Viral Enteritis of Rabbits

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Abstract: The three most important viruses of rabbits include: Myxoma virus (MV), the poxvirus that causes Myxomatosis, the calici virus (*genus* Lagovirus) of Rabbit Haemorrhagic Disease (RHDV), and Lapine Rotavirus (LRV), which is an enteric agent. In particular, MV and RHDV can cause severe losses and a huge economic impact due to high level of morbidity and mortality, and their occurrence in most countries is followed by the application of strict measures of health policy. The impact of LRV is lower but indeed it should be considered an important aetiological agent of the so-called "enteritis complex". These viral infections can be efficiently controlled and limited by a correct management plan through the use of hygienic measures of direct prophylaxis together with the application of specific vaccination programs. There are other viral agents in rabbits, but both their occurrence and their pathological value are negligible. Most of them have been detected in rabbits with enteritis, *i.e.* parvovirus, coronavirus, adenovirus, calicivirus (*genus* Vesuvius), enterovirus-like, reovirus, and are generally not considered as primary agents of disease. Herpesvirus and coronavirus (the agent of pleural effusion disease) cancause a systemic disease but they have been very rarely reported.
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Introduction:

Myxomatosis:

From a virological point of view, Rabbit Haemorrhagic Disease virus (RHDV) and Myxoma Virus (MV) are the main health and economical problems for rabbit farmers because both virus infections cause rapid, systemic and lethal diseases with a mortality rate often over 80%. Differently, while MV, illegally introduced into Europe more than 50 years ago from South America **(Fenner, 1994; Fenner and Fantini, 1999)**, still represent a current and real problem, RHDV became a solved problem with the introduction of a reliable and efficient vaccine after its sudden and dramatic appearance. The main reason of this major difference is because RHDV and M belong to two very distant virus families, characterized by peculiar strategies used to survive in the host over time. MV belongs to the *Poxviridae* family; genus Leporipoxvirus with a very large linear double stranded DNA encoding 171 unique genes (twenty times more than RHDV). The entire genomes of the South American strain, Lausanne **(Cameron *et al.*, 1999)** and the North American strain MSW **(Labudovic *et al.*, 2004)** have been sequenced. While the central part of the genome includes approximately 100 gene encoding structural and essential proteins, the extreme parts of the genome include many immunomodulatory genes involved in contrasting the host immune system response towards MV infection. Actually, successful MV replication and the consequent degree of disease induction are related to its ability to avoid recognition and clearance by the innate host and acquired immune system of the infected rabbits **(Kerr and McFadden, 2002; Jeklova *et al.*, 2008; Stanford *et al.*, 2007)**. Immunomodulatory MV proteins (im-MV proteins) are included in three main categories in relation to the target specific pathways: 1) virokines and viroreceptors, 2) immune modulators and 3) antiapoptoticfactor **(Stanford *et al.*, 2007).** Most of the im-MV proteins interfere in specific host pathways "miming" one of the host proteins involved in the transmission of the signal throughout the pathways (i.e., they have a similar structure that allows them to compete with the normal proteins but they have a reduced capacity, if any, to transmit the signal). The final result is that the specific pathway is partially or totally blocked and as a consequence MV replicate more easily. The main ways to control myxomatosis in areas where MV is endemic are a combination of direct and indirect measures of prophylaxis. Basically, they include the application of biosecurity measures, in order to avoid the introduction of the infection by infected animals or by contacts with arthropod vectors, and the use of the vaccine **(Stanford *et al.*, 2007).** The commercially available vaccines belong to the

category of the live attenuated ones and are obtained by serial passage of the virus on tissue culture or in a heterologous host. Albeit they are able to induce immunity to MV for a variable time (even 9 to 10 months) that could be easily traced by using serological methods for detecting antibodies, the protection of rabbits from the infection is not fully guarantee. However, because of knowledge gained in the two last decades from research on MV (in particular on the im-MV proteins), a new family of vaccines will soon be produced and made available in a few years. Biotechnology deleted vaccines will have at least two advantages: first, to be more safe and able to induce a wider immunity since it will be well known which im-MV protein (s) have been deleted. Secondly, it will be possible to apply the DIVA strategy that is based on use of a "marker vaccine". This will allow the use of serology to ascertain if the anti-MV antibodies detected in a rabbit originated by an infection or a vaccination. In this view, it will be necessary to develop serological assays that are able to detect specific antibodies for the single most important MV proteins. One example of these assays was developed a tour laboratory where the MV serology is based on ELISA's that specifically detect the antibodies produced against the m71L protein **(Cristoni *et al.*, 2007)**. The ELISA used in routine assays is a competitive type one **(Botti *et al.*, 2007)**. A monoclonal antibodies (MAb) specific for the m71L is adsorbed at the solid phase. Sera are diluted in the microplate wells starting from the dilution 1/10 and the antigen, which are easily obtained from cells infected with MV. The competition for the binding of the antigen is between the MAb adsorbed onto the solid phase and the serum antibodies. Finally, the MAb anti m71L conjugated to the peroxidase enzyme is used to measure how much antigen is linked to the solid phase. The test has been used since 2000 in different epidemiological situations and it has been shown to be reliable and sensitive **(Lavazza *et al.*, 2004a; Ferrazzi *et al.*, 2007)**. Presently, more studies are in progress on in order to identify the level of antibody production with respect to the main MV proteins, included the im-MV ones.

Calicivirus in Rabbits

Rabbit haemorrhagic disease (RHD) is a highly contagious and fatal acute hepatitis of wild and domestic European rabbits (*Oryctolagus cuniculus*), which was first reported in 1984 in China **(Liu *et al.*, 1984).** It appeared in Europe in late 1986-87 causing enormous devastation to the rabbit industry, at least until the development of an inactivated vaccine and introduction of its use in prophylactic programs. RHD has been reported in over 40 countries and is presently endemic in Asia, Europe Central America. Outbreaks have also been recorded in Saudi Arabia and West and North Africa. RHD has been intentionally introduced in Australia and New Zealand **(Cooke and Saunders, 2002),** The European rabbit is the only species affected by RHD and no other American lagomorphs (*i.e.*, *Romerolagus diazzi*, *Lepus californicus, and Sylvilagus floridanus*) have been shown to be susceptible **(Gregg *et al.*, 1991).**

The causative agent of RHD and EBHS:

For some years (1984-1990), the identification and classification of RHDV have been debated and various hypotheses were put forward (i.e., parvovirus, picornavirus, calicivirus). The definitive classification of RHD (and EBHSV) as calicivirus and the subsequent definition of the new genus Lagovirus inside the *Caliciviridae* family was achieved between 1991-1992, when various authors purified the non-cultivable virus from liver organ homogenates, amplified and sequenced the capsid protein, and studied its antigenic properties.

RHDV is 32 to 35 nm in diameter, has a single major capsid polypeptide (60 kDa), a positively stranded RNA genome of 7437 kb and a sub-genomic RNA of 2.2 **(Capucci *et al.*, 1990, 1991; Ohlinger *et al.*, 1990; Parra and Prieto, 1990; Meyers *et al.*, 1991a, 1991b).** The RHDV VP60 capsidprotein folds in two distinct domains held together by a hinge region: the N-terminal 1 – 234 residues constitute the inner domain and the C-terminal residues beyond 235–579 constitute the protruding domain. In the overall picture of the capsid, these domains form the inner shell and the outer shell, respectively, which is characterized by arch-like structures **(Barcena *et al.*, 2004).** This structure also correlates with the antigenic characteristics of RHDV. In fact, the main antigenic determinants are located on the C-terminal end of the VP60 **(Wirblich *et al.*, 1994; Capucci *et al.*, 1995a, 1998; Schirrmaier *et al.*, 1999).** Presently, it has become clear that EBHSV is not the same disease. In fact, the aetiology of EBHS remained unclear for many years until it was shown by animal experiments and electron microscopy EM analysis **(Eskens and Volmer, 1989; Lavazza and Vecchi, 1989)** that it was caused by a virus showing morphological characteristics indistinguishable from those of the rabbit haemorrhagic disease virus (RHDV) with biochemical features typical of the Caliciviridae family. However, significant antigenic, structural and molecular differences between the two viruses were found using RHDV monoclonal antibodies (MAbs) **(Capucci *et al.*, 1991, 1995a)**, and cross-hybridization and genomic **sequence** analysis **(Wirbilch *et al.*, 1994).** Alignment of the RNA sequences of the EBHSV and RHDV genomes reveals 71% nucleotide identity, and amino acid alignment shows 78% identity and 87%similarity (**LeGall *et al.*, 1998)**. Indeed, cross-infection did not occur by experimental

infection of rabbits with EBHSV and hares with RHDV **(Lavazza *et al*., 1996).** A second type of virus particle (s-RHDV) is commonly found as the main component in approximately 5% of RHDV-positive specimens (i.e., those taken from rabbits showing a protracted course of the disease) **(Capucci *et al.*, 1991; Granzow *et al.*, 1996; Barbieri *et al.*, 1997).** The main characteristics of this particle, called "smooth RHDV" (s-RHDV) are shown in Table 1. It corresponds to the inner shell of RHDV with large amounts detected, especially from 3 to 4 days post-infection, when specific anti-RHDV IgM are appearing, but only in the liver and spleen, not the bloodstream. These data, in association with the finding of fragments of the VP60 having different molecular weight (41–30 kDa), during transition from RHDV to s-RHDV, led **Barbieri *et al.* (1997)** to conclude that the genesis of the particle is due to a degradative process that is probably the consequence of the physiological clearance of the RHDV-IgM immuno-complex formed in large amounts at the beginning of the humoral response. Therefore, the identification of this second particle in the liver of a rabbit can be considered to be a marker of the subacute/chronic form of RHD that usually evolves between 4 and8 days post-infection, and is followed either by the death of the rabbit or, more often, by its recovery **(Barbieri *et al.*, 1997)**.

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Rotavirus

The Group A rotavirus, a member of the *Reoviridae* family, is considered to be the main cause of acute viral gastroenteritis in different animals including rabbits **(Schoeb *et al.*, 1986; Thouless *et al.*, 1996).** Lapine Rotavirus (LRV) is considered only mildly pathogenic **(Thouless *et al.*, 1988),** but it can primarily cause enteric disease in post-weaning rabbits and be involved in the aetiology of more severe enteritis outbreaks in association with other viruses, bacteria (*E. coli*, *Clostridium* spp) and parasites. Rabbits become infected by the oro-fecal route, and the extension and the severity of the lesions are dose dependent (i.e., the consequences of the infection (microvillus degeneration, malabsorption and diarrhea) are higher when the infectious dose is also high). The persistence of maternal antibodies until 30 to 45 days can reduce the symptoms of the disease. Thus, until 4 to 5 weeks of age, rabbits mostly became sub-clinically infected with particle excretion for only 3 days. The LRV infection is more frequent in growing rabbits (35 to 50 days old) and is characterized by a high rate of morbidity, with non-specific clinical signs (i.e., diarrhoea, anorexia, and depression). Diarrheic symptoms appear at the beginning of viral excretion that lasts for 6 to 8 days, and are generally followed by constipation. Lesions observed at necropsy are not constant: catarrhal, haemorrhagic or necrotic entero-tiflitis and caecal impaction. Meat rabbits suffering from enteritis can die due to dehydration and secondary bacterial infections. In rabbits that recover from the infection, adecrease in productivity is commonly observed due to reduced absorption capacity. A virological diagnosis can be achieved by testing faces and intestinal contents by ELISA, including negative staining by electron microscopy (nsEM) and PCR. LRV was detected in 16.4% **(Nieddu *et al*., 2000)** and 23% of post-weaning rabbits with enteric signs **(Cerioli *et al.*, 2004);** however, seroepidemiological surveys have shown that most adult rabbits are seropositive for rotavirus, thus indicating that there is normally a constant circulation of low amounts of rotavirus in industrial rabbit farms **(Peeters *et al.*, 1984; Di Giacomo and Thouless, 1986).** The introduction of breeders of unknown origin, without application of a quarantine period, is an important risk factor. Thus, a reduction in biosecurity and hygienic activities (e.g., cleaning, disinfection, removal of litters) can lead to a dramatic increase of the environmental contamination with rotavirus. The classification of rotavirus strains is based on the characterization of two outer capsid proteins, VP4 and VP7, the main antigenic determinants that independently elicit neutralising antibodies and induce a protective immunity response. Based on both antigenic or genetic characterization, 15 VP7types (G types) and 26 VP4 types (P genotypes) have been recognized **(Estes, 2001).** A few LRV strains have been analysed in detail in early investigations. Analyses of the few strains identified in various parts of the world (Canada, USA, Japan, Italy) have revealed a substantial antigenic/genetichomogeneity of LRV's, as all the viruses analyzed so far belong to the VP7 serotype G3 **(Petric *et al*., 1978; Sato *et al*., 1982; Conner *et al*., 1988; Thouless *et al*., 1988; Ciarlet *et al*., 1997)** and to the VP4 serotype P11[14] **(Ciarlet *et al*., 1997; Hoshino *et al*., 2002)**. The epidemiological surveys carried out to investigate the distribution of the VP7 and VP4 antigenic specificities of LRVs in Italy are fully reported by **Martella *et al.* (2003, 2004, and 2005).** Almost all the strains were characterized as P [22], G3 **(Martella *et al.*, 2005),** confirming the presence of the newly-recognized rotavirus P [22] VP4 allele in Italian rabbits. Only one P [14], G3 LRV strain was identified and two samples contained a mixed (P [14] + [22], G3) rotavirus infection. All the LRV strains analysed exhibited genogroup I VP6specificity and a long dsRNA electropherotype. However, one of the P [14], G3 strains possessed a super-short pattern. Overall, these

data highlight the epidemiological relevance of the P [22] LRV's inn Italianrabbitries.

Coronavirus

Rabbit Coronavirus (RbCoV) is an unassigned member in the *Coronaviridae* family. It has been described as an agent of two different path ologic forms in the rabbit: a systemic disease (known as pleural effusion disease or cardiomyopaty of rabbit) and an enteric disease **(Lapierre *et al.*, 1980; Osterhaus *et al.*, 1982).** The systemic disease is characterized by fever, anorexia, leucocytosis, lymphocytopenia, anaemia, hypergamma globulinemia, iridocyclitis, which is often followed by death. The lesions are localized to the myocardial and pleuric levels. The enteric disease shows the lesions and symptoms typical of enteritis caused by coronavirus in other species. The RbCoV replicates in small intestine with necrosis of apical villi and is followed by diarrhoea **(Descoteaux *et al.*, 1985; Descoteaux and Lussier, 1990).** A high prevalence has been found in seroepidemiological surveys **(Deeb *et al.*, 1993),** indicating a wide diffusion of the RbCoV in rabbitries. Diagnosis of coronavirus could be achieved by using negative staining electron EM. The important increase of coronavirus-like positivity from our previous surveys **(Nieddu *et al.*, 2000; Cerioli *et al.*, 2004).**

Other viruses

The Rabbit Parvovirus, first described by **Matsunaga *et al.* (1977)**, has very low pathogenicity and it is commonly isolated from the gut contents of healthy animals. It could cause very mild clinical signs (lethargy, disorexia, and depression) in experimentally infected animals and a mild to moderate enteritis in the small intestine **(Matsunaga and Chino, 1981).** Its primary pathogenic role is still unclear, but considering its frequency of identification, it could be important only in multiple infections when combined with other infectious agents (viruses, bacteria, and other parasites).

Some of the other viruses detected during diagnostic activity has only had a sporadic occurrence, thus their pathogenic role is probably negligible. Adenovirus has been previously reported only once **(Bodon and Prohaszka, 1980).** Reovirus and enterovirus have never been described as enteric agents of rabbits. However, we cannot exclude that enterovirus-like particles correspond to picobirna virus **(Gallimore *et al.*, 1993),** stating that strict morphological similarities exist with this group of non-cultivable RNA viruses as identified in several species (humans, pigs, chickens, guinea pigs) including rabbits**. Lusert *et al.* (1995)** found that picobirna virus was commonly excreted by 10% of rabbits without causing any symptoms or lesions. A cultivable calicivirus, *genus* vesivirus, has been recently identified from juvenile growing rabbits showing symptoms of diarrhoea **(Martin-Alonso *et al.*, 2005)** and it was shown to be neither related to Rabbit Haemorrhagic Diseases virus (RHDV) nor to Rabbit Calicivirus (RCV).

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