

***Actinobacillus suis* and *Actinobacillus equuli*, emergent pathogens of septic embolic nephritis, a new challenge for the swine industry**

Actinobacillus suis y *Actinobacillus equuli*, patógenos emergentes de nefritis embólica séptica, un nuevo desafío para la industria porcina

CE Benavente^a, IC Fuentealba^{a,b*}

^aDepartment of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary, Alberta, Canada.

^bDepartment of Ecosystem and Public Health, Faculty of Veterinary Medicine, University of Calgary, Alberta, Canada.

RESUMEN

Las lesiones renales son una causa importante de decomiso en los mataderos. Además de las posibles consecuencias en salud pública, el decomiso de órganos tiene un gran impacto económico en la industria de alimento animal. Recientemente, nefritis embólica séptica con lesiones semejantes a infecciones con *Actinobacillus equuli* en potrillos ha sido detectada en reproductoras y cerdos con peso de mercado. *Actinobacillus equuli* es fenotípica y genéticamente similar a *Actinobacillus suis*. Ambas son bacterias Gram-negativas difíciles de diagnosticar en exámenes de rutina. *A. suis* es un patógeno oportunista capaz de producir septicemia en cerdos, neumonía, poliartrosis, nefritis embólica séptica, aborto y fetos momificados. Brotes de la enfermedad clínica parecieran ocurrir con más frecuencia en plantales de cerdos con estrictas medidas de bioseguridad. En cerdos adultos, las lesiones de piel pueden confundirse con erisipela porcina. *A. suis* y *A. equuli* son patógenos oportunistas emergentes en la industria porcina y ambos tienen potenciales consecuencias en salud pública, principalmente en aquellas personas que manipulan productos cárneos. El objetivo de esta publicación es presentar una revisión bibliográfica sobre el rol de *A. suis* y *A. equuli* en la patogénesis de nefritis en cerdos.

Key words: *Actinobacillus suis*, *Actinobacillus equuli*, nephritis, swine.

Palabras clave: *Actinobacillus suis*, *Actinobacillus equuli*, nefritis, cerdos.

INTRODUCTION

Recently, *Actinobacillus equuli* was associated with death of over 300 sows in a period of 2 months in a swine farm in Manitoba, Canada (Thompson *et al* 2010). The pattern of the inflammatory process corresponded to multifocal embolic nephritis. This condition is unique as the histopathological features resemble *Actinobacillus equuli* infection in foal. Common swine pathogens like *Actinobacillus suis* have been associated with polyserositis, pericarditis, pneumonia, arthritis, and very rarely with septicemia in adult pigs. Septicemia is important because of the potential of bacterial emboli that lodge in small capillaries and cause further lesions such as embolic nephritis or glomerulitis. Few reports of *A. equuli* infections in pigs have originated from North America in the last decade (Ramos-Vara *et al* 2008, Thompson *et al* 2010). Cases of embolic nephritis due to *A. equuli* infection have been diagnosed by several diagnostic laboratories in North America (personal communications).

Although the pathogenesis and etiology of renal diseases involve diverse modes and patterns of infection, all inflammatory lesions detected at the slaughter plants are classified under the broad category of “nephritis”, often called “white-spotted kidneys” (Drolet *et al* 2002). Various pathogens have been associated with the presence of nephritis in condemned kidneys from swine. The purpose of this paper is to review the role of *A. suis* and *A. equuli* as emergent pathogens causing nephritis in swine.

NEPHRITIS IN SWINE

Renal disease which encompasses any deviation from normal renal structure or function is usually subclinical (Maxie 2007). Since by definition a subclinical condition is characterized by absence of clear clinical signs, disease in affected animals is not diagnosed and treatment is not implemented. Once the hogs reach the market weight, they are sent to the slaughterhouse and if lesions are detected by food inspectors the affected organs are condemned. The renal system is exposed to injurious agents by various routes, including: a) ascending infections, b) hematogenous, and c) exposure to preformed or locally metabolized substances that are excreted through the renal tubular epithelium.

Accepted: 10.11.2011.

* 3330 Hospital Dr NW, Calgary, AB 2TN, Canada; cfuentealba@rossvet.edu.kn

CLASSIFICATION OF NEPHRITIS

Renal diseases are complex and may primarily affect one of four subdivisions of the kidney: 1) renal blood vessels or its vascular supply, 2) glomeruli, 3) tubules, and 4) interstitium (Maxie 2007). However, due to the anatomic and functional interdependence of the components of the kidney it is common to find that damage to one structure almost always results in secondary damage to others (Alpers 2005). The main general types of nephritis are glomerulonephritis and tubulointerstitial diseases. Primary glomerular damage often occurs as a result of deposition of immune complexes, entrapment of bacterial emboli, or direct viral or bacterial infection of glomerular structures. Hematogenous lesions localized within blood vessels are classified as septic embolic nephritis, and non-septic necrosis with infarction caused by substances such as crystalline salts, and filtered toxins secreted into the filtrate (Golinski *et al* 1984, Newman *et al* 2007).

CAUSES OF NEPHRITIS

Bacteremia can produce embolic nephritis, also known as suppurative glomerulitis, in which bacteria lodge in random glomeruli and within interstitial capillaries forming multiple foci of inflammation (microabscesses) throughout the renal cortex. Pigs infected with *Erysipelothrix rhusiopathiae* (Wood and Henderson 2006), or *A. equuli* subsp. *equuli* (Thompson *et al* 2010), and foals infected with *A. equuli* subsp. *equuli* (Berthoud *et al* 2004) are specific examples of this condition. Grossly, multifocal random, raised, tan pinpoint foci are seen beneath the renal capsule and on the cut surface throughout the renal cortex. Microscopically, glomerular capillaries contain numerous bacterial colonies intermixed with necrotic debris that often obliterate the glomerulus (Newman *et al* 2007).

Bacterial infections with *Escherichia coli*, *Corynebacterium* sp., *Staphylococcus* sp., *Streptococcus* sp. (*S. dysgalactiae* subsp. *equisimilis*, *S. suis*, *S. salivarius*) have been isolated from kidneys of animals with interstitial nephritis (Martínez *et al* 2006). Viral infections also have been associated with this type of nephritis (Drolet *et al* 2002). Interstitial nephritis is traditionally associated with inflammatory cell infiltration composed of lymphocytes and plasma cells and surrounding the peritubular structures in the renal interstitium (veins, arteries, lymphatics and connective tissue) (Newman *et al* 2007). Interstitial nephritis, commonly known as “white-spotted kidneys”, may be of infectious or non-infectious origin and according to the duration it is further classified as acute, subacute or chronic. Although this type of lesions can be caused by a variety of infectious agents, an association between interstitial nephritis and leptospirosis has been described (Baker *et al* 1989, Maxie 2007) but, this association is controversial (Jones *et al* 1987, Boqvist *et al* 2003). Leptospirosis is a zoonotic infectious disease caused by various serovars of

Leptospira interrogans, which affect a large number of wild and domestic species. The incidence of leptospirosis has decreased after the widespread use of vaccines; however, kidney condemnations are still common suggesting that additional organisms may be involved in the pathogenesis of interstitial nephritis (Drolet *et al* 2002). It has also been stated that vaccines do not prevent leptospira infection or provide a cure for chronically infected animals (Campagnolo *et al* 2000). It is clear that although numerous studies have attempted to elucidate which infectious agents are involved in interstitial nephritis in swine, the results varied and there is no convincing evidence that links a specific etiology for this condition (Martínez *et al* 2006).

In addition to bacteria, many emergent viral diseases have tropism for renal tissue (Drolet *et al* 2002, Imai *et al* 2006, Martínez *et al* 2006), including porcine reproductive and respiratory syndrome virus (PRRSV), porcine circovirus type 2 (PCV-2), porcine parvovirus (PPV), and porcine adenovirus (Nietfeld and Leslie-Steen 1993, Cooper *et al* 1997, Allan and Ellis 2000, Krakowka *et al* 2000, Drolet *et al* 2002, Segales *et al* 2005, Zimmerman *et al* 2006, Sarli *et al* 2008). Renal lesions in pigs inoculated with PRRS virus were characterized by moderate to marked interstitial nephritis, and mild to severe vascular changes (Cooper *et al* 1997). PCV-2 has been associated with tubulointerstitial nephritis (Sarli *et al* 2008), and a condition characterized by a systemic necrotizing vasculitis with marked cutaneous tropism (Langohr *et al* 2010). The latter syndrome, originally called porcine dermatitis and nephropathy syndrome, has been reported in several countries (Helie *et al* 1995) and is observed mainly in weaned and feeder pigs (Thibault *et al* 1998). There is evidence that PRRSV is also involved in the pathogenesis of this syndrome, since (a) its appearance coincided with the emergence of PRRSV, (b) characteristic lesions were seen in specific-pathogen free pigs infected with PRRSV (Cooper *et al* 1997), and (c) PRRSV antigens were detected by immunohistochemistry in macrophages surrounding affected vessels in skin and kidney in both acute and chronic spontaneous cases (Thibault *et al* 1998). Infection with PRRSV renders pig more susceptible to some bacterial and viral diseases, as an additive or synergistic effect, creating more severe disease than either agent alone (Zimmerman *et al* 2006, Xu *et al* 2010).

CHARACTERISTICS OF *ACTINOBACILLUS SUI* AND *ACTINOBACILLUS EQUULI*

ACTINOBACILLUS SUI

Actinobacillus suis has emerged as a new threat to swine health, particularly in high health status herds; and the occurrence of the disease in this group of pigs has been attributed to lack of herd immunity in these closed herds, but there is minimal information about the immunogenicity of *A. suis* (Yaeger 1996, MacInnes and

Desrosiers 1999, Wilson and McOrist 2000, Lapointe *et al* 2001, Oliveira 2007). *Actinobacillus suis* is an early colonizer of the upper respiratory tract of swine (Oliveira *et al* 2007) and the nasopharynx and palatine tonsils are the main colonization sites (Ojha *et al* 2005). In order to learn more about the initial stages of *A. suis* disease, Ojha *et al* (2010) analyzed colonization-deficient mutants of *A. suis* which adhered to the epithelium (*in vitro*) in lower numbers than the wild type. In a study of 50 swine herds of Ontario, 78% of them were diagnosed positive for *A. pleuropneumoniae* by *apxIV* PCR, and 94% of the herds tested were found positive for both *A. pleuropneumoniae* and *A. suis* by *apxII* PCR, as evidenced by presence of these organisms in samples of tonsils and nostrils from weanling pigs. In another study, at least 16% and as many as 94% of the herds were *A. suis* positive (MacInnes *et al* 2008). *Actinobacillus suis* infection can take place via the aerosol route, close contact, or breaks in the skin (Sanford *et al* 1990, MacInnes and Bossé 2004). The systemic spread of *A. suis* involves septic emboli, which reach various organs including the kidney and produce septic embolic nephritis characterized by presence of bacterial microcolonies surrounded by areas of hemorrhage and necrosis (Odin 1994, Yaeger 1996, Oliveira 2007).

Species that belong to the genus *Actinobacillus* are mostly commensals or pathogens of animals, but have also been described as a potential opportunistic pathogens of humans, especially in people who are occupationally exposed to infected horses or pigs. For example, *A. suis* was isolated from a wound of a farmer after a pig bite (Escande *et al* 1996), and in a bone biopsy taken from an injured arm 3 months after a horse bite (Peel *et al* 1991). *A. equuli* was isolated from a butcher with septicemia due to a cut in his thumb three days earlier (Ashhurst-Smith *et al* 1998), and from a horse trainer with septicemia and multiple joint involvement (Vaz *et al* 2001).

Actinobacillus suis or *A. suis*-like bacteria have been isolated sporadically from other species, such as a Canada goose with conjunctivitis (Maddux *et al* 1987), an alpaca with endocarditis, embolic suppurative nephritis, pulmonary abscesses and interphalangeal arthritis (Hill and Johnstone 1992), lungs from a cat after undergoing an ovariohysterectomy (Daignault *et al* 1999), neonatal calves with septicemia (DeBey *et al* 1996), a buffalo with multiple abscesses (Sulochana *et al* 1985), a colt with ocular and nasal purulent discharge (Harbourne *et al* 1978), horses with abscesses, respiratory and genital infections (Carman and Hodges 1982, Carr *et al* 1997, Jeannotte *et al* 2002), and foals with septicemia (Nelson *et al* 1996). Mice can be infected with *A. suis* and subsequently develop pneumonia and bacteremia comparable to that seen in pigs, suggesting that mice may be used as a model for studying infection in swine (Ojha *et al* 2007). This organism is considered an opportunistic pathogen of both swine and horses (Pedersen 1977, Liven *et al* 1978, Jang *et al* 1987, Miniats *et al* 1989, Bada *et al* 1996, Ramos-Vara *et al* 2008), and

it can cause fatal septicemia in young pigs (MacDonald *et al* 1976, Sanford *et al* 1990, MacInnes and Desrosiers 1999), pneumonia (Yaeger 1996), endocarditis (Ashford and Shirlaw 1962), polyarthritis (Wilson and McOrist 2000), and suppurative lesions in the kidney. *Actinobacillus suis* infection may also cause lesions resembling erysipelas in mature sows and gilts (Sanford and Miniats 1988, Miniats *et al* 1989, Wilson and McOrist 2000). *A. suis* can colonize the vagina of healthy sows and may cause abortion in gilts (Mauch and Bilkei 2004). *Actinobacillus suis*, characterized by biochemical properties, has been associated with infection of horses (Kim *et al* 1976, Harbourne *et al* 1978, Carman and Hodges 1982, Jang *et al* 1987), and septicemia in foals (Nelson *et al* 1996).

Actinobacillus suis has a wide geographical distribution. Cases have been reported from United States (Cutlip *et al* 1972, Maddux *et al* 1987, Nelson *et al* 1996), Canada (MacDonald *et al* 1976, Miniats *et al* 1989, Sanford *et al* 1990, Odin and Helie 1993), Great Britain (Harbourne *et al* 1978), New Zealand (Carman and Hodges 1982, Hill and Johnstone 1992), India (Sulochana *et al* 1985), Australia (Peel *et al* 1991, Wilson and McOrist, 2000), Hungary and Croatia (Mauch and Bilkei 2004).

Actinobacillus suis, a member of the family of *Pasteurellaceae*, genus *Actinobacillus*, is a small, gram-negative, oval to rod-shaped, capnophilic, non-mucoid, non-motile, nonspore producer, coccobacillary organism with short chains of bacillary and filamentous forms. India ink-crystal violet stain revealed that the organism is encapsulated (Cutlip *et al* 1972, MacDonald *et al* 1976, Harbourne *et al* 1978, DeBey *et al* 1996, Taylor 2006, Ojha *et al* 2007). *Actinobacillus suis* is catalase and oxidase positive, can grow on MacConkey's agar, and is nitrate and urease positive but indole negative. This microorganism is hemolytic when grown upon 5% sheep blood agar and hydrolyses esculin. Mannitol is not fermented by *A. suis* (Mair *et al* 1974, Sulochana *et al* 1985, DeBey *et al* 1996, Yaeger 1996, Daignault *et al* 1999, Rycroft and Garside 2000, Mauch and Bilkei 2004, Woldehiwet 2004). Although iron is plentiful in animal hosts, it is not readily available to pathogens due to iron-withholding properties of transferrin and lactoferrin. *A. suis* is an iron-requiring pathogen that must be capable of acquiring iron from its host despite the iron-restricted environment. Pathogenic members of *Pasteurellaceae* can obtain iron directly from the host proteins, most notably from transferrins (Tfs), by means of siderophore-independent, receptor-mediated mechanisms. This mechanism involves two surface receptor proteins referred to as Tf-binding proteins A and B (Bahrami *et al* 2003). *Actinobacillus suis* also has the ability to acquire iron from hemoglobins for growth and involves a single-component receptor that is up-regulated in response to iron restriction (Bahrami and Niven 2005). *Actinobacillus suis* has been described to secrete metalloproteases *in vitro* and these proteins displayed proteolytic activity. Metalloproteases degrade pig and bovine IgG

and they may have a role in diseases caused by *A. suis* (Negrete-Abascal *et al* 2004). Microbial proteases exert direct pathological effects by destroying host tissues and potentiate inflammatory processes.

Actinobacillus suis is not easy to routinely diagnose (Minton 2008), as it can be isolated along with other bacteria, and may be present in chronic cases (MacDonald 1976, Yaeger 1996). Moreover, isolation *A. suis* from clinical samples may be influenced by treatment with antibiotics, or poor handling of samples prior to submission to the diagnostic laboratory. In this case, polymerase chain reaction (PCR) can be used as an alternative tool to help with the final diagnosis of *A. suis* infection (Oliveira 2007).

The pathogenicity of disease caused by *A. suis* is not well understood. Potential virulence factors that have been reported for this microorganism include production of toxins, capsule expression, urease, and resistance to complement-mediated killing. *Actinobacillus suis* has genes that encodes pore-forming protein toxins belonging to the RTX (repeats in the structural toxin) family and are very similar to *ApxI* and *ApxII* of *Actinobacillus pleuropneumoniae* (Burrows and Lo 1992, Kamp *et al* 1994, Van Ostaaijen *et al* 1997, Frey and Kuhnert 2002), resulting in the development of similar lesions caused by these two microorganisms (Fenwick *et al* 1996, Jeannotte *et al* 2002). It is likely that two RTX toxins (*ApxI* and *ApxII*), capsular polysaccharides (CPSs) (K) and lipopolysaccharides (LPSs) (O), an iron-regulated outer-membrane proteins, and resistance to complement-mediated killing contribute to virulence (Slavic *et al* 2000^a, Slavic *et al* 2000^b, Bahrami *et al* 2003, Kuhnert *et al* 2003^a, Bahrami and Niven 2005, Ojha *et al* 2007, Oliveira 2007, Ramos-Vara *et al* 2008). RTX toxins are produced by a broad range of pathogenic Gram-negative bacteria. The toxins exhibit both a cytotoxic and often a hemolytic activity *in vitro* and few RTX toxins have cytotoxic activity only against cells of specific hosts and/or cell-type, suggesting that they may play a role in host specificity of certain pathogens (Frey and Kuhnert 2002). For example, *A. suis* and *A. equuli* have host specific specificity toxins, whereby *A. suis* has the *apxICA* and *apxIICA* genes, (Kuhnert *et al* 2003^a, Kuhnert *et al* 2003^b) that are not present in *A. equuli* (Ramos-Vara *et al* 2008).

The cell surface CPSs and LPSs of Gram-negative bacteria also play key roles in bacteria-host interactions. Monteiro *et al* (2000) described the presence of (1→6)-β-D-glucan in the LPSs and CPSs of *A. suis*, and the strains expressing that homopolymer as LPS-O-chains and CPSs were designed serotype O1/K1. The presence of (1→6)-β-D-glucan is also found in common environmental fungal organisms and yeast, and some pigs may have low levels of antibody resulting in false positive results for *A. suis* by using LPS/CPS based in enzyme-linked immunosorbent assay (ELISA). A study was also done with the O-antigen polysaccharide (PS) chemical structure of an O2 serogroup strain of *A. suis*, which is associated with

severely diseased animals and produce a more complex O-chain PS. The capsule PS (K2) of these strains contains sialic acid, a residue that has been associated with many immunological events (Rullo *et al* 2006). A cell surface antigen-typing was devised for *A. suis* and used to examine the prevalence of different lipopolysaccharide (O) types in healthy and diseased pigs and the authors concluded that O2/K3-reactive strains may be more virulent than O1/K1 strains (Slavic *et al* 2000^a, Slavic *et al* 2000^b). Although O1/K1 and O1/K2 strains were isolated from clinically "healthy" pigs (asymptomatic animals), they both have a potential to cause disease. However, differences in the histopathologic changes and in the ability to spread peritonitis between *A. suis* serotypes O1/K1, O1/K2, and O2/K2 have been reported (Slavic *et al* 2000^a).

The rapid spread of the disease between two isolated herds suggested that *A. suis* can be readily transmitted by humans and/or by carrier pigs (Miniats *et al* 1989). The ability of *A. suis* to survive in the environment has not been fully described but there is evidence that the organism can persist in an infected herd for at least 18 months (Miniats *et al* (1989). *A. suis* is killed within 15 minutes at a temperature of 60°C, is sensitive to most disinfectants, and will die out within a few days in clinical specimens (Oliveira 2007).

Despite the fact that *A. suis* is sensitive to a wide range of antibiotics (procaine penicillin G, trimethoprim sulfadoxine, oxytetracycline HCl (Miniats *et al* 1989), the rapid onset of the disease makes effective treatment difficult. Sanford *et al* (1990) reported that in their study all 28 *A. suis* isolates were susceptible to ampicillin, carbenicillin, gentamicin, kanamycin, penicillin G, polymyxin B, and trimethoprim-sulfamethoxazole; one isolate was resistant to tetracycline and sulfisoxazole, another isolate was resistant to tetracycline only. On the other hand, Wilson and McOrist (2000) reported that all *A. suis* isolates were susceptible *in vitro* to a lincomycin-spectinomycin combination and resistant to tetracyclines, macrolides and penicillins, while two were resistant to apramycin and trimethoprim-sulphamethoxazole. Oliveira (2007) observed that *A. suis* isolates sharing similar genomic fingerprints may have completely different susceptibility profiles, suggesting that antibiotic resistance genes may be carried in plasmids, and strains with similar genetic makeup may carry different plasmids.

Clinical signs and lesions caused by *A. suis* are usually non-specific, and a list of differential diagnoses associated with other pathogens that can cause septicemia is necessary for the development of effective control strategies. Bacterial pathogens that can cause systemic infection in swine include members of the family *Pasteurellaceae* as *Haemophilus parasuis* (cause fibrinous pleuritis, pericarditis and polyserositis) and *A. pleuropneumoniae* (common cause of pneumonia), and *Erysipelothrix rhusiopathiae* (typical lesions include endocarditis, arthritis and skin lesions) (Robinson and Maxie 1993) causing

significant production losses. *A. suis* can be isolated from clinical samples or it can be detected by PCR (Oliveira 2007). The most promising technique for identification of *Actinobacillus* spp. and other pathogens is PCR tests based on species specific genetic elements including virulence genes (Christensen and Bisgaard 2004).

Vaccination and serodiagnostic testing are complicated by the presence of multiple serotypes, and cross-reactive antigens (Rosendal and Mittal 1985, Fenwick *et al* 1996, MacInnes and Desrosiers 1999, Lapointe *et al* 2001, Oliveira 2007). Currently, no sero-diagnostic tests or vaccines are commercially available to help controlling *A. suis* infections (Oliveira *et al* 2007). Autogenous vaccines are sometimes used in herds with clinical problems, but their efficacy has not been critically evaluated. Serologic profile could be used to determine the duration of passive immunity in a specific herd in order to help implementing the best vaccination strategy. The use of autogenous *A. suis* vaccine increased the specific humoral immunity in gilts (Lapointe *et al* 2001). Oliveira *et al* (2007) reported that *A. suis* affecting North American swine herds are highly clonal and this information may be important for the selection of vaccine strains. Some commercial *A. pleuropneumoniae* vaccines, containing *Apx* toxoids, might provide some cross protection. Furthermore, Lillie *et al* (2006) characterized porcine plasma lectins with bacteria-binding functions against *A. suis* and *Haemophilus parasuis* which may play a role on innate resistance to bacterial pathogens in pigs.

Review of the literature seems to indicate that porcine actinobacillosis, which previously was considered to be a disease of minor importance, present a health hazard to naïve, susceptible swine population. This seems to be particularly important in farms using modern management practices such as segregated weaning, closed breeding and in minimal disease herds.

ACTINOBACILLUS EQUULI

Actinobacillus equuli is phenotypically and phylogenetically related to *A. suis* (Bisgaard *et al* 1984) and some strains have been previously misidentified or at least misnamed as equine “*A. suis*” (Kuhnert *et al* 2003^b). For many years the uncertain taxonomy have represented a diagnostic problem and prevented progress on studies of virulence and epidemiology of these organisms (Ross *et al* 1972). *Actinobacillus equuli* is a small, non-motile, gram-negative rod and differs from *A. suis* by producing acid from mannitol, and not hydrolyzing esculin (Sanford *et al* 1990). Early attempts to distinguish between isolates from healthy horses and clinically ill cases using ribotyping and biochemical fingerprinting were not useful (Sternberg and Brandstrom 1999) but in subsequent studies *A. equuli* was reclassified in two subspecies: *A. equuli* subsp. *equuli* and *A. equuli* subsp. *haemolyticus*, showing different disease pattern and epidemiology. The main features used for differentiation of the two subspecies are haemolysis

and the CAMP reaction (Christie *et al* 1944); *A. equuli* subsp. *equuli* is non-haemolytic and CAMP-negative. Haemolysis is observed in infections due to *A. equuli* subsp. *haemolyticus* and *A. suis* (Christensen *et al* 2002). RTX toxin activity has been found in strains of *A. equuli* subsp. *haemolyticus* and the *Aqx* haemolysin has been shown to be toxic for horse lymphocytes (Berthoud *et al* 2002). A toxin gene analysis revealed that all *A. equuli* subsp. *haemolyticus* strains specifically contained *aqx* gene which confers the hemolytic phenotype of this subspecies, while *A. suis* strains harbored the genes *apxI* and *apxII*. Moreover, *A. equuli* subsp. *equuli* contained no *aqx* nor any of the other RTX genes tested. The specificity of *aqx* for the hemolytic equine *A. equuli* and *apxI* and *apxII* for the porcine *A. suis* indicates a role of these RTX toxins in host species predilection of the two closely related species of bacterial pathogens and allows polymerase chain reaction (PCR) based diagnostic differentiation of the two (Kuhnert *et al* 2003^a). The *Aqx* toxin was associated with pulmonary hemorrhage and endothelial damage in an adult horse (Pusterla *et al* 2008).

The natural host of *A. equuli* is the horse and the organism is found in the oral cavity and alimentary tract of horses, which commonly leads to the exposure of their immune system to this bacterial species and its antigens. Adult horses had antibodies directed to *Aqx* toxin of *A. equuli* (Berthoud *et al* 2004, Holyoak *et al* 2007). *Actinobacillus equuli* has been associated with several diseases in foals and adult horses, and the most important condition is fatal septicemia in neonatal foals which is thought to be associated with a failure of passive transfer of immunoglobulins via the colostrum. Interestingly, only *A. equuli* subsp. *equuli*, a non-hemolytic subspecies is associated with “sleepy foal disease”, a clinical condition characterized by acute septicemia of foals with purulent nephritis which eventually becomes chronic in the form of “joint ill”, a polyarthritis (Kuhnert *et al* 2003^a). Infections in adult horses due to *A. equuli* are less common and generally more localized as it is described in cases of arthritis, endocarditis (Aalbaek *et al* 2007), abortion (Webb *et al* 1976), septicemia, nephritis, pneumonia (Carr *et al* 1997, Pusterla *et al* 2008), and orchitis (Patterson-Kane *et al* 2001). A few cases of acute and chronic peritonitis caused by *A. equuli* infection have also been documented in adult horses (Gay and Lording 1980, Golland *et al* 1994, Patterson-Kane *et al* 2001). The pathogenesis of peritoneal infection caused by *A. equuli* is unclear. In addition to septicemia resulting in polyserositis, and or peritonitis, other routes of infection are possible. Carriage of *A. equuli* by *Strongylus sp.* larvae from the intestinal tract may play a role in peritoneal invasion (Gay and Lording 1980, Golland *et al* 1994). The feasibility of this route of infection is supported by the fact that *A. equuli* has been isolated from verminous aneurysms of the cranial mesenteric arteries caused by *Strongylus vulgaris* larvae (Golland *et al* 1994). Mesenteric and cecocolic verminous arteritis lesions were observed in one horse with chronic

A. equuli peritonitis (Gay and Lording 1980). However, *A. equuli* peritonitis is a rare diagnosis in adult horses but because appropriate antimicrobial treatment in small numbers of horses with acute *A. equuli* peritonitis has resulted in clinical improvement and a return to original activity, diagnosis Patterson-Kane *et al* (2001) suggested that pathologists and clinicians examining smears of abdominal fluid from equine colic cases should be aware of this etiologic agent.

Reports of *A. equuli* infection in pigs are uncommon and come mostly from European countries (Bell 1973, Ramos-Vara *et al* 2008). Only few reports have been published during the last decades in North America: *A. equuli* has been associated with vegetative endocarditis in pigs (Jones and Simmons 1971), isolated from an aborted porcine fetus (Werding *et al* 1976), reported as a cause of metritis, valvular endocarditis with secondary septicemia in a pregnant gilt (Ramos-Vara *et al* 2008), and recently, *A. equuli* subsp. *equuli* was isolated from a sow herd affected with peracute clinical disease progression and abnormally high mortality of 300 sows from an initial population of 3000 females and 1 to 4 day-old piglets (Thompson *et al* 2010).

The most likely method of spread of the genus *Actinobacillus* between horses and pigs seems to be previous contact between both species in the farm (Windsor 1973, Werding 1976, Harbourne *et al* 1978, Nelson *et al* 1996), but a case of *A. equuli* infection in swine was reported from a farm in which pigs were raised in an environment without contact with horses (Ramos-Vara *et al* 2008). Cases of *A. equuli* infection were reported in a farm with excellent biosecurity standards, but it was also reported that although the sows had no direct contact with horses several barn employees were known to be in contact with horses (Thompson *et al* 2010).

Septicemic actinobacillosis in pigs is usually attributed to *A. suis* (Odin 1994) but *A. equuli* can produce septicemia in piglets and sows, with similar lesions in kidneys, joints and endocardium (Taylor 2006, Ramos-Vara *et al* 2008). To date, *A. equuli* subsp. *haemolyticus* has only been isolated from horses, whereas *A. equuli* subsp. *equuli* has been isolated from pigs and horses. Ramos-Vara *et al* (2008) utilized a molecular approach to detect and identify the bacteria in the affected pig tissues. Analysis of the amplified nucleotide sequences revealed 100% homology with two *A. equuli* isolates (GenBank AY634640 and AY465359) and PCR typing of the RTX genes ruled out *A. suis* and *A. equuli* subsp. *haemolyticus*. Moreover, Thompson *et al* (2010) identified *A. equuli* subsp. *equuli* from the lung and kidney tissue of sows using a bacterial identification system and the 16S ribosomal RNA gene sequencing.

In recent cases of *A. equuli* subsp. *equuli* infection in sows antibiotic susceptibility tests indicated that the bacterium was sensitive to tetracycline, neomycin, trimethoprim, ceftiofur, spectinomycin, and ampicillin (Thompson *et al* 2010). An autogenous killed vaccine was

developed and within 6 weeks following the onset of the clinical outbreak, the entire sow herd was vaccinated. In order to prevent clinical disease in replacement animals, gilts were vaccinated twice prior to entry into the herd (Thompson *et al* 2010).

CONCLUDING REMARKS

Although a differential diagnosis of porcine actinobacillosis as the result of *A. equuli* is not commonly considered in swine, veterinarians should be aware of the importance of this pathogen in cases of septicemia. The recent report of an outbreak of *A. equuli* infection in swine (Thompson *et al* 2010), the isolation of the organism in pure culture from species other than equine (Moyaert *et al* 2007), and the unpublished observations from diagnostic laboratories support the interpretation that this is either an emerging pathogen, or has been previously under-diagnosed. Bacterial endocarditis in pigs is usually linked to *Streptococcus* spp. and *Erysipelothrix rhusiopathiae* infections (Robinson and Maxie 1993), but valvular endocarditis has been reported in natural and experimental *A. equuli* infections of piglets and in natural infections in foals. Any septicemic condition has the potential to cause embolism in small blood vessels, and cause endothelial damage including endocarditis. The pathogenesis of thromboembolism starts with primary infection, followed by secondary bacteremia, bacterial colonization of multiple organs and culminating with thromboembolism (Odin 1994). Thus, it is important to recognize that embolic nephritis is an entity with many possible causes, including *A. suis* and *A. equuli*. Both pathogens are associated with infection in humans, particularly people involved in activities that puts them in close contact with horses and pigs, or individuals that handle tissues from these animals. Isolation and identification of the etiologic agent are required to achieve an accurate diagnosis and to implement adequate therapeutic and management strategies.

SUMMARY

Kidney lesions are an important cause of tissue condemnation in slaughterhouses. In addition to the potential public health implications, organ condemnations have a significant economic impact on the food animal industry. The condition classified broadly as "nephritis" is one of the main causes of tissue condemnation. Embolic nephritis resembling *Actinobacillus equuli* infection in foals has been recently detected in sows and market hogs. *Actinobacillus suis* is phenotypically and phylogenetically closely related to *A. equuli*. Both are Gram-negative bacteria, not easy to detect in routine exams. *A. suis* is an opportunistic pathogen that can produce fatal septicaemia in pigs, pneumonia, polyarthritis, septic embolic nephritis, abortion and mummified foetuses. Outbreaks of clinical disease appear to occur more frequently in high-health-status herds. In adult pigs the skin lesions may be confused with porcine erysipelas. *A. suis* and *A. equuli* are emerging opportunistic pathogens in the porcine industry and both have potential public health consequences to people that handles meat products. The objective of this paper is to present a literature review regarding the role of *A. suis* and *A. equuli* in the pathogenesis of nephritis in swine.

REFERENCES

- Aalbaek B, S Ostergaard, R Buhl, HE Jensen, H Christensen, M Bisgaard. 2007. *Actinobacillus equuli* subs. *equuli* associated with equine valvular endocarditis. *APMIS* 115, 1437-1442.
- Allan GM, JA Ellis. 2000. Porcine circoviruses: a review. *J Vet Diagn Invest* 12, 3-14.
- Alpers CE. 2005. The kidney. In: Kumar AK, Fausto N (eds). *Robbins and Cotran. Pathologic Basis of Disease*. 7th ed. Elsevier, Philadelphia, USA, Pp 955-960.
- Ashford WA, JF Shirlaw. 1962. A case of verrucous endocarditis in piglet caused by an organism of the *Actinobacillus* genus. *Vet Rec* 74, 1417-1418.
- Ashhurst-Smith C, R Norton, W Thoreau, MM Peel. 1998. *Actinobacillus equuli* septicemia: an unusual zoonotic infection. *J Clin Microbiol* 36, 2789-2790.
- Bada R, KR Mittal, R Higgins. 1996. Biochemical and antigenic relationships between porcine and equine isolates of *Actinobacillus suis*. *Vet Microbiol* 51, 393-396.
- Bahrami F, A Ekins, DF Niven. 2003. Iron acquisition by *Actinobacillus suis*: identification and characterization of transferring receptor proteins and encoding genes. *Vet Microbiol* 94, 79-92.
- Bahrami F, DF Niven. 2005. Iron acquisition by *Actinobacillus suis*; identification and characterization of a single-component haemoglobin receptor and encoding gene. *Microb Pathog* 39, 45-51.
- Baker TF, SA McEwen, JF Prescott, AH Meek. 1989. The prevalence of leptospirosis and its association with multifocal interstitial nephritis in swine at slaughter. *Can J Vet Res* 53, 290-294.
- Bell JC. 1973. *Actinobacillus equuli* infection in pigs. *Vet Rec* 92, 543-544.
- Berthoud H, J Frey, P Kuhnert. 2002. Characterization of *Aqx* and its operon: the hemolytic RTX determinant of *Actinobacillus equuli*. *Vet Microbiol* 87, 159-174.
- Berthoud H, J Frey, S, Sternberg, R Straub, P Kuhnert. 2004. Antibodies to *Aqx* toxin of *Actinobacillus equuli* in horses and foals. *Vet Rec* 155, 231-233.
- Bisgaard M, K Piechulla, YT Ying, W Frederiksen, W Mannheim. 1984. Prevalence of organisms described as *Actinobacillus suis* or haemolytic *Actinobacillus equuli* in the oral cavity of horses. Comparative investigations of strains obtained and porcine strains of *A. suis sensu stricto*. *Acta Pathol Microbiol Immunol Scand Sect B* 92, 291-298.
- Boqvist S, JM Montgomery, M Hurst, HT Thu, EO Engvall, A Gunnarsson, U Magnusson. 2003. Leptospira in slaughtered fattening pigs in southern Vietnam: Presence of the bacteria in the kidneys and association with morphological findings. *Vet Microbiol* 93, 361-368.
- Burrows LL, LO RY. 1992. Molecular characterization of an RTX toxin determinant from *Actinobacillus suis*. *Infect Immun* 60, 2166-2173.
- Campagnolo ER, MC Warwick, HL Jr Marx, RP Cowart, HD Jr Donnel, MD Bajani, SL Bragg, JE Esteban, DP Alt, JW Tappero, CA Bolin, DA Ashford. 2000. Analysis of the 1998 outbreak of leptospirosis in Missouri in humans exposed to infected swine. *J Am Vet Med Assoc* 216, 676-682.
- Carman MG, RT Hodges. 1982. *Actinobacillus suis* infection of horses. *New Zeal Vet J* 30, 82-84.
- Carr EA, GP Carlson, WD Wilson, DH Read. 1997. Acute hemorrhagic pulmonary infarction and necrotizing pneumonia in horses: 21 cases (1967-1993). *J Am Vet Med Assoc* 210, 1774-1778.
- Christensen H, M Bisgaard, JE Olsen. 2002. Reclassification of equine isolates previously reported as *Actinobacillus equuli*, variants of *A. equuli*, *Actinobacillus suis* or Bisgaard taxon 11 and proposal of *A. equuli* subsp. *equuli* subsp. nov. and *A. equuli* subsp. *haemolyticus* subsp. nov. *Int J Syst Evol Microbiol* 52, 1569-1576.
- Christensen H, M Bisgaard. 2004. Revised definition of *Actinobacillus sensu stricto* isolated from animals. A review with special emphasis on diagnosis. *Vet Microbiol* 99, 13-30.
- Christie R, NE Atkins, E Munch-Petersen. 1944. A note on a lytic phenomenon shown by group B Streptococci. *Aust J Exp Biol Med Sci* 2, 197-200.
- Cooper VL, RA Hesse, AR Doster. 1997. Renal lesions associated with experimental porcine reproductive and respiratory syndrome virus (PRRSV) infection. *J Vet Diagn Invest* 9, 198-201.
- Cutlip RC, WC Amtower, MR Zinober. 1972. Septic embolic actinobacillosis of swine: A case report and laboratory reproduction of the disease. *Am J Vet Res* 33, 1621-1626.
- Daignault D, L Chouinard, K Moller, P Ahrens, S Messier, R Higgins. 1999. Isolation of *Actinobacillus suis* from a cat's lung. *Can Vet J* 40, 52-53.
- DeBey BM, PC Blanchard, RL Walker. 1996. *Actinobacillus suis*-like organisms associated with septicemia in neonatal calves. *J Vet Diagn Invest* 8, 248-250.
- Drolet R, S D'Allaire, R Laroche, R Magar, M Ribotta, R Higgins. 2002. Infectious agents identified in pigs with multifocal interstitial nephritis at slaughter. *Vet Rec* 150, 139-143.
- Escande F, A Bailly, S Bone, J Lemozy. 1996. *Actinobacillus suis* infection after a pig bite. *The Lancet* 348, 888.
- Fenwick B, M Rider, MMJ Chengappa, J Montaraz. 1996. Cross protective immunity between *Actinobacillus suis* and *Actinobacillus pleuropneumoniae*. *Proceedings 14th of the Congress International Pig Veterinary Society*, Bologna, Italy.
- Frey J, P Kuhnert. 2002. RTX toxins in *Pasteurellaceae*. *Int J Med Microbiol* 292, 149-158.
- Gay CC, PM Lording. 1980. Peritonitis in horses associated with *Actinobacillus equuli*. *Aust Vet J* 56, 296-300.
- Golinski P, K Hult, J Grabarkiewicz-Szczesna, J Chelkowski, P Kneblewski, K Szebiotko. 1984. Mycotoxic porcine nephropathy and spontaneous occurrence of Ochratoxin A residues in kidneys and blood of Polish swine. *Appl Environ Microbiol* 47, 1210-1212.
- Golland LC, DR Hodgson, JL Hodgson, MA Brownlow, DR Hutchins, RJ Rawlinson, MC Collins, SA Mc Clintock, AL Raisia. 1994. Peritonitis associated with *Actinobacillus equuli* in horses: 15 cases (1982-1992). *J Am Vet Med Assoc* 205, 340-343.
- Harbourne JF, NS Mair, SG Keighley. 1978. Isolation of *Actinobacillus suis* from a colt. *Br Vet J* 134, 122-127.
- Helie P, R Drolet, MC Germain, A Bourgault. 1995. Systemic necrotizing vasculitis and glomerulonephritis in grower pigs in southwestern Quebec. *Can Vet J* 36, 150-154.
- Hill FI, AC Johnstone. 1992. *Actinobacillosis* in an alpaca (*Lama pacos*). *New Zeal Vet J* 40, 28-30.
- Holyoak GR, CM Smith, R Boyette, M Montelongo, JH Wray, S Ayalew, VE Duggan, AW Confer. 2007. Serum antibodies in mares and foals to *Actinobacillus equuli* whole cells, outer membrane proteins, and *Aqx* toxin. *Vet Immunol Immunopath* 118, 310-316.
- Imai DM, J Cornish, R Nordhausen. 2006. Renal tubular necrosis and interstitial hemorrhage ("turkey-egg kidney") in a circovirus-infected Yorkshire cross pig. *J Vet Diagn Invest* 18, 496-499.
- Jang SS, EL Biberstein, DC Hirsh. 1987. *Actinobacillus suis*-like organisms in horses. *Am J Vet Res* 48, 1036-1038.
- Jeannotte ME, D Slavic, J Frey, P Kuhnert, JI MacInnes. 2002. Analysis of non-porcine isolates of *Actinobacillus suis*. *Vet Microbiol* 85, 83-93.
- Jones JE, JR Simmons. 1971. Endocarditis in a pig caused by *Actinobacillus equuli*: A field and an experimental case. *Br Vet J* 127, 25-29.
- Jones RT, BD Millar, RJ Chappel, B Adler. 1987. Macroscopic kidney lesions in slaughtered pigs are an inadequate indicator of current leptospiral infection. *Aust Vet J* 64, 258-259.
- Kamp EM, TM Vermeulen, MA Smits, J Haagsma. 1994. Production of *Apx* toxins by field strains of *Actinobacillus pleuropneumoniae* and *Actinobacillus suis*. *Infect Immun* 62, 4063-4065.
- Kim BH, JE Phillips, JG Atherton. 1976. *Actinobacillus suis* in the horse. *Vet Rec* 98, 239.
- Krakowka S, JA Ellis, B Meehan, S Kennedy, F McNeilly, G Allan. 2000. Viral wasting syndrome of swine: Experimental reproduction of postweaning multisystemic wasting syndrome in gnotobiotic

- swine by confection with porcine circovirus type 2 and porcine parvovirus. *Vet Path* 37, 254-263.
- Kuhnert P, H Berthoud, H Christensen, M Bisgaard, J Frey. 2003^a. Phylogenetic relationship of equine *Actinobacillus* species and distribution of RTX toxin genes among clusters. *Vet Res* 34, 353-359.
- Kuhnert P, H Berthoud, R Straub, J Frey. 2003^b. Host cell specific activity of RTX toxins from haemolytic *Actinobacillus equuli* and *Actinobacillus suis*. *Vet Microbiol* 92, 161-167.
- Langohr IM, GW Stevenson, EA Nelson, SD Lenz, H HogenEsch, H Wei, RM Pogranichniy. 2010. Vascular lesions in pigs experimentally infected with porcine circovirus type 2 serogroup b. *Vet Pathol* 47, 140-147.
- Lapointe L, S D'Allaire, S Lacouture, M Gottschalk. 2001. Serologic profile of a cohort of pigs and antibody response to an autogenous vaccine for *Actinobacillus suis*. *Vet Res* 32, 175-183.
- Lillie BN, JD Hammermueller, JJ MacInnes, M Jacques, MA Hayes. 2006. Porcine mannan-binding lectin A binds to *Actinobacillus suis* and *Haemophilus parasuis*. *Develop Comp Immun* 30, 954-965.
- Liven E, HJ Larsen, B Lium. 1978. Infection with *Actinobacillus suis* in pigs. *Acta Vet Scand* 19, 313-315.
- MacDonald DW, MP Hewitt, GS Wilton, S Rawluk, L Childs. 1976. *Actinobacillus suis* infections in Alberta swine, 1973-75: Pathology and bacteriology. *Can Vet J* 17, 251-254.
- MacInnes JI, R Desrosiers. 1999. Agents of the "suis-ide diseases" of swine: *Actinobacillus suis*, *Haemophilus parasuis*, and *Streptococcus suis*. *Can J Vet Res* 63, 83-89.
- MacInnes JI, JT Bosse. 2004. *Actinobacillus*. In: Gyles CL, Prescott JF, Songer JG, Thoen CO (eds). *Pathogenesis of bacterial infections in animals*. 3rd ed. Blackwell Publishing, Ames, Iowa, USA, Pp 225-241.
- MacInnes JI, M Gottschalk, AG Lone, DS Metcalf, S Ojha, T Rosendal, SB Watson, RM Friendship. 2008. Prevalence of *Actinobacillus pleuropneumoniae*, *Actinobacillus suis*, *Haemophilus parasuis*, *Pasteurella multocida*, and *Streptococcus suis* in representative Ontario swine herds. *Can J Vet Res* 72, 242-248.
- Maddux RL, MM Chengappa, BG McLaughlin. 1987. Isolation of *Actinobacillus suis* from a Canada goose (*Branta Canadensis*). *J Wildlife Dis* 23, 483-484.
- Mair NS, CJ Randall, GW Thomas, JF Harbourne, CT McCrea, KP Cowl. 1974. *Actinobacillus suis* infection in pigs: a report of four outbreaks and two sporadic cases. *J Comp Pathol* 84, 113-119.
- Martínez J, J Segales, G Aduriz, R Atxaerandio, P Jaro, J Ortega, B Peris, JM Corpa. 2006. Pathological and etiological studies of multifocal interstitial nephritis in wasted pigs at slaughter. *Res Vet Sci* 81, 92-98.
- Mauch C, G Bilkei. 2004. *Actinobacillus suis*, a potential cause of abortion in gilts and low parity sows. *Vet J* 168, 186-187.
- Maxie MG. 2007. The urinary system. In: Maxie MG (ed). *Pathology of Domestic Animals*. 5th ed. Elsevier Saunders, Philadelphia, USA, Pp 452-522.
- Miniats OP, MT Spinato, SE Sanford. 1989. *Actinobacillus suis* septicemia in mature swine: two outbreaks resembling erysipelas. *Can Vet J* 30, 943-947.
- Minton B. 2008. *Actinobacillus suis* poses uncertain risk. *National Hog Farmer* 53, 34.
- Monteiro MA, D Slavic, F St.Michael, JR Brisson, JI MacInnes, MB Perry. 2000. The first description of a (1→6)-beta-D-glucan in prokaryotes: (1→6)-beta-D-glucan is a common component of *Actinobacillus suis* and is the basis for a serotyping system. *Carbohydr Res* 329, 121-130.
- Moyaert H, A Decostere, M Baele, K Hermans, P Tavernier, K Chiers, F Haesebrouck. 2007. An unusual *Actinobacillus equuli* strain isolated from a rabbit with Tyzzer's disease. *Vet Microbiol* 124, 184-186.
- Negrete-Abascal E, SV Pacheco, GL Paniagua, AP Mendez, JI Caballero, VM Marquez, VR Tenorio. 2004. Metalloproteases secreted by *Actinobacillus suis*. *Curr Microbiol* 49, 55-58.
- Nelson KM, BJ Darien, DM Konkle, FA Hartmann. 1996. *Actinobacillus suis* septicemia in two foals. *Vet Rec* 138, 39-40.
- Newman SJ, AW Confer, RJ Panciera. 2007. Urinary system. In: McGavin (ed). *Pathologic basis of veterinary disease*. 4th ed. Mosby Elsevier, Philadelphia, USA. Pp 613-680.
- Nietfeld JC, P Leslie-Steen. 1993. Interstitial nephritis in pigs with adenovirus infection. *J Vet Diagn Invest* 5, 269-279.
- Odin M, P Helie. 1993. *Actinobacillus suis* in swine in southwestern Quebec. *Can Vet J* 34, 634.
- Odin M. 1994. Les infections à *Actinobacillus suis* au Québec: une étude rétrospective de 22 cas. *Le Médecin Vétérinaire du Québec* 24, 61-65.
- Ojha S, M Sirois, JI MacInnes. 2005. Identification of *Actinobacillus suis* genes essential for the colonization of the upper respiratory tract of swine. *Infect Immun* 73, 7023-7039.
- Ojha S, MA Hayes, PV Turner, JI MacInnes. 2007. An experimental model of *Actinobacillus suis* infection in mice. *Comp Med* 57, 340-348.
- Ojha S, S Lacouture, M Gottschalk, JJ MacInnes. 2010. Characterization of colonization-deficient mutants of *Actinobacillus suis*. *Vet Microbiol* 140, 122-130.
- Oliveira S. 2007. Update on *Actinobacillus suis* diagnosis, epidemiology, and control: On the path from good to great. *American Association of Swine Veterinarians* 38, 371-376.
- Oliveira S, J Tomaszewski, J Collins. 2007. *Actinobacillus suis* molecular epidemiology. *AAVLD Annual Conference Proceedings*, Reno, Nevada, USA, 137.
- Patterson-Kane JC, JM Donahue, LR Harrison. 2001. Septicemia and peritonitis due to *Actinobacillus equuli* infection in adult horse. *Vet Pathol* 38, 230-232.
- Pedersen KB. 1977. *Actinobacillus* infections in swine. *Nord Vet* 29, 137-140.
- Peel MM, KA Hornidge, M Luppino, AM Stacpoole, RE Weaver. 1991. *Actinobacillus* spp. and related bacteria in infected wounds of humans bitten by horses and sheep. *J Clin Microbiol* 29, 2535-2538.
- Pusterla N, M Jones, F Mohor, J Higgins, S Mapes, S Jang. 2008. Fatal pulmonary hemorrhage associated with RTX toxin-producing *Actinobacillus equuli* subsp. *haemolyticus* infection in an adult horse. *J Vet Diagn Invest* 20, 118-121.
- Ramos-Vara JA, CC Wu, I Mitsui, TL Lin, MA Miller. 2008. Metritis, valvular endocarditis, and septicemia by *Actinobacillus equuli* in a gilt in the United States. *Vet Pathol* 45, 495-499.
- Robinson WF, MG Maxie. 1993. The cardiovascular system. In: Jubb KVF, Kennedy PC, Palmer N (eds). *Pathology of domestic animals*. 4th ed. Academic Press, California, USA, Pp 24-27.
- Rosendal S, KR Mittal. 1985. Serological cross-activity between a porcine *Actinobacillus* strain and *Haemophilus pleuropneumoniae*. *Can J Comp Med* 49, 164-170.
- Ross RF, JE Hall, AP Orning, SE Dale. 1972. Characterization of an *Actinobacillus* isolated from the sow vagina. *Int J Syst Bacteriol* 22, 39-46.
- Rullo A, E Papp-Szabo, FS Michael, JI MacInnes, MA Monteiro. 2006. The structural basis for the serospecificity of *Actinobacillus suis* serogroup O:2. *Biochem Cell Biol* 84, 184-190.
- Rycroft AN, LH Garside. 2000. *Actinobacillus* species and their role in animal disease. *Vet J* 159, 18-36.
- Sanford SE, OP Miniats. 1988. *Actinobacillus suis* septicemia mimicking erysipelas in sows. *Can Vet J* 29, 595.
- Sanford SE, GK Josephson, AJ Rehmtulla, AM Tilker. 1990. *Actinobacillus suis* infection in pigs in southwestern Ontario. *Can Vet J* 31, 443-447.
- Sarli G, L Mandrioli, S Panarese, B Brunetti, J Segales, J Dominguez, PS Marcato. 2008. Characterization of interstitial nephritis in pigs with naturally occurring postweaning multisystemic wasting syndrome. *Vet Pathol* 45, 12-18.
- Segales J, GM Allan, M Domingo. 2005. Porcine circovirus diseases. *Anim Health Res Rev* 6, 119-142.
- Slavic D, J DeLay, MA Hayes, JI MacInnes. 2000^a. Comparative pathogenicity of different *Actinobacillus suis* O/K serotypes. *Can J Vet Res* 64, 81-87.

- Slavic D, TL Toffner, MA Monteiro, MB Perry, JI MacInnes. 2000b. Prevalence of O1/K1 and O2/K3 reactive *Actinobacillus suis* in healthy and diseased swine. *J Clin Microbiol* 38, 3759-3762.
- Sternberg S, B Brandstrom. 1999. Biochemical fingerprinting and ribotyping of isolates of *Actinobacillus equuli* from healthy and diseased horses. *Vet Microbiol* 66, 53-65.
- Sulochana S, D Sudharma, ES Mathew, PT Georgekutty. 1985. A note on the isolation of *Actinobacillus suis* from a buffalo calf. *In J Comp Microbiol Immun Inf Dis* 6, 181-182.
- Taylor DJ. 2006. *Actinobacillus suis*. In: Straw BE, Zimmerman JJ, D'Allaire S, Taylor DJ (eds). *Diseases of Swine*. 9th ed. Blackwell Publishing, Ames, Iowa, USA, Pp 827-829.
- Thibault S, R Drolet, MC Germain, S D'Allaire, R Larochelle, R Magar. 1998. Cutaneous and systemic necrotizing vasculitis in swine. *Vet Pathol* 35, 108-116.
- Thompson AB, RC Postey, T Snider, T Pasma. 2010. *Actinobacillus equuli* as a primary pathogen in breeding sows and piglets. *Can Vet J* 51, 1223-1225.
- Van Ostaaijen J, J Frey, S Rosendal, JI MacInnes. 1997. *Actinobacillus suis* strains isolated from healthy and diseased swine are clonal and carry apxICABD_{var.suis} and apxIICA_{var.suis} toxin genes. *J Clin Microbiol* 35, 1131-1137.
- Vaz R, K Kennedy, G Shannon, M Peel. 2001. Septicemia in a horse trainer caused by *Actinobacillus equuli*. *Clin Microbiol Newsletter* 23, 151-153.
- Webb RF, FA Cockram, L Pryde. 1976. The isolation of *Actinobacillus equuli* from equine abortion. *Aust Vet J* 52, 100-101.
- Werdin RE, JP Hurtgen, FY Bates, FC Borgwardt. 1976. Porcine abortion caused by *Actinobacillus equuli*. *J Am Vet Med Assoc* 169, 704-706.
- Wilson RJ, S McOrist. 2000. *Actinobacillus suis* infection in pigs in Australia. *Aust Vet J* 78, 317-319.
- Windsor RS. 1973. *Actinobacillus equuli* infection in a litter of pigs and a review of previous reports on similar infections. *Vet Rec* 92, 178-180.
- Woldehiwet Z. 2004. *Actinobacillus suis* abortion: a possible cause for concern in pigs. *Vet J* 168, 116-117.
- Wood RR, LM Henderson. 2006. Erysipelas. In: Straw BE, Zimmerman JJ, D'Allaire S, Taylor DJ (eds). *Diseases of Swine*. 9th ed. Blackwell Publishing, Ames, Iowa, USA, Pp 629-638.
- Xu M, S Wang, L Li, L Lei, Y Liu, W Shi, J Wu, L Li, F Rong, M Xu, G Sun, H Xiang, X Cai. 2010. Secondary infection with *Streptococcus suis* serotype 7 increases the virulence of highly pathogenic porcine reproductive and respiratory syndrome virus in pigs. *Virology* 407, 184.
- Yaeger MJ. 1996. An outbreak of *Actinobacillus suis* septicemia in grow/finish pigs. *J Vet Diagn Invest* 8, 381-383.
- Zimmerman J, DA Benfield, MP Murtaugh, F Osorio, GM Stevenson, M Torremorell. 2006. Porcine reproductive and respiratory syndrome virus (Porcine arterivirus). In: Straw BE, Zimmerman JJ, D'Allaire S, Taylor DJ (eds). *Diseases of swine*. 9th ed. Blackwell Publishing, Ames, Iowa, USA, Pp 387-417.