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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 μικροσκοπηση, 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 ευρετηρίασης: 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 (Iturriza-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; Matthijnsens et al., 2008b; 2011a
2	VP2	120	C	1-9	Inner shell of core	Stimulator of RNA replication	Matthijnsens et al., 2008b; 2011a; McClain et al., 2010
3	VP3	<25	M	1-8	Edges of core	Guanylyl-transferase mRNA capping enzyme	Donelli and Superti, 1994; Matthijnsens et al., 2008b; 2011a
	VP4				Surface spike	Host cell attachment	Matthijnsens 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; Matthijnsens et al., 2008b; 2011a
6	VP6	780	I	1-16	Inner capsid	Intermediate capsid layer -species specific	Matthijnsens et al., 2008b; 2011a; McClain et al., 2010
7	NSP3	-	T	1-12	Non-structural	Support viral mRNA transcription	Poncet et al., 1993; Matthijnsens et al., 2008b; 2011a
8	NSP2	-	N	1-9	Non-structural	Formation of viroplasm	Taraporewala and Patton; 2004; Matthijnsens et al., 2008b; 2011a
9	VP7	780	G	1-27	Surface	Outer protein layer, virus penetration	Matthijnsens et al., 2008b; 2011a; Hyser et al., 2010
10	NSP4	-	E	1-14	Non-structural	Enterotoxin	Matthijnsens et al., 2008b; 2011a; Aoki et al., 2009
11	NSP5/6	-	H	1-11	Non-structural	Formation of viroplasm	Taraporewala and Patton; 2004; Matthijnsens 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 viroplasms (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 (Mebius 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 disdigestion 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; Matthijssens, 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. ■

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