FOOT AND MOUTH DISEASE

Foot and mouth disease (FMD) is a severe, highly contagious viral disease of global concern. It causes severe illness in cows, pigs, sheep, deer, and other animals which have cloven or cleft hooves. It does not affect horses, dogs, or cats. It is not a public health disease or a food safety threat, and even does not relate to hand, foot and mouth disease that is common as childhood illness in human characterized by blisters in affected areas by viruses such as Coxsackie virus A16 (most common) and Enterovirus 71 (second most common). The foot and mouth disease of split hooved animals are caused by picornavirus and Foot and mouth disease virus characterized by fevers followed by blisters in the mouth and on the foot that may rupture and cause lameness (disability of walking due to dysfunction of the locomotor system). It may cause heart failure in lambs but usually does not cause death of the animals. Sometimes, secondary infections worsen the health condition of the animals. In cattle, it is particularly serious for the long-term health of the cow and can lead to loss of milk yield, chronic mastitis (inflammation of breast or udder), sterility and chronic lameness and sometimes chronic heart disease.

Geographical distribution

Foot and mouth disease is endemic in parts of Asia, Africa, the Midlle East and South America. While the serotypes O and A are widely distributed, SAT viruses occur mainly in Africa (with periodic incursions into the Middle East) and Asia 1 is currently found only in Asia. North and Central America, New Zealand, Australia, Greenland, Iceland and Western Europe are free of foot and mouth disease viruses. America eradicated the viruses completely in 1929, while Canada and Mexico became foot and mouth disease free in 1952. Since then no case has been reported yet from both country. India is equally inflicted with foot and mouth disease virus as other African as well as Asian country.

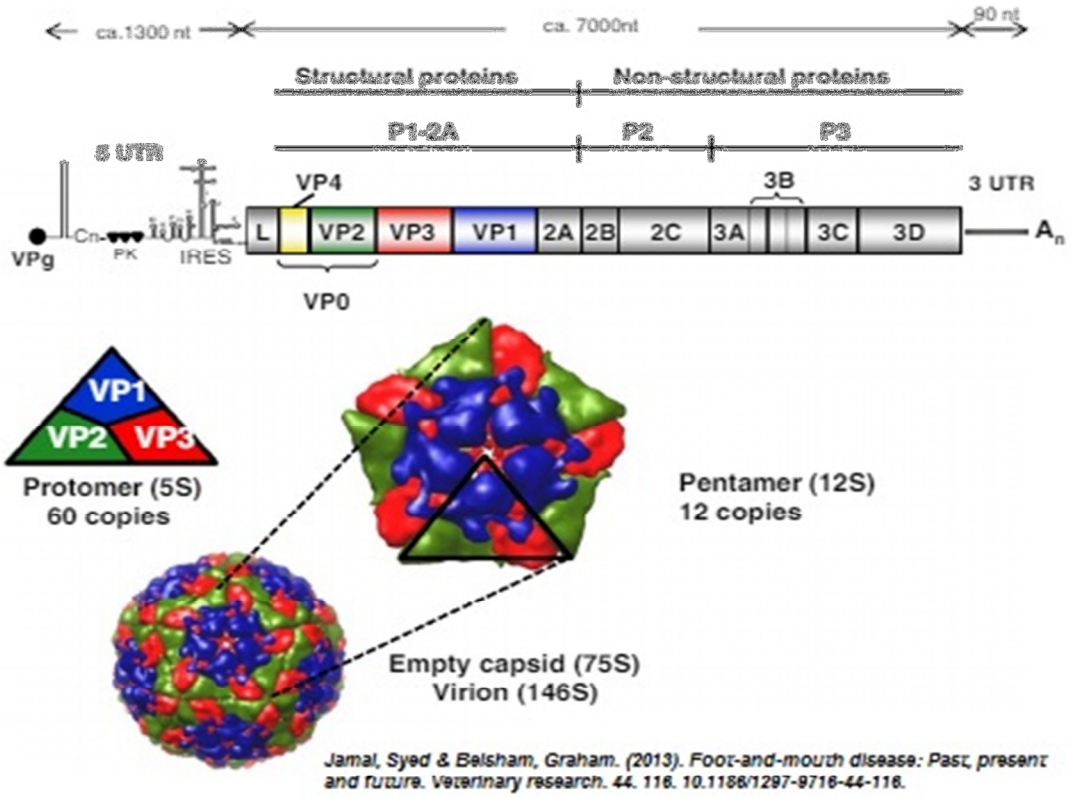
Classification of foot and mouth disease virus

As described above, foot and mouth disease in split hooved animals are caused by picornavirus and Foot and mouth disease virus. Picornavirus is a virus belonging to *Picornaviridae family* in *order Picornavirales* containing very large number of genera, while Foot and mouth viruses are also a Picornavirus in a genus *Aphthovirus* in a family *Picornaviridae* of order *Picornavirales* causing blisters in infected animals.

Structure of foot and mouth disease virus

Foot and mouth disease virus is a non-enveloped virus which has icosahedral capsid with pentameric protein subunits held together by noncovalent interactions and are often unstable. It is the basic picornavirus structure in all seven serotypes such as O, A, C, Asia, SAT1, SAT2 and SAT3. The foot and mouth disease virus particle is roughly spherical in shape and about 25-30 nm in diameter. It consists of the RNA genome surrounded by a protein shell or capsid. The capsid is composed of 60 copies of the capsomeres. Each capsomere consists of four structural polypeptides e.g. VP1, VP2, VP3 and VP4. The VP1, VP2 and VP3 are exposed on the surface of the virus while VP4 is located internally.The protein coat surrounds a single stranded (+) sense RNA genome of about 8400 nucleotides (nt) in length. The RNA includes three separate parts i.e. the 5′ untranslated region (5′ UTR), a long coding region and the 3′ untranslated region (3′ UTR). A small protein of about 24 or 25 residues long termed as VPg that is encoded by the 3B portion of the viral genome region, is covalently linked to the 5′ end of the genome.

The 5′ UTR is about 1300 nucleotides in length and consists of S fragment at its 5′ end, a poly C tract, 4 RNA pseudoknot, a cis-acting replication element (cre) (also known as 3B-uridylylation site; bus), and the internal ribosome entry site (IRES). The coding region is the major portion of the viral genome and is about 7000 nt in length. It encodes a large polyprotein which is then cleaved by viral proteases to form four different structural and eleven different non-structural proteins plus a variety of precursors, some of which have distinct functions. The 3′ UTR is much shorter than the 5′ UTR. It is about 90 nucleotides long and folds to form a specific stem-loop structure followed by a poly A tract of variable length. The 3′ UTR play an important role in viral genome replication.



Structure and Genome organization of Picornavirus

Replication of foot and mouth disease virus

Foot and mouth disease viruses enter host cells through receptor-mediated endocytosis followed by acid-pH-dependent release and translocation of RNA across the endosomal membrane as do almost all viruses. Attachment of viral particle is facilitated by arginine-glycine-aspartic acid (RGD)-binding integrin molecules. The RGD tripeptide motif that recognizes the integrin is located in a long, flexible loop on the surface of the virion and is found on all seven serotypes. As described above, the foot and mouth disease virus genome consists of an 8.5 kb long single-stranded, positive sense RNA genome that is translated into a single polyprotein, which is processed into four structural and ten non-structural proteins. The non-structural RNA-dependent RNA polymerase (RdRp) protein also known as 3Dpol is coded within the 3′ end of the FMDV genome. It is essential for the synthesis of viral RNA and pivotal to the virus lifecycle. Due to

single stranded RNA and non-specific transcription, foot and mouth disease virus shows high genetic and antigenic variability that limits treatment strategies.

Pathogenesis of foot and mouth disease virus

After infection of foot and mouth disease virus, it takes 2 to 12 days for visible symptoms to occur i.e. the incubation period ranges from 2-12 days. The disease is characterized by high fever that declines rapidly after two or three days, blisters inside the mouth that lead to excessive secretion of stringy or foamy saliva and to drooling, and blisters on the feet that may rupture and cause lameness as described above.

Foot and mouth viral disease (FMD) viral transmission is generally going through oral route. Pathogenesis of FMD is characterized by three basic phases as pre-viremia characterized by infection and replication at the primary replication site(s), sustained viremia with generalization and vesiculation at secondary infection sites and post-viremia/convalescence including resolution of clinical disease that result in long-term persistent infection.

Pre-viremia (Primary infection): It is general view that epithelial tissues of the oropharynx constitute the main sites of virus replication during early infection, whereas abundant amplification of virus occurs in vesicular lesions at secondary (peripheral) replication sites. It has been also found detectable in the tonsil of the soft palate, lingual tonsil, and the dorsal soft palate, suggesting that these sites may also be potential sites of primary infection detected as early as 24 hrs after virus exposure. It is associated with substantial increase in shedding of infectious virus via the oropharynx route.

Viremia and clinical disease: After pre-viremia phase, the virus undergoes rapidly to viremia phase by multiplying very fast in oropharyngeal cells. Viremia is characterized by fever, loss of appetite, and the appearance of vesicular lesions on feet, snout, and within the oral cavity, however the outcome of pre-viremia and its progression to viremia may prolonged following exposure to a strain of virus with reduced virulence, presence of suboptimal exposure conditions, exposure route, low challenge dose, or time-limited exposure. The initial phase of infection, consisting of the progression from primary, pre-viremic, infection to viremia and clinical disease may be prolonged following exposure to an FMDV strain of reduced virulence, or if exposure conditions are less stringent (e.g., suboptimal exposure route, low challenge dose, or time-limited exposure).

Anti-viral host response: The clinical phase subsides within approximately 7-14 days post infection (dpi) and infected animals generally recover from FMDV infection. It has been found that the virus elicits a rapid humoral response in infected animals which can be measured after 4-7 days post infection (dpi). However, later these humoral responses found to be decreased. In addition, cellular immune response and cytokines response (IFNs) are equally activated achieved by interactions between pathogens and cellular components of the innate immune response such as natural killer (NK) cells, dendritic cells (DCs), and macrophages impart their role in pathogen clearance. However, during infection, the virus stimulates DCs to produce interleukin (IL)-10, thus directive the adaptive immune response toward a stronger humoral rather than a T-cell mediated response leading to persistent infection. The cell is then forced to produce thousands of copies of the virus, and eventually bursts, releasing the new particles in the blood, a phase named as **viremia**. The virus is genetically highly variable which also limits the effectiveness of vaccination.

Control and treatment of foot and mouth disease

To control the spread of foot and mouth infection disinfection of people and equipment coming into contact with infected animals is very important. Sometimes, all animals of affected premises are slaughtered, movement restrictions are put in place with protection and surveillance zones, infected animals are vaccinated.

Vaccination can be used as part of a wider control strategy for foot and mouth but not as an overall solution due to several limitations. The vaccine must be strain specific to elicit virus type specific immune response. However, a current vaccine provides only 6 months of protection and it might be possible that they may become carriers if they are exposed to a new outbreak of the virus.

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