Swine dysentery

History

Swine dysentery (SD) is a contagious diarrheic disease in pigs, characterized by a mucohemorrhagic colitis. The disease was originally described 75 years ago and is still prevalent in its classical form in most pig-rearing countries.

Swine dysentery was first described in 1921 in Indiana, USA by Whiting et al. (1921) as a bloody diarrhea caused by necrotic hemorrhagic inflammation of the mucosa of the stomach and the large intestine. The disease has since been reported from most pig-rearing areas worldwide. The first observation in Europe dates from Italy, in 1935 (Ubertini, cited by Duthie, 1966). Swine dysentery was reported from Australia in 1938 (McLennan et al., 1938), Holland 1953 (van Ulsen, 1953), Britain 1957 (Birrel, 1957) and in Scandinavia in 1960 (Ronéus, 1960). Finally, in 1971, Taylor & Alexander were able to fulfill all the preconditions of Koch's postulate in a transmission experiment, thereby providing evidence that a large spirochete was indeed the etiological agent of SD.

The spirochete was named *Treponema (T.) hyodysenteriae* by Harris et al. (1972a). Twenty years later, DNA–DNA reassociation experiments, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS–PAGE) profiles of whole-cell proteins and analysis of 16S rRNA sequence data from strains of *T. hyodysenteriae*, all indicated that the organism was only distantly related to *T. pallidum*, type species of the genus *Treponema* (Stanton et al., 1991). Consequently, the genus name was changed to *Serpulina* (Stanton 1992). Later, and due to phylogenetic rules, the genus name was again changed to *Brachyspira* (Ochiai et al., 1997; Validation list 1998) and the current designation of the etiological agent of SD is *Brachyspira (B.) hyodysenteriae*.

Description of Brachyspira hyodysenteriae

*Brachyspira hyodysenteriae* is a Gram-negative, oxygen-tolerant, anaerobic spirochete. It flourishes in 3–6 days on a blood agar medium not containing reducing agents. It measures 6–8.5 µm in length, 320–380 nm in diameter, is loosely coiled, motile and strongly hemolytic. The organism contains 7-14 endoflagella (Hovind-Hougen et al., 1990) inserted at each cell end. Most strains produce indole, have - and -glucosidase activity, ferment fructose, but lack -galactosidase activity. The properties described have been used to distinguish *B. hyodysenteriae* from other species of *Brachyspira*.

The outer envelope of *B. hyodysenteriae* contains lipooligosaccharide (LOS), a semi-rough form of the more usual lipopolysaccharide (LPS) of gram-negative bacteria. A number of serotypes have been proposed, based on serological reactions between lipopolysaccharide (LPS) extracts and hyperimmune rabbit sera raised against formalinized whole spirochetal cells (Mapother & Joens, 1985; Achaacha & Mittal, 1995). However, because of the existence of more than one major antigen in some isolates of *B. hyodysenteriae* and complex cross-reactions between serotypes, Hampson et al. (1989) proposed that isolates of *B. hyodysenteriae* should be organized into serogroups, each of which represented by a type strain. To date, eleven serogroups have been proposed (Hampson et al., 1997). Cross-reactivity in immunological tests between *B. hyodysenteriae* and *B. innocens* has frequently been reported (Hunter & Saunders, 1977; Joens et al., 1978a), which indicates close similarity between the surface antigens (Lemcke & Burrows, 1981).

Genetic organisation of Brachyspira hyodysenteriae

The *B. hyodysenteriae* type strain B78 genome is a single circular chromosome about 3.2 Mb in size (Zuerner & Stanton, 1994). Several genes of the organism have been characterized and some of them localized on the physical map of the genome (Zuerner & Stanton, 1994); e.g. genes encoding for 16S rRNA (Stanton et al., 1991), periplasmatic flagella subunits flaA,flaB (Koopman et al., 1992; Koopman et al., 1993; Gabe et al., 1995), hemolysin (Muir et al., 1992), a 16-kDa antigen (Thomas & Sellwood, 1993), which has been named BmpA by Lee et al., 2000, and NADH oxidase (nox) (Stanton & Jensen, 1993; Stanton et al., 1995). Many isolates contain plasmids (Combs et al., 1992; Adachi et al., 1994; Buller & Hampson 1994), but the role plasmids play in the biology of the spirochetes has not been established. The presence of bacteriophages (Ritchie et al., 1978;
Humphrey et al., 1995, reported as long ago as 1971 by Ritchie & Brown, and of plasmids (Buller & Hampson, 1994), may suggest the existence of natural genetic exchange mechanisms in *B. hyodysenteriae* (Rosey et al., 1995). The species is recombinant and has an epidemic population structure, meaning that epidemic clones exist that may be widespread (Trott et al., 1997).

**Clinical signs**

The first evidence of the disease is usually soft, yellow to grey feces, but the most consistent sign of SD is a bloodstained, mucoid diarrhea. Appearance of white mucofibrinous grains in the stools is almost pathognomonic as the disease progresses. An arched back suggests abdominal pain. Anorexia and fever may follow. Swine dysentery is a severe diarrheal disease with high mortality in typical cases, if the condition is not treated (Raynaud et al., 1980). However, the severity may vary, and the use of antibacterials as growth promoters, can suppress clinical symptoms. If the condition is not treated, prolonged diarrhea may lead to severe dehydration followed by death.

**Pathology, macroscopic lesions**

Lesions are present only in the large intestine. Lesions start in the centrifugal and centripetal coils near the apex of the colon and may then extend to the whole colon and from day 4 to the cecum (ter Huurne, 1993), and in some instances the whole large intestine may become involved. Typical changes in the acute stage of SD include hyperemia and edema of the walls and mesentery of the large intestine. Mesenteric lymph nodes may be swollen and colonic submucosal glands are often more prominent than normal. The mucosa is usually covered by mucus and fibrin with flecks of blood. As the condition progresses, mucosal lesions may become more severe with increased fibrin exudation and may form thick, mucofibrinous pseudomembranes. As the lesions become chronic, the mucosa may take on the appearance of marked necrosis, though superficial (Harris & Lysons, 1992).

**Pathology, microscopic lesions**

The damage to the mucosa and submucosa is characterized by superficial necrosis, eroded epithelium, edema, leukocytic infiltration and hyperplasia of goblet cells. Clumps of epithelial cells may detach from the lamina propria, resulting in exposure of capillaries followed by focal areas of hemorrhage. Large spirochetes are found in the lumen, within crypts and in the lamina propria. By transmission electron microscopy (TEM), *B. hyodysenteriae* cells can be visualized, invading epithelial cells, goblet cells and the lamina propria (Harris & Lysons, 1992).

**Infection route**

Swine dysentery is caused by proliferation of *B. hyodysenteriae*. Only *B. hyodysenteriae* will initiate the disease. However, many details in the pathogenesis are still not understood. The disease is usually introduced into a herd by carrier pigs, e.g. animals that have recovered from a previous infection (Windsor & Simmons, 1981). Such pigs may continue to shed the infectious agent for months, without manifesting clinical signs (Songer et al., 1978, Fisher & Olander, 1981). Moreover, wild rodents may be carriers of *B. hyodysenteriae* (Joens & Kinyon, 1982, Fellström et al., 2004). Infection occurs by ingestion of fecal material. The organism is protected from stomach acid by mucus in the dysenteric feces (Taylor, 1995). It invades the mucus and crypts of the mucosa in the large intestine and penetrates into colonic enterocytes and goblet cells (Taylor & Blakemore, 1971). Early lesions can be observed before penetration and, therefore, penetration of cells is probably not a precondition for the initiation of SD (Wilcock & Olander, 1979; Albassam et al., 1985).

Challenge trials have indicated that the occurrence and severity of swine dysentery is related to a number of things, including the amount of stress on the pig, the quantity of infectious inoculum administrated, the growth-phase of the culture, the diet, the group size, and the weight of the pig (Jacobson et al., 2004).
Pathophysiology

The damage to the epithelium suggests that fluid losses in SD result primarily from passive filtration secretion into the colonic lumen due to increased mucosal permeability and increased hydrostatic pressure in tissue. However, Argenzio et al. (1980) demonstrated that the fluid losses are exclusively the result of failure of the colon to reabsorb the endogenous secretions, due to a failure of the epithelial transport mechanisms to actively transport sodium and chloride from lumen to blood. Extensive fluid losses and ion imbalance occur with the disease, but *B. hyodysenteriae* does not invade the body or produce a septicemic state (Kinyon et al., 1980). Systemically, the disease is characterized by dehydration, acidosis and hyperkalemia, followed in severe cases by death.

Colonization

Studies in uncontaminated gnotobiotic/germ-free pigs have indicated that *B. hyodysenteriae* is able to colonize the large intestine without the support of other microorganisms (Harris et al., 1972b; Meyer et al., 1974; Brandenburg et al., 1977; Whipp et al., 1982). However, several reports suggest that other colonic anaerobes act as supporting organisms (Harris et al., 1978; Whipp et al., 1982; Siba et al., 1994). Flagella and motility are probably involved in the colonization process (Kennedy & Yancey, 1996). The organism moves effectively at high speed by chemotaxis through viscous material such as mucin (Kennedy et al., 1988). The high speed may facilitate penetration into the mucosa. Milner & Sellwood (1994) measured chemotaxis of a variety of porcine intestinal spirochetes towards mucin and were able to show that virulent *B. hyodysenteriae* strains are more chemotactic than avirulent strains of *Brachyspira* spp. and strains of *B. intermedia* and *B. pilosicoli*. They concluded that the pathogenicity of *B. hyodysenteriae* strains may, in part, be attributed to their attraction to porcine intestinal mucus. A mutant strain of *B. hyodysenteriae* (Rosey et al., 1995), deprived of a flagellar gene, has been reported to be avirulent in swine, which further shows that motility is an important virulence factor (Rosey et al., 1994). Wilcock & Olander (1979) reported that *B. hyodysenteriae* adhered to the surface of a number of different cell lines in vitro. Bowden et al. (1989) demonstrated that surface antigens of *B. hyodysenteriae* competitively inhibited adherence to Henle intestinal epithelial cells. Sialic acid residues probably serve as binding adhesins in mucus and the mucosa, but whether attachment is an important feature in the disease has not been conclusively demonstrated (Harris & Lysons, 1992). Kennedy et al. (1988) found no evidence of adhesion to the epithelium. They suggested that penetration of, or trapping in, the mucous gel may be the predominant mechanism of mucosal association.

Oxygen utilization

It has been speculated by Savage (1980) that an important virulence mechanism for pathogens of the intestinal tract could be their ability to utilize oxygen in order to colonize aerated environments such as the oxygen-respiring epithelial surfaces of the porcine large intestine. Stanton (1989) demonstrated that *B. hyodysenteriae* can metabolize substantial amounts of oxygen. He also suggested three major ways for the organism to recycle NADH generated from glucose consumption. The versatility in methods of NADH oxidation and the ability to metabolize oxygen could provide a selective advantage for *B. hyodysenteriae* over intestinal bacteria lacking these properties, in the colonization of the porcine large bowel.

Influence of diet and interaction with other microorganisms

Interaction between *B. hyodysenteriae* and a fermentative bacterial flora in the colon and cecum for the development of SD has been suggested (Siba et al., 1994; Pluske et al., 1996, 1998). Pigs fed a highly fermentative diet based on wheat and dehulled lupin seeds all developed SD in a challenge trial with *B. hyodysenteriae*, while pigs fed a diet based on boiled rice and animal protein were spared. Mean pH of cecal content in pigs before challenge was 5.4 for pigs fed the fermentative diet and 6.5 for pigs on the rice-based diet.
These authors suggested that a reduction or modification of microbial fermentation would indirectly inhibit colonization by *B. hyodysenteriae*. Prohaszka & Lukacs (1984), on the other hand, demonstrated a pH-dependent antibacterial effect, attributed to volatile fatty acids (VFAs), in the contents of the large intestine of pigs. *In vitro*, a low pH (≤ 6.0) resulted in loss of motility of *B. hyodysenteriae*. They suggested that a diet based on maize silage is protective against SD because of the resulting acidic metabolic status of the pigs. Whether the synergism observed between *B. hyodysenteriae* and other anaerobes facilitates colonization or expression of pathogenicity (or both) has not been clearly demonstrated. Beckmann (1992) reported a CAMP-like phenomenon in 40 *Brachyspira* isolates, including type/reference strains of *B. hyodysenteriae*, when the isolates were streaked onto an isolate of *Staphylococcus aureus*. Whether such synergistic reactions could occur *in vivo* and if so, whether they might be of importance for pathogenicity is not known. Noteworthy in this context are several observations (Harris et al., 1972b; Meyer et al., 1974; Brandenburg et al., 1977; Neef et al., 1994) indicating that the disease produced in germ-free/gnotobiotic pigs colonized with *B. hyodysenteriae* is less severe than in conventional pigs, or even absent altogether. Albassam et al. (1985) suggested that epithelial necrosis and vascular leakage late in the disease might create conditions favouring overgrowth by opportunistic bacteria, which may be a contributing factor in the pathogenesis. Teige et al. (1977; 1978) suggested that a diet deficient in vitamin E and selenium weakened resistance to SD. The incubation time was distinctly longer and clinical signs, as well as patho-morphological lesions, less pronounced in a group of pigs which were fed a diet supplemented with vitamin E and selenium, compared with pigs fed a diet deficient in those components, when both groups of pigs were challenged with colonic material from cases of SD.

**Hemolysin**

There is a close correlation between strong -hemolytic activity and pathogenicity among *Brachyspiro* strains. In fact, strong -hemo lysis on blood agar plates has traditionally been the most important feature that has been used to identify pathogenic *Brachyspira* strains in routine diagnostics. However, the exact role played by the hemolysins is not known and the actual causes of the initial damage are not understood. The purified hemolysin (Kent et al., 1988) of *B. hyodysenteriae* has proved cytotoxic for a number of cell types, both *in vitro* and *in vivo* (Lysons et al., 1991). Lysons et al. (1991) demonstrated damage to epithelial cells in germ-free pig ligated ileal and colonic loops injected with the hemolysin. The lesions, characterized by swelling and shedding of cells with disrupted organelles, were similar to those observed following early changes after injecting pig colonic loops with cultures of *B. hyodysenteriae* (Kang & Olander, 1990). Furthermore, erythrocytes can act as a source of essential substrates, especially cholesterol and lipids (Stanton, 1987; Stanton & Cornell, 1987).

The importance of the hemolysin as a virulence factor has been emphasized by experimental infections in mice and pigs performed by ter Huurne et al. (1992) and Hyatt et al. (1994). These workers used recombinant DNA-techniques to produce mutants of *B. hyodysenteriae* deprived of a hemolysin (tlyA) regulatory gene. The mutants did not cause dysentery, but still produced mild lesions. From these experiments it seems fair to conclude that the hemolysin is involved in the pathogenesis of SD, though others may also be involved. Unfortunately, there has been considerable confusion about the nature of the hemolysins involved. Three previously described genes (ter Huurne et al., 1994) encoding putative hemolysins (tlyA, tlyB, tlyC) probably do not encode hemolysins themselves. Instead these genes seem to be regulatory elements for hemolysin production. Recently, a distinct gene (hlyA) has been characterized which has haemolytic activity (Hsu et al., 2001). Hudson et al. (1974), Kinyon et al. (1977) and Jensen & Stanton (1993), observed that extended laboratory passages can produce strains that remain strongly -hemolytic, but are no longer pathogenic for pigs. A few reports of avirulent isolates of *B. hyodysenteriae* have also been published (Burrows & Lemeke, 1981; Lysons et al., 1982; Lee et al., 1993). In addition, Amtsberg et al. (1984) and Blaha et al. (1984) potentiated pathogenicity by *in vivo* passages of strongly -hemo lytic *B. hyodysenteriae* in susceptible pigs.

**Endotoxines**
Another toxin that may be involved in causing lesions has been described. This toxin, a lipopolysaccharide (LPS), originally described by Baum & Joens (1979), has shown an endotoxic activity that may involve direct induction of lesion formation or indirect mechanisms by activation of host defence mechanisms (Nuessen et al., 1983). Greer and Wannemuehler (1988; 1989a; 1989b), suggested that LPS possesses endotoxic properties that may help provoke inflammatory lesions following infection with \textit{B. hyodysenteriae}. They demonstrated that a butanol–water purified component (endotoxin) of \textit{B. hyodysenteriae} is capable of inducing inflammatory mediators (interleukin-1 and tumour necrosis factor). However, the difference in virulence between \textit{B. hyodysenteriae} and \textit{B. innocens} could not be attributed to the biologic activity of LPS or endotoxin preparations. Even so, \textit{in vivo} studies in mice and pigs demonstrated that \textit{B. hyodysenteriae} endotoxine also can induce production of pro-inflammatory cytokines such as interleukin-6 (Nibbelink et al., 1997).

\textbf{Immunity}

A specific humoral immune response to outer membrane antigens of \textit{B. hyodysenteriae} following infection is elicited (Wannemuehler et al., 1988). Clinical disease is associated with the development of specific IgG, IgA and IgM antibodies in serum and local production of IgA in gut mucosal tissues. Joens et al. (1984) suggested that the antibody secreted in the colon is the mechanism by which the recovered pig is protected against re-exposure to SD. Mucosal infection stimulates the production of memory cells, but humoral immunity alone is probably not responsible for the onset of a protective response to \textit{B. hyodysenteriae} (Rees et al., 1989). Repeated infection provides protection in varying degrees (Olson, 1974; Joens et al., 1979; Adachi et al., 1984; Rees et al., 1989).

Several putative immunogenic surface lipoproteins have been described (Joens & Marquez, 1986; Thomas et al., 1992; Gabe et al., 1998; Lee et al., 2000; McCaman et al., 2003; Cullen et al., 2003). Sellwood et al. (1989) demonstrated that polyclonal antiserum raised against the outer membrane of 11 \textit{B. hyodysenteriae} strains contains antibodies to the 16-kDa antigen (\textit{BmpA}), in contrast to two non-pathogenic strains of \textit{Brachyspira}. \textit{In vitro} and \textit{in vivo} tests both indicated that antibodies to the 16-kDa antigen agglutinate and inhibit growth of \textit{B. hyodysenteriae}.

It seems unlikely that there are immune-mediated components to the lesions of SD, as in mouse models the changes observed in numbers of mast cells in the lamina propria are not correlated with lesion development (Nibbelink and Wannemuehler, 1990).

\textbf{Serologic assays and vaccines}

Efficient serological assays for detection of, or vaccines against, \textit{B. hyodysenteriae} are not available.

\textbf{Therapy}

Eradication of the infectious agent \textit{B. hyodysenteriae} should be the preferred option. Only pleuromutilins can be relied on as effective for eradication purposes. However, the use of pleuromutilins should be restricted to
specific therapy due to the potential long-term threat to the pig industry that is caused by a slow, but continuous, development of resistance of *B. hyodysenterae* to these drugs.

In spite of extensive *in vitro* resistance, other drugs may have a clinical effect, e.g. macrolides or lincomycin and those should, if possible, be preferred when the purpose of the treatment is restricted to improved clinical health. Medication against SD should always be accomplished by free access to drinking water.

**Prophylaxis**

All in–all out production, careful cleaning and disinfection procedures, availability of SD-free stock, environments free from stress, efficient rodent control and eradication of the infectious agent from affected herds are all fundamental ingredients in an effective prophylaxis against SD.

**References**


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