutenegger CM (2012) Enteropathogens identified in dogs entering a Florida animal shelter with normal feces or diarrhea. *J Am Vet Med Assoc* 241:338-343.
- Tzipori SR (1976) Human rotavirus in young dogs. *Med J Aust* 11:922-923.
- Tzipori SR, Makin TJ (1978) Propagation of human rotavirus in young dogs. *Veterinary Microbiol* 3:55-63.
- Tzipori SR, Makin TJ, Smith ML (1980) The clinical response of gnotobiotic calves, pigs and lambs to inoculation with human, calf, pig and foal rotavirus isolates. *Aust J Exp Biol Med Sci* 58:309-318.
- Varshney KC, Bridger JC, Parsons KR, Cook R, Teucher J, Hall GA (1995) The lesions of rotavirus infection in 1- and 10-day-old gnotobiotic calves. *Vet Pathol* 32:619-627.
- Vasquez-del Carpio R, Morales JL, Barro M, Ricardo A, Spencer E (2006) Bioinformatic prediction of polymerase elements in the rotavirus VP1 protein. *Biol Res* 39:649-659.
- Vega C, Bok M, Chacana P, Saif L, Fernandez F, Parreno V (2011) Egg yolk IgY: protection against rotavirus induced diarrhea and modulatory effect on the systemic and mucosal antibody responses in newborn calves. *Vet Immunol Immunopathol* 142:156-169.
- Vesikari T, Isolaur E, D'Hondt E, Delem A, Andre FE, Zissis G (1984) Protection of infants against rotavirus diarrhea by RIT 4237 attenuated bovine rotavirus strain vaccine. *Lancet* 1:977-981.
- Vesikari T, Matson D, Dennehy P, Van Damme P, Santosham M, Ro-

- driguez Z, Dallas M, Heyse J, Goveia MG, Black S, Shinefield H, Christie C, Ylitalo S, Itzl R, Coia ML, Onorato M, Adey B, Marshall G, Gothefors L, Campens D, Karvonen A, Watt J, O'Brien K, DiNubile M, Clark HF, Boslego J, Offit PA, Heaton PM (2006) Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 354:23-33.
- Vonsover A, Shif I, Silberstein I, Rudich H, Aboudy Y, Mendelson E, Shulman L, Nakagomi T, Nakagomi O (1993) Identification of feline- and canine-like rotaviruses isolated from humans by restriction fragment length polymorphism assay. *J Clin Microbiol* 31:1783-1787.
- Wani SA, Bhat MA, Ishaq SM, Ashrafi MA, Buchh AS, Haq M (2003) Detection of a mammalian-like group A rotavirus in diarrhoeic chicken. *Vet Microbiol* 94:13-18.
- Ward RL, McNeal MM (2010) VP6: A candidate rotavirus vaccine. *J Infect Dis* 202:101-107.
- Woode GN (1978) Epizootiology of bovine rotavirus infection. *Vet Rec* 103:44-46.
- Zarate S, Espinosa R, Romero P, Méndez E, Arias CF, López S (2000) The VP5 domain of VP4 can mediate attachment of rotaviruses to cells. *J Virol* 74:593-599.
- Zhang M, Zeng CQ, Morris AP, Estes MK (2000) A functional NSP4 enterotoxin peptide secreted from rotavirus-infected cells. *J Virol* 74:11663-11670.
- Zijlstra RT, Donovan SM, Odle J, Gelberg HB, Petschow BW, Gaskins HR (1997) Protein-energy malnutrition delays small-intestinal recovery in neonatal pigs infected with rotavirus. *J Nutr* 127:1118-1127.