Foot-and-Mouth Disease (FMD)

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### PATHOGENESIS

The pathogenesis of FMD has recently been reviewed in detail; these reviews not only reveal the complexity of FMD's pathogenesis but identify many gaps in the level of present understanding – altogether 33 knowledge gaps are listed in the two papers – so a simple account of the pathogenesis of FMD is currently impossible (Arzt *et al.*, 2011a; Arzt *et al.*, 2011b).

The route of infection of cloven-hoofed animals, other than in pigs where it is generally oral (Terpstra, 19720), is thought to be respiratory. In cattle the tissues most consistently infected during the pre-viraemic phase of the disease are the epithelia of the naso-pharynx and larynx (Arzt *et al.*, 2011a). It is therefore likely this is the primary replication site in ruminants.

The tissues of the naso-pharynx and FMD viruses have a complex relationship because not only does initial infection of ruminants take place there but the naso-pharynx is also the site of viral persistence in chronically infected animals (so-called carriers). Vesicle formation, cell lysis and significant inflammation occur at secondary replication sites (oral mucosa, skin of the horn-hoof junction & skin of the teats) but not in the epithelium of the primary replication site. The cells which support viral replication are located in the basal layer of naso-pharyngeal epithelium. However, the mechanism by which viral replication occurs in the naso-pharyngeal epithelium without causing cell lysis is unknown; nor is there an explanation as to why virus can be readily cultured from pharyngeal scrapings (obtained using probing cups) that, in recently infected animals, may contain high levels of antibody (mainly IgA) directed against the infecting virus. In pigs, delayed clearance of viral RNA from pharyngeal and lymphoid tissues has been observed but that has not been shown for infectious virus (Arzt *et al.*, 2011b). It is currently concluded that persistent infection of pigs does not occur or at least is not epidemiologically important.

One or two days before the onset of clinical signs, cattle and pigs develop viraemia which may endure for up to 3 days. The source of virus in the circulation remains a matter of conjecture (i.e. another knowledge gap) but viraemia ensures distribution of virus to all parts of the animal’s body. In infected animals the vesicles which develop at the sites of secondary replication contain by far the highest levels of infectivity; however, high concentrations of virus can also be found in lymph nodes, myocardium, lungs and skin even in the absence of obvious lesions (Burrows *et al.*, 1981; Zhang & Alexandersen, 2004; Arzt *et al.*, 2010). Virus may also accumulate in the spleen, liver, adrenals, myocardium, pancreas, thyroid and mammary glands. In mammary tissue and myocardium, however, viral replication occurs in secretory epithelial cells of the alveoli and myocytes respectively, resulting in clear microscopic lesions.
There is an association between FMDV and dendritic cells in lymph nodes that results in localization of virus in germinal centres but the details of this association remain to be elucidated (Arzt et al., 2011a).

Epithelial lesions at secondary replication sites are initiated by infection of single cells in the stratum spinosum (Woodbury, 1995). Following infection of these cells, bullae develop either by lysis of cells swollen as a result of ballooning degeneration and the release of intracellular fluid, or by the formation of areas of focal intercellular oedema. The bullae then coalesce, rupture or, more rarely, the fluid seeps away resulting in desiccation of the lesion.

Development of characteristic vesicular lesions in FMD is dependent on persistent local irritation or friction. In transplantation studies in guinea pigs it was shown that epithelium from predilection sites grafted to other body areas lost that predilection and vice versa (Platt, 1960). This explains why the mouth, feet and teats are predilection sites for the development of lesions and why pigs often develop lesions on the dorsum of the snout, i.e. as a result of “snuffling”. Similarly, warthog which often “kneel” on their carpal joints while feeding tend to develop lesions on their “knees”.

In various parts of the world including South America, East Africa and India/Pakistan, a heat-intolerance syndrome (sometimes referred to as ‘hairy panters’) has been associated with previous infection or ‘chronic FMD’, with a putative endocrine-related pathogenesis. The limited information available on this syndrome has been reviewed recently indicating that the extent of the syndrome’s association with FMD remains speculative (Arzt et al., 2011b).

Immunity

The immune response of domestic animals to FMD is characteristically ephemeral and this, together with the wide immunological diversity of FMD viruses (SAT serotypes particularly) often results in ineffective herd immunity following vaccination and even following disease outbreaks.

Although the responses of very young piglets and calves differ from those of more mature animals, they are immunologically competent to FMD viruses from an early age. The poor antibody responses of calves and piglets to immunization are probably due more to immunological interference by colostral antibody than to immunological immaturity.

Cattle are immune to re infection with homologous virus for one to three years, and occasionally for up to 4.5 years (Bachrach, 1968). Circumstantial evidence suggests that the duration of immunity after infection with SAT serotypes may be shorter. The duration of immunity in other domestic species is largely unknown, but it is probably shorter than in cattle.
Since recovery from infection with FMD is the rule, little attention has been paid to the immunological mechanisms involved in recovery from infection. Conversely, since it is clear that the level of neutralizing antibody in the circulation correlates with resistance to infection or re-infection in immunized and recovered animals respectively, the humoral immune response and the antigens which are able to induce it have been better studied. The relationship between neutralizing antibody activity and the degree of resistance to infection is, however, not simple and depends on the virus serotype as well as in immunized animals the period between immunization and exposure to infection. It is important to appreciate that vaccinal immunity may not prevent infection but it rather prevents subsequent spread within the body of infected animals. Thus FMD vaccines do not induce so-called sterile immunity (Thomson & Bastos, 2004a).

The antibody response to FMDV is T cell dependent (Francis et al., 1987). However, since different species recognize different determinants as T cell recognition sites, not all FMDV antigens are equally immunogenic in different species.