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Virulence Factors and Pathogenesis of Some *Streptococcus* Species: Review

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Abstract: *The Streptococci are a group of bacteria that can infect many animal species, causing suppurative conditions such as mastitis, metritis, polyarthritis and meningitis. They are gram positive, catalase negative, facultative anaerobes, non-motile, fastidious bacteria and require the addition of blood or serum to culture media for growth. The majority of pathogenic Streptococci possess a serologically active carbohydrate antigenically different from one species or group of species to another. These cell wall antigens, designated A-H and K-V, are the basis of the Lancefield grouping system and are widely used by clinical laboratories for serogrouping. Most of the Streptococci that are pathogenic for animals are pyogenic and are associated with abscess formation, other suppurative conditions and septicaemia. Streptococcus suis, which is non-pyogenic, is a major pathogen of pigs, causing septicaemia, meningitis and pneumonia among other conditions. Beta-haemolytic Streptococci are generally more pathogenic than those producing alpha-haemolysis. Virulence factors include enzymes and exotoxins such as streptolysins (haemolysins), hyaluronidase, DNase, streptokinase and proteases. Polysaccharide capsules, which are major virulence factors of S. pyogenes, S. pneumoniae and most strains of S. equi, are antiphagocytic. The cell-wall M proteins of S. pyogenes, S. equi and S. porcinus are also antiphagocytic. These virulence factors play great role in the pathogenesis of different Streptococcus species.*

Keywords: *Pathogenesis, Streptococcus, Virulence Factors*

1. INTRODUCTION

Pathogenicity is defined as the ability of an organism or microbe to cause harm or disease in a host. It is thought to depend on possession by the microbe of certain virulence factors that mediate the disease outcome in the host. Virulence, on the other hand, is defined as the relative capacity of the microbe to cause disease or harm in the host. Whilst pathogenicity is often considered in terms of the presence or absence of this ability in the microbe, i.e. whether or not the microbe is pathogenic or not, virulence often refers to the extent or degree of damage or pathology caused by the microbe to the host.

Pathogenesis is the mechanism of entrance of microorganism and the process by which disease develops (Ebruke, 2018).

Streptococci are gram positive spherical chain forming bacteria (Fig. 1) less than 2 μm that typically grow by cell division in one plane, so that nascent cells form a linear array. Most are facultatively anaerobic and catalase negative with complex and variable nutritional requirements, which reflect adaptation as commensals or parasites. Identification is based on colony characteristics; hemolytic properties; carbohydrate and protein antigen composition; fermentation and other biochemical reactions; DNA sequence of 16 and 23S rRNA genes; and, within species, multilocus enzyme electropherotype and multilocus sequence typing (MLST) (Gyles, *et al*., 2010; Quinn *et al*., 2011).

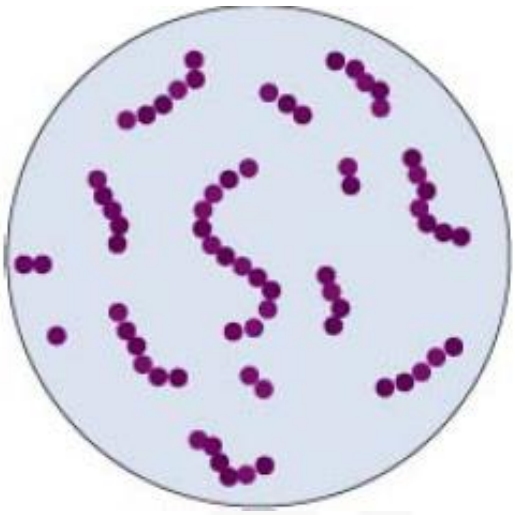

Figure 1. *Streptococcus* showing chain arrangement

The *Streptococci* are a group of bacteria that can infect many animal species, causing suppurative conditions such as mastitis, metritis, polyarthritis and meningitis. *Streptococcus* species are non-motile, fastidious bacteria and require the addition of blood or serum to culture media. They can be differentiated by Lancefield grouping, type of haemolysis and biochemical fermentation patterns. The optimal temperature for *Streptococcus* species is around 37°C, although most can grow in the range of 20-42°C (Lindahl, 2013). *Streptococci* can exhibit three types of haemolysis: Alpha (α) haemolysis – green or partial haemolysis, Beta (β) haemolysis – clear zone of haemolysis, and Gamma (γ) haemolysis – no haemolysis. The type of haemolysis depends on the species of *Streptococcus*, the type of blood used in the culture medium, and environmental conditions (Quinn *et al*., 2011).

The majority of pathogenic *Streptococci* possess a serologically active carbohydrate antigenically different from one species or group of species to another. These cell wall antigens, designated A-H and K - V, are the basis of the Lancefield grouping system and are widely used by clinical laboratories for serogrouping. The antigens are extracted by autoclaving, formamide treatment, or enzymatic digestion for testing with commercially available sera. Groups B, C, D, E, G, L, U, and V contain the pyogenic *Streptococci* responsible for suppurative (pus - producing) infections in a variety of host species. Some pathogenic *Streptococci*, notably *Streptococcus uberis*, *Streptococcus parauberis*, and *Streptococcus pneumoniae*, are not groupable in the Lancefield scheme and are identified by features such as fermentation behavior, ability to grow at different temperatures, salt tolerance, optochin sensitivity, bile solubility, and 16S rRNA gene sequences (Gyles, *et al*., 2010).

With the exception of *S. pneumoniae* and *S. suis*, all are loosely categorized as pyogenic. Comparison of the available genome sequences of the pyogenic *Streptococci* shows that about 66% of their genetic content is common to all; the remainder is variable and formed by genes associated with prophages, integrative conjugative elements, insertion elements, and other genes acquired by horizontal transfer. *S. mutans*, *S. salivarius*, *S. sanguis*, and *S. mitis* are some of the non-pathogenic species that are collectively referred to as Viridans *Streptococci* (Mishra and Agrawal, 2013).

Streptococcal virulence is based on surface and secreted proteins and on structures that directly or indirectly impede phagocytosis, are involved in adhesion and carbohydrate metabolism, or induce release of pro-inflammatory cytokines. The best understood streptococcal virulence factors are the hyaluronic acid capsule, the antiphagocytic M proteins, and the pyrogenic exotoxins. However, other molecules, including streptolysins, proteases, leukocidal toxins, plasminogen activators (streptokinase), and possibly plasmin receptors found on the surface or secreted, also contribute to pathogenicity. The *Streptococci* pathogenic for domestic animals can be grouped by their adaptation to specific organs/body systems. Thus, *S. agalactiae, S. dysgalactiae*, and *S. uberis* cause disease in the udder; *S. equi*, are pathogens of the lymphatics of the head and neck; *S. pneumoniae* causes lower respiratory tract disease in horses; *S. suis* is adapted to survive on/in blood mononuclear cells that transport it to the central nervous system (CNS), lungs, and joints (Gyles, *et al*., 2010).

There are several stages of the bacterial pathogenic process. This includes adherence to and colonisation of mucosal and/or epithelial surface(s) of the host; invasion into deeper tissue and translocation in the bloodstream; breaching of the blood-brain barrier; interaction with host cells; stimulation of the excessive inflammatory response and tissues, and inflammation (Dutkiewicz *et al*., 2018).

1.1. Virulence Factors of *Streptococcus* Species

Streptococcal virulence factors (Fig. 2) can be the categories of surface proteins, extracellular toxins which include Streptolysin-S, Streptolysin-O, streptokinase, and pyrogenic exotoxins. Streptolysin-S is mostly produced by members of Group A, C, and G. Streptolysin-O destroys hemoglobin and suppresses chemotaxis. It can also cause lysis of leukocytes and erythrocytes. Streptokinase causes lysis of blood clots and facilitates the spread of bacteria. Streptococcal pyrogenic exotoxins A, B, and C are believed to be responsible for the rashes in scarlet fever and for the symptoms of toxic shock syndrome. A rise in the distribution of streptococcal pyrogenic toxin producing strains is believed to be associated with the rise in Group A streptococcal invasive infections. The others are cell-associated factors which include M protein, which helps bacterium in evading host's immune system, and lipoteichoic acid (mostly associated with *S. pneumoniae*), which facilitates adherence. Capsules as seen in *S. pneumoniae* protect the pathogen from the host's defenses and also from the effects of antibiotics and other chemicals (Mishra and Agrawal, 2013).

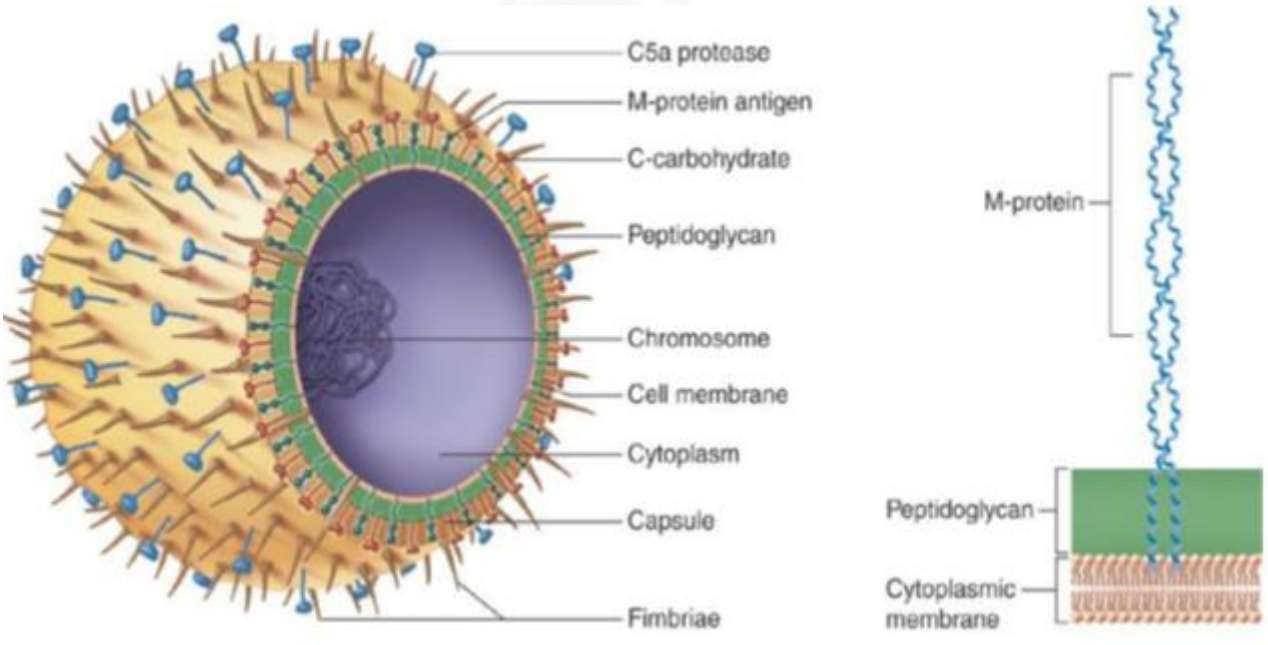

Figure 2. Virulence factors of *Streptococci*

1.1.1. Virulence Factors of Streptococcus agalactiae

Much of the information on potential virulence factors of *S. agalactiae* has been derived from studies on human isolates in mouse and rat models and therefore must be cautiously interpreted in the context of bovine mastitis. Bovine isolates generally have different properties from those of their counterparts from humans and usually lack well studied virulence factors, such as ScpB, Lmb, and IgA binding β protein. Capsular polysaccharide, including its type specific antigen, is antiphagocytic, and specific antibodies are mouse protective and contribute to resistance of human infants to infection. Terminal sialic acid on type III capsular polysaccharide inhibits activation of the alternate complement pathway and blocks deposition of C3 on the bacterial surface. The capsule also increases the affinity of the complement control factor H for C3b bound to the surface of the cell wall and thereby reduces both the activity of the C3 convertase and further deposition of C3b on the cell (Gyles, *et al*., 2010).

1.1.2. Virulence Factors of Streptococcus dysgalactiae

S. dysgalactiae express numerous surface-exposed and secreted proteins that bind to plasma or host tissue components. These streptococcal proteins include protein G, fnbA, fnbB, IgG, IgA, and α2 macroglobulin receptor Mig, plasminogen receptor (GAPC), and M - like proteins, which bind IgG, fibronectin, α2 macroglobulin, plasminogen, and fibrinogen, respectively. Secreted proteins include streptokinase, pyrogenic exotoxin G (SPEG), streptolysin O or S, streptodornase (DNase), pyrogenic exotoxin G, and hyaluronidase. *S. dysgalactiae* subsp. *Equisimilis* includes group G and L strains from humans, and C and L strains from animals. Isolations of subsp. *equisimilis* are made only infrequently from horses, cattle, dogs, and cats. It is most frequently isolated from joints of piglets that have acquired infection from sows that are tonsil carriers. Piglets are invaded via wounds, umbilicus, or tonsil and develop suppurative arthritis (Gyles, *et al*., 2010).

1.1.3. Virulence Factors of Streptococcus uberis

Resistance to phagocytosis and the bactericidal activity of neutrophils is a hallmark of *S. uberis* infection. A hyaluronic acid capsule protective against phagocytosis and intracellular killing is expressed on a small percentage of isolates, the majority of isolates of *S. uberis* do not produce mucoid colonies, and so the capsule is not an essential virulence factor. Furthermore, *hasA* or *C* gene deletion mutants, although less resistant to phagocytosis by bovine neutrophils, are nevertheless pathogenic following entry into the mammary gland. Resistance to the bactericidal activity of neutrophils may be due to factors released by *S. uberis* as it replicates in milk. In addition, binding of casein to the bacterial surface increases resistance to phagocytosis. Other potential virulence factors include hyaluronidase, a 28 kDa uberis factor similar to the CAMP factor of *S. agalactiae*, an adhesin specific for cubic mammary gland cells, the plasminogen activator, and the manganese scavenger lipoprotein MtuA. Activation of plasmin may be important in the generation of essential amino acids from casein and in uncovering target sites for adhesins expressed on the bacterial surface (Gyles, *et al*., 2010).

S. uberis is one of the most common pathogens isolated from cases of bovine mastitis and it impacts negatively on animal health, welfare and the economics of milk production. S. *uberis* has been shown in experimental infection models within the dairy cow to colonize the mammary gland rapidly, induce neutrophil diapedesis and cause an acute local inflammation during which milk becomes denatured and the mammary gland distended, swollen and painful. *S. uberis* persists within the mammary gland in the presence of neutrophils and other host defenses, which seem to offer little control. However, the infection remains localized to the mammary gland and the bacterium is found largely in the secretion present within the lumen of the gland (Leigh *et al*., 2010).

1.1.4. Virulence Factors Streptococcus equi

The known or putative virulence factors of *S. equi* include a non-antigenic hyaluronic acid capsule, hyaluronidase, streptolysin S, streptokinase, streptodornase, IgG Fc - receptor proteins, ADP-ribotransferase, pyrogenic exotoxins SePE-I, H, L, and M, peptidoglycan, antiphagocytic SeM, Se18.9 and IdeE, equibactin, and fibronectin - binding FNE and FNEB. A leukocidal toxin may also be produced. Isolates of *S. equi* are almost always highly encapsulated and produce very mucoid colonies. Non-encapsulated mutants are much less virulent for mice and horses. The hyaluronic acid capsule greatly reduces the number of *Streptococci* that become associated with the surface of neutrophils and

are subsequently ingested and killed. The capsule increases the negative charge and hydrophilicity of the bacterial surface and produces a localized reducing environment that protects oxygen-labile proteases. The capsule is also required for the functionality of SeM and possibly other surface exposed hydrophobic proteins. Streptokinase (Skc, plasminogen activator) released *in vivo* by *S. equi* interacts with the C-terminal serine protease domain of equine plasminogen to form active plasmin, a serine protease that hydrolyses fibrin. A role for plasmin in the pathogenesis of strangles has not been proven, but its lytic action on fibrin and host matrix protein may aid in the spread and dispersion of the bacteria in tissue. Convalescent sera contain significant amounts of Skc - specific antibody. Other possible roles include *in situ* activation of complement and production of low molecular weight nitrogenous substrates for bacterial growth. The surface of *S. equi* has a receptor for plasmin. The oxygen stable 36 amino acid oligopeptide, streptolysin S, is responsible for the betahemolysis produced by *S. equi*. Production of this bacteriocin-like cytotoxin is encoded by a nine - gene locus, and biologic activity requires stabilization by association with a carrier molecule (Gyles, *et al*., 2010).

1.1.5. Virulence Factors Streptococcus zooepidemicus

S. zooepidemicus produces many of the virulence factors listed for *S. equi*. Greater than 96% DNA homology shared by these species, their protein profiles are similar. Notable differences are absence of genes for known pyrogenic exotoxins, iron binding equibactin E, a functionally antiphagocytic homologue of SeM or Se18.9, as well as homologues of a few other surface - exposed or secreted proteins. Capsule synthesis is highly variable and usually quickly lost following primary culture. Synthesis is tightly regulated, unlike *S. equi*, in which expression is constitutive. Also, many isolates of *S. zooepidemicus* produce hyaluronidase. Isolates from the tonsil and other mucosal sites of healthy animals are almost always unencapsulated. Toxigenic strains have been implicated in outbreaks of septicemia and hemorrhagic pneumonia in greyhounds and shelter dogs but lack genes for the known pyrogenic exotoxins. Three putative fimbriae- encoding operons have been found in *S. zooepidemicus* MGCS 10565 and two in H70. There are also at least three proteins with fibronectin-binding activity, FNZ, FNZ2, and SFS. Thus, the organism is predicted to have greater attachment/colonizing ability than *S. equi* (Gyles, *et al*., 2010).

1.1.6. Virulence Factors Streptococcus pyogenes

The potency of *S. pyogenes* is attributed to several virulence factors that contribute to its pathogenic complexity. One of the most important virulence determinants, M protein encoded by the emm gene, facilitates adhesion and resistance to opsonophagocytosis and contributes to the overall burden of GAS infections. Furthermore, variability in the N terminus of the M protein has been used as an epidemiological marker to characterize worldwide GAS isolates. *S. pyogenes* is also an important contributor to the so-called excess mortality associated with influenza, which occurs when influenza infections are succeeded by secondary bacterial infections. Excess mortality contributes to human morbidity and mortality during both influenza epidemics and pandemics (Dmitriev and Chaussee, 2010).

GAS strains express many virulence factors including surface M protein, streptolysins, streptokinase **(**fibrinolysin**)**, hyaluronidase and hyaluronic acid capsule, peptidoglycan, teichoic acid, pyrogenic exotoxins of *Streptococcus pyogenes* (SPEs) types A, B and C which act as superantigens, Deoxyribonucleases (streptodornase DNase) and proteases. M Protein is considered as the main virulence factor, limiting phagocytosis, disturbing the function of complement, and being responsible for adhesion (Walker *et al*., 2014). Moreover, invasive S. pyogenes strains, which cause deep soft-tissue infections and fasciitis as well as streptococcal toxic shock syndrome (STSS) and sepsis, also produce highly specific toxins with special pro-inflammatory properties. Streptococcal pyrogenic toxins (SPE) possess superantigen properties and bridge antigen-presenting cells with immune system effector cells, leading to their polyclonal activation. This activation leads to accelerated T lymphocyte proliferation and liberation of significant quantities of proinflammatory cytokines, leading to toxic shock. Furthermore, the emm gene forms the basis for epidemiological typing of GAS at the same time correlating serotyping with pathogenicity (Oehmcke *et al*., 2010).

1.1.7. Virulence Factors of Streptococcus pneumoniae

The microorganism produces a plethora of virulence factors, including the polysaccharide capsule, several surface-located proteins, and the toxin pneumolysin. The capsule is a major virulence determinant due to its anti-phagocytic activity. Among the surface-associated proteins, the pneumococcal surface protein A (PspA) and C (PspC) are the best characterised choline-binding proteins. PspA interferes with complement activation and deposition mediated by both the classical and alternative pathways and also binds lactoferrin. PspC interacts with human immunoglobin A and with the polymeric immunoglobulin receptor, thereby promoting adhesion and transcytosis of pneumococci across mucosal surfaces. PspC also shows anti-phagocytic properties due to its capability to bind to complement C3 and factor H (Ricci *et al*., 2013).

PsaA (pneumococcal surface adhesion A) is part of an ABC transporter operon in which PsaA is a substrate binding lipoprotein, PsaB, the ATP-binding protein and PsaC the permease likely involved in transporting manganese and zinc into the cytoplasm of pneumococcus. It is thought to function as an adhesin. Strains of the pneumococcus lacking this gene have been found to be avirulent in animal model tests. The pneumococcal cell surface is made up of several proteins which contribute significantly to the virulence of the organism. They are marked by one of three motifs; a choline binding domain, a lipoprotein domain or the LPXTG cell wall anchor. The cell wall is made up of lipoteichoic acid (LTA), a phospholipid membrane (LM), peptidoglycan (PG), teichoic acid (TA) and phosphoryl choline (PCho) which anchors choline binding proteins to the cell wall (CBP) (Ebruke, 2018).

1.1.8. Virulence factor of Streptococcus suis

Feng *et al*. (2014) classified temporarily the *S. suis* virulence-associated factors into the following four groups: i) surface/secreted elements; ii) enzymes, including proteases; iii) transcription factors/regulatory systems; iv) others (transporters/secretion systems).

Capsular polysaccharide as a major virulence factor of *S. suis.* Other virulence factors of *S. suis* include extracellular protein, fibronectin binding adhesion, muramidase released protein, a protein of 38 kDa localized on bacterial surface (38 kDa), secreted thio-activated heamolysin (suilysin) which is not only a toxic factor for various cell types, but also interferes with complement-mediated phagocytosis and killing, surface-associated subtilisin-like serine protease that modulates cytokine secretion by macrophages contributing to the process of meningitis; a histidine triade immunogenic cell surface protein; Sat surface protein; a novel serum opacity factor; surface antigen protein; sortase A, catalyzing cell wall sorting reaction; pili and hair-like appendages composed of pilin proteins that are active in biofilm formation (Dutkiewicz *et al*., 2018).

1.2. Pathogenesis of *Streptococcus* Species

1.2.1. Pathogenesis of Streptococcus agalactiae

S. agalactiae enters through the teat meatus, and colonization of the gland is favored by adhesion to the epithelium of the gland sinuses. Back - jetting of contaminated milk against the teat ends at milking time is an important factor in the introduction of infection past the teat sphincter. Keratin and associated bacteriostatic long chain fatty acids of the teat canal are the first barriers to physical penetration of the epithelial lining. Bacterial multiplication is controlled by the lactoperoxidase - thiocyanante - H_2O_2 system, by lysozyme, and by the flushing action of milk during milking. Multiplication on the epithelium of the teat and duct sinuses results in a slowly progressing inflammation and fibrosis. Although *S.agalactiae* rarely penetrates the epithelium, some cows may experience a transient invasion during the first few days in which the organism enters the lymphatics and travels to the supramammary lymph nodes. Release of chemoattractants from damaged host cells and *S. agalactiae* attracts polymorphonuclear leukocytes (PMNs), which then ingest and kill many of the invading *Streptococci*. Since normal milk has very low complement content and thus cannot itself serve as a source of C3, opsonization is probably derived from C3 in the inflammatory exudate, which becomes fixed on the bacterial surface following activation of the alternative complement pathway. Initial invasion is more likely to result in colonization in older cows and in mammary glands, where there is delay in the arrival of PMNs at the site of invasion. Death of PMNs and release of lysosomal enzymes cause further tissue damage and inflammation. Fibrin plug formation in the smaller milk ducts

may lead to involution of secretory tissue and loss of milk-producing capacity ("agalactiae"). Without treatment, the organism persists in the face of the host's immune response, and the infection and mastitis become chronic. The antiphagocytic effect of capsular sialylated polysaccharide may be the important bacterial virulence factor in persistence (Gyles, *et al*., 2010).

1.2.2. Pathogenesis of Streptococcus dysgalactiae

Surface coating with plasma proteins including immunoglobulins in combination with M proteins may serve to reduce phagocytosis. Immunization of cows with Mig and GAPC reduces cell counts in milk following challenge. GAPC-immunized cows also showed reductions in the number of challenge bacteria in their milk. Release of hyaluronidase and fibrinolysin may be of value in tissue penetration and dissemination. Bovine sera contain an antibody specific for SPE-G, and the recombinant protein stimulates proliferation of bovine PBMCs. However, its significance in the pathogenesis of mastitis is unknown. Infections of the mammary gland are usually associated with damage, such as insect bites or other injury to the teat or udder epithelium, which would facilitate direct access of surface exposed or secreted virulence bacterial proteins to their targets in the host. Since infections are opportunistic, cases occur sporadically with an acute clinical course (Gyles, *et al*., 2010).

1.2.3. Pathogenesis of Streptococcus uberis

S. uberis is a tonsillar, intestinal, mucosal, and epithelial commensal of cattle and responsible for cases of clinical mastitis in dairy cattle. Many infections are opportunistic invasions of the mammary gland of older cows under conditions of heavy environmental soiling with feces. Analysis of the genomic sequence of *S. uberis* reveals a great variety of metabolic capabilities and nutritional flexibility but relatively few classical streptococcal virulence factors. Following entry through the teat canal, the organism attaches, proliferates, and induces an influx of neutrophils into the secretory acini that is evident in 24 h. This is followed by septal edema, vacuolation of secretory cells, necrosis of alveoli, and infiltration of septa by lymphocytes. As the disease progresses, there is hypertrophy of ductular epithelium, involution of glandular tissue, and early stage fibrosis. *Streptococci* are free and within alveolar epithelial cells and macrophages in the alveolar lumina but are infrequent in neutrophils. The organism is also present in lymphatic vessels and lymph nodes and attaches to ductular epithelium (Gyles, *et al*., 2010).

1.2.4. Pathogenesis of Streptococcus equi

Infection appears to occur following entry of the organism into the tonsils with extension to the regional lymph nodes. The bacteria multiply in the lymph nodes, eliciting an inflammatory response, outpouring of neutrophils and abscess formation. Large numbers of neutrophils are attracted to the sites of invasion and replication of *S. equi*, because the peptidoglycan in its cell wall reacts with C and stimulates the generation of chemotactic factors. The organism has many virulence factors which protect it from the host immune response and allow it to continue to multiply despite the presence of many neutrophils. It possesses a hyaluronic capsule and M proteins which protect it against ingestion and killing and it may also produce a leukocidal toxin. The M proteins which project from the surface of the cell wall prevent activation of the alternative and classical complement pathways. However, once antibodies against these proteins are produced by the host, these effects are neutralized and organisms are effectively phagocytosed. Streptokinase may facilitate the spread of bacteria in tissue, and streptolysin S causes lysis of erythrocytes and appears to damage keratinocytes also. *S. equi* produces a number of phage-encoded superantigens. These superantigens non-specifically stimulate T cells and are in part responsible for the clinical findings of high fever, neutrophilia and fibrinogenaemia observed in horses with strangles. There is also pus formation in lymph nodes (Quinn *et al*., 2011).

1.2.5. Pathogenesis of Streptococcus zooepidemicus

Although it has wide ranging pathogeniciy, it is generally considered a mucosal commensal and an opportunistic pathogen of the upper respiratory tract of horses. It has also been associated with inflammatory airway disease. In the pathogeneisis of *S. zooepidemicus* Fibronectin-binding proteins is used for Binding, Hyaluronic acid apsuleand M- proteins are ued for Protection against phagocytosis and Fc receptors is used for Recognition. In the overall complex interaction the disease develops. *S.*

zooepidemicus is also recognized as a cause of lower airway disease, e.g., pneumonia. As an opportunistic pathogen, disease caused by *S. zooepidemicus* may have predisposing factors such as concurrent viral infection, stress or tissue injury. *S. zooepidemicus* is not host restricted, nor limited to the respiratory organ system. In horses, *S. zooepidemicus* is also associated with various non-respiratory problems, including wound infections, joint infections, sepsis in foals, and uterine infections (Lindahl, 2013).

1.2.6. Pathogenesis of Streptococcus pyogenes

S. pyogenes, also called Group A *Streptococcus*, causes infections involving the upper respiratory tract (pharyngitis or strep throat) and mucocutaneous tissues, as well as skin infection, scarlet fever, and muscle infection (hence the term "flesh-eating bacteria"). The incubation period of strep throat infection is very short and the symptoms may include sore throat, fever, and headache. The cervical lymph nodes may be affected. In some cases, streptococcal throat infection may lead to scarlet fever, characterized by body rashes that may heal in about 1 week. The skin infection may begin with exposure of bruised skin to *S. pyogenes* either through direct contact or through inanimate objects (fomite). Pus-filled vesicles develop and eventually rupture and crust over. Another form of skin infection, called necrotizing fasciitis, involves deeper subcutaneous tissue and results in a severe destruction of the muscles. The disease often develops into a systemic infection and eventual death in many cases. Infection with this bacterium is also known to lead to secondary, or post streptococcal glomerulonephritis, which is characterized by inflammation due to immune complex formation in glomeruli, resulting in hematuria (blood in urine) and proteinuria (high protein concentration in urine). Another secondary consequence of *S. pyogenes* infection is rheumatic fever. This usually occurs 2-3 weeks after acute pharyngitis with *S. pyogenes*. It may involve the heart (resulting in damaged heart valves), joints (multiple joint arthritis), central nervous system, and skin (Mishra and Agrawal, 2013).

1.2.7. Pathogenesis of Streptococcus pneumoniae

S. pneumoniae, also referred to as pneumococcus, is known to cause pneumonia, otitis media (midear infection), sinusitis, meningitis, and bacteremia (septicemia). Most strains of *S. pneumoniae* are non-hemolytic. The common serotypes isolated from clinical specimens are referred to as serotype 6, 14, 18, and 19. This bacterium can also be isolated from the respiratory tract of apparently healthy individuals. Infections occur when pneumococci get into the lungs or bloodstream. Under normal circumstances nonspecific immune components, especially phagocytes and macrophages, keep these bacteria under control. Pneumococcal pneumonia is often accompanied by high fever and chill and the symptoms may be mistaken for viral infection. The cough may be productive and blood tinged. Children and the elderly are more prone to pneumococcal pneumonia. Ear infections are more common in children, but the sinusitis can affect adults as well. Bacteremia is more serious form of infection and not an uncommon complication in pneumonia. Bacteremia can also lead to endocarditis and meningitis (Mishra and Agrawal, 2013).

1.2.8. Pathogenesis of Streptococcus suis

S. suis, a commensal of upper respiratory tract of pigs, can cause serotype (type)–dependent disease both in pigs and humans, mostly manifested as meningitis (Dutkiewicz *et al*., 2018). In early infection, an important role is played by enzymes produced by *S. suis*, mostly proteases (such as fibrinogen-degrading subtilisin) and deoxyribonucleases (DNases). They are involved in bacterial growth, biofilm formation and evasion of the host immune system. The enzymes were detected in *S. suis* membrane vesicles, small globular structures of 10–200 nm diameter formed by membrane blebbing, which can promote colonization by reaching areas not accessible to the whole bacteria (Segura *et al*., 2016).

A hallmark of *S. suis* pathogenicity is its ability to disseminate in the blood circulation and to maintain bacteraemia for certain time. This is considered to be crucial in causing meningitis. Thus, major mechanisms in pathogenesis of *S. suis* infections are those involved in (i) invasion of *S. suis* through the epithelial cell barriers, (ii) evasion of killing by complement and phagocytosis, and (iii) invasion into the cerebrospinal fluid (CSF) or other target sites (Fulde and Weigand, 2013).

Streptococcus suis is able to survive in the bloodstream and disseminate to the central nervous system (CNS) and other organs of the host, due to the efficient protection provided by CPS against neutrophils- and monocyte/macrophage-mediated phagocytosis and killing. According to the early theory of a 'Trojan horse', bacteria are taken-up by monocytes (in the absence of specific antibodies), survive intracellularly and then invade the CNS. However, contemporary studies conducted by different laboratories demonstrate that bacteria travel extracellularly, either free in circulation or attached to the surface of monocytes. Phagocytic cells are unable to efficiently phagocytose encapsulated *S. suis* in the absence of specific antibodies, and suilysin further protects bacteria upon complement-mediated uptake and killing (Dutkiewicz *et al*., 2018).

After survival in blood and following dissemination, *S. suis* invades multiple organs, including the spleen, liver, kidney, lung, and heart. If *S. suis* present in blood fails to cause fatal septicaemia, it is able to cross the blood-brain barrier (BBB) and/or blood–cerebrospinal fluid barrier (BCSFB) made by the brain microvascular endothelial cells (BMECs) and/or the choroid plexus epithelial cells (CPECs) to gain access to CNS and cause meningitis. The mechanisms by which bacteria reach the CNS are only partially known and include adhesion to BMECs or CPECs, which have been reported to be independent of the capsular polysaccharide expression and mediated by cell wall components, such as the LTA, LPXTG cell wall-anchored proteins and enolase. The next step is penetration into these cells either by direct invasion of bacteria into the cells by endocytic mechanisms, or by disrupting the cell junctions. *S. suis* can also bind and activate plasminogen to proteolytically render the BBB leaky to bacteria. Furthermore, the *S. suis* CPS and cell wall can synergistically induce human macrophages to secrete prostaglandin PGE2 and matrix metalloproteinase 9, which also may be involved in disruption of the BBB. Permeability of the BBB could be increased as well by pro-inflammatory cytokines induced by *S. suis* and produced by BMECs and/or by suilysin produced by the pathogen. Finally, *S. suis* breaches the BBB function and integrity by killing its cells, mostly by necrosis and less often by apoptosis (Fittipaldi *et al*., 2012; Fulde and Weigand, 2013).

Clinical presentations of *S. suis* infection vary from asymptomatic bacteraemia to fulminant systemic disease with septic shock similar to Gram-negative sepsis, which suggests a massive inflammation process. Clinical signs of meningitis in pigs and humans have also been associated with inflammation in the CNS. Thus, it is evident that inflammation plays a key role in the pathogenesis of both systemic and CNS infections caused by *S. suis*. The pathogen induces the overproduction of pro-inflammatory cytokines and the recruitment and activation of different leukocyte populations, causing acute inflammation of the CNS (Dutkiewicz *et al*., 2018).

2. CONCLUSION

Diverse virulence factors and pathogenic mechanisms are involved in streptococcal infections resulting in a variety of clinical manifestations. The clinical patterns varies depending on the particular species of *Streptococcus* involved, the site of initial colonization, the tissue or organ affected, and the status of the host. *Streptococcus* bacteria are common on the bodies of animals along with numerous other types of bacteria, as part of the normal flora. When the bacteria enter cuts, abrasions, other wounds or when the immune system becomes weakened, disease may occur. There are many different species and strains of *Streptococcus*, so a wide range of disease signs may be seen. Infection can be mild to severly fatal. They can cause wound infections, abscesses, respiratory infection, and other illness. In horses, signs of disease may include runny nose, coughing, breeding problems, abortion, or mastitis. In swine, infection can cause swollen joints, fever, incoordination, blindness, and convulsions and death.

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