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Chapter: **Pathogenicity factors in group C and G Streptococci**

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This chapter is dedicated to the memory of Professor Singh Chatwal, an inspiring 'streptococcologist' who leaves us with wonderful memories of Lancefield 2002 held in Goa, India.

INTRODUCTION

The pyogenic streptococci of Lancefield groups C and G were initially recognized as a cause of animal infections long before they were even considered as agents of human disease, even though they are widely distributed in animals and humans. They comprise a heterogeneous complex of streptococcal species that act as causative agents of a spectrum of diseases ranging from mild pharyngitis, skin infection to life threatening systemic infections associated with high mortality rates. In this chapter we provide an overview of the various group C and group G streptococcal species, the diseases they cause, and the major pathogenicity factors that contribute towards their virulence (Table 1).

TAXONOMY AND IDENTIFICATION

Taxonomic classification of group C streptococci (GCS) and group G streptococci (GGS) has always proven to be a complex issue. However, extensive taxonomic studies over the last few years have distinguished most of the veterinary pathogens belonging to Lancefield groups C and G from the human pathogens. Previously, GCS and GGS were divided into the following species, *Streptococcus equisimilis* (only GCS, human pathogen), *Streptococcus sp.* (GGS, human pathogen), *Streptococcus dysgalactiae* (GCS, animal pathogen), *Streptococcus equi* (animal GCS), *Streptococcus zooepidemicus* (animal and human GCS), *Streptococcus canis* (animal GGS), the *Streptococcus anginosus* group and *Streptococcus phocae* (1). GCS and

GGS of human origin are now considered to constitute a single subspecies, *Streptococcus dysgalactiae* subsp *equisimilis*. Therefore, the current taxonomy characterises the species as follows; *S. dysgalactiae* is divided into the subspecies *S. dysgalactiae* subsp. *equisimilis* and *S. dysgalactiae* subsp. *dysgalactiae* (hereafter referred to in this chapter as *S. equisimilis* and *S. dysgalactiae*). *Streptococcus equi* is divided into the subspecies *S. equi* subsp. *equi* and *S. equi* subsp. *zooepidemicus* (hereafter referred to as *S. equi* and *S. zooepidemicus*). On the basis of genetic evidence, *Streptococcus dysgalactiae*, *Streptococcus equi*, *Streptococcus canis* are more closely related to each other than to the '*S. anginosus* group', and constitute species with the 'large-colony' colony phenotype. Recent data now suggests that *S. equi* may simply be a subclone of *S. zooepidemicus* (2). *S. phocae* is a new species expressing the group C antigen thus far only isolated from seals (3, 4). Some of these species may also contain strains which express the Lancefield group A or group F antigens (Table 2).

HUMAN DISEASE AND DIAGNOSIS

GCS and GGS can cause a wide range of diseases from mild to severe, both among human and animal populations. GCS and GGS generally colonize the human respiratory, gastrointestinal and genitourinary tracts, with an estimated <4% asymptomatic pharyngeal carriage rate in adults (5-7). Human invasive infections caused by GCS and GGS have been associated with underlying conditions, such as diabetes, cardiovascular diseases and chronic skin conditions (8-10). While *S. dysgalactiae* is considered an animal pathogen, *S. equisimilis* is almost exclusively a human pathogen, with increasing prevalence and overlaps in clinical manifestations with group A *Streptococcus* (GAS). *S. equisimilis* infections include acute pharyngitis, pneumonia, endocarditis, cellulitis, peritonitis, septic arthritis, bacteraemia, and toxic shock syndrome (11-23). Like GAS, *S. equisimilis* has also been linked to the post streptococcal sequelae rheumatic heart disease, and in high endemic areas of rheumatic fever, carriage rates of GCS/GGS have been found to be higher than GAS (24, 25).

Infections with *S. zooepidemicus* and *S. canis*, normally considered zoonotic species, have also been reported in humans (26-29), including severe infective endocarditis (30). Generally, person to person transmission of GCS/GGS occurs via respiratory droplets or skin contacts, however, other zoonotic vehicles of transmission such as unpasteurized milk products are also possible (26, 27, 31).

S. dysgalactiae predominantly resides in domestic animals such as cattle, sheep, cats, and dogs that either constitute healthy carriers of the bacterium or go on to develop diseases such as pneumonia, arthritis, septicemia, and abscesses, particularly bovine mastitis. S. *equi*, a pathogen primarily restricted to horses and donkeys, causes strangles which is a highly contagious disease characterized by purulent discharges from the respiratory tract and the development of abscesses (32). This organism is not considered to be part of the normal flora because of its close association with disease. In contrast, *S. zooepidemicus* is an opportunistic commensal that colonizes mucosal surfaces, and causes rhinopharyngitis, pneumonia (33), endometritis, neonatal septicemia, and wound infections in horses (34) as well as disease in other domestic animals such as cattle, sheep, pigs, and chicken. Although uncommon, *S. zooepidemicus* is also responsible for a range of zoonotic infections in humans (26, 27).

The small-colony phenotype of group C and G streptococci is expressed by the *Streptococcus anginosus* group, formerly known as *Streptococcus milleri.* The group contains three species *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius* (1). Strains belonging to the *S. anginosus* group express group antigens F, C, A and G, or no antigen. These strains are also likely to be non-beta-hemolytic. Members of these species are recognized as common commensal organisms of the human oral cavity, gastrointestinal tract, and genitourinary tract. They are also associated with access formation in the mouth and other bodily sites (35, 36) as well as pharyngitis (37) and endocarditis (38, 39). It has also been reported that *S. anginosus*, along with *Streptococcus mitis* and *Treponema denticola* can

be isolated from esophageal cancer tissue and by initiating inflammation in the cancerous tissue have a role in the development or progression of these cancers (40, 41).

Several assays are available to detect, classify and genetically describe group C and group G streptococci. Routine microbiological diagnosis follows the same guidelines in use for the identification of the other beta-haemolytic streptococci (BHS) (42). The BHS isolates are divided into large and small colonies forming groups based on the growth on sheep blood agar: the large-colony-forming group are "pyogenic". The small colony forming species comprise the 'anginosus group' and are not referred to as GCS or GGS even though they may cross react with C or G sera. Lancefield agglutination tests are still used to group BHS into the Lancefield groups. Fermentations tests are used to classify GCS as *S. equisimilis* or *S. zooepidemicus* and are based upon a spectrum of biochemical tests which are now available commercially (43). More recently, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS) has been described as a rapid alternative for the identification of streptococci (44). In addition, multilocus sequence analysis (MLSA) of seven housekeeping genes (45) and other sequenced based assays are performed to analysis the streptococcal phylogenies. In particular, sequencing of the *emm* gene, that encodes the hyper-variable surface protein M, and 16s rRNA genes is undertaken for phylogenetic analysis of these streptococci based upon sequence similarities (46, 47).

Next generation sequencing is increasingly being used for genetic characterization, phylogenetic analyses, virulence and pathogenicity profiles and antibiotic resistance analyses (22, 48). *S. equisimilis* and *S. pyogenes* (or GAS) share a high genetic similarity (~72%) and similar virulence genes, suggesting a common evolutionary origin and genetic exchange (22, 25, 49).

MECHANISMS FOR ADHERENCE

S. equisimilis causes a similar spectrum of disease in humans to *S. pyogenes* and molecular studies have demonstrated virulence determinants that are almost identical. Putative virulence determinants of *S. equisimilis* include adhesins, toxins, and factors that are essential for dissemination in human tissues and for interference with the host immune responses. Adhesion of microorganisms to host tissues represents a critical phase in the development of infection. It is therefore unsurprising that micro-organisms have evolved dedicated mechanisms for attachment and adherence to extracellular matrix (ECM) components of the host (50, 51). Of these components the high-molecular-weight glycoprotein fibronectin appears to be the major attachment target of Gram-positive cocci, including group G streptococci and group C streptococci. Fibronectin itself is responsible for substrate adhesion of eukaryotic cells via specific cell surface factors of the integrin family. It also specifically interacts with other matrix components, such as collagen, fibrin, and sulfated glycosaminoglycans demonstrating this molecule fulfills multifunctional roles within the extracellular network (52). Being present in the extracellular matrix of most tissues, as well as in plasma and other body fluids in its soluble form, fibronectin represents an exquisite target for bacteria to exploit the cell attachment properties of this molecule by linking the pathogen to specific target cells. Epithelial cells of the upper respiratory tract of humans are bathed in secretions containing fibronectin in its soluble form. Once bound to the bacterial surface, it will enable the pathogen to attach and subsequently colonize the primary site of infection.

Fibronectin binding proteins (FBP's) were first identified in *Staphylococcus aureus* and *S. pyogenes* (53) and approximately eleven have been defined in *S. pyogenes*, highlighting their importance for this pathogen (54). Binding by these bacteria to eukaryotic cells via fibronectin is also an important preliminary event prior to the invasion of these cells (55-57).

The FBP's from streptococci and staphylococci share a common architecture, with a putative signal sequence at the N terminus and a wall- and membrane-spanning region. The major fibronectin binding domains are located within the C-terminal part of the proteins and are composed of 3 to 5 repetitive units that consist of 35 to 37 amino acid residues and bind to the 29kDa N-terminal fragment of fibronectin. Further binding studies of PrtF/SfbI from *S. pyogenes*, and FnBPA in *S. aureus* also indicate the presence of a secondary fibronectin binding sites upstream of the repeat regions (53).

The first FBPs to be identified group C and G streptococci were FnbA and FnbB from *S. dysgalactiae* (58). FnbA can opacify serum as well as bind fibrinogen, like the serum opacity factor of *S. pyogenes* (59). Both FnbA and FnbB bind fibronectin through C-terminal repeat regions (50).

Three FBPs have been defined in *S. zooepidemicus*: FNZ, FNZ2 and SFS. Although the modular organization of FNZ, a *S. zooepidemicus* FBP, is similar to those from other species, homology at the amino acid level is weak (60). Fibronectin binding is mediated through a repeat region and a second upstream region containing the amino acid motif LAGESGET. This motif is also present in the secondary binding domain of SfbI (61) where it acts independently from the repeat region in binding to fibronectin (62). This domain is also present in GfbA, the homologue of SfbI in *S. dysgalactiae* (63). *fne* is the homologous gene to *fnz* in *S. equi* (64). However FNE is unique in that a single nucleotide deletion in *fne* gene has resulted in the truncation of the protein and so, with the loss of the cell-wall binding motif, it is secreted into the surrounding environment. The truncated FNE also lacks the classic fibronectin binding repeats found in the C-terminal region of FNZ, but is able to bind fibronectin through amino-half domain, also found in FNZ. Consequently, fibronectin binding at the bacterial surface is much lower for *S. equi* than *S. zooepidemicus* although both

have an additional cell wall anchored FBP; FNEB and FNZ2 (65). FNZ2 has both collagen and fibronectin binding properties (66). SFS of both *S. equi* and *S. zooepidemicus* strains and contains a signal peptide, but no cell-wall binding motifs, or the traditional fibronectin binding motifs. SFS inhibits binding between fibronectin and collagen. If SFS were to bind fibronectin attached to bacterial surface through FNEB/FNZ/FNZ2 this may inhibit binding of fibronectin to collagen, which could have several physiological consequences (67).

Some of the FBPs and also collagen binding proteins identified in *S. pyogenes* are chromosomally located within the **F**ibronectin and **C**ollagen binding proteins and **T** antigen encoding (FCT) locus. There are at least 9 different types of FCT regions within *S. pyogenes* that vary by gene content and order, but within this region are the genes required to make the pili. The pilus has been shown to contribute to the formation of biofilm and mediate adherence to host cells (68-71). Whole genome sequence analysis of group C and G streptococci have also identified potential FCT regions. One putative pilin locus, FimI exists within the genome of *S. equi* strain 4047 (72). Although no pili structures have been identified for *S. equi*, the proteins of FimI are expressed during growth and have the potential to affect adherence *in vivo* (73). The gene encoding the collagen binding protein CNE of *S. equi* (74) is present within this FimI locus. A homologous locus was also found within *S. zooepidemicus* isolates, as well as an additional one or two potential pili loci (72, 75). Two FCT regions were also found in *S. equisimilis*, that share high levels of genetic identity to FCT regions from different *S. pyogenes* genotypes, suggesting multiple horizontal gene transfer events (22, 76).

An alternative for group C and G streptococci to adhere to host cells is via binding to other ECM molecules including fibrinogen, vitronectin, laminin, collagen and plasminogen (77, 78). The M-protein like **f**ibrinogen binding protein **o**f **G** streptococci (FOG) can act as an

adhesin by binding collagen IV (79) and has been shown to also bind collagen I fibrils in dermis *in vivo* (80).

Vitronectin is a multifunctional serum protein that affects the humoral immune system by binding to and inhibiting the complement membrane attack complex (81) and is also a major matrix-associated adhesive glycoprotein that regulates blood coagulation. The ability of group C and G streptococci specifically interact with vitronectin (82) and mediate the adherence to both epithelial and endothelial cells (83, 84) was demonstrated sometime ago. However a specific vitronectin binding protein has never been identified in *streptococci*.

ANTIPHAGOCYTIC FACTORS

A major requirement of pathogenic streptococci is to be able to resist phagocytosis. The streptococcal M protein, first identified and characterized in *S. pyogenes*, is the major antiphagocytic factor (85). It is a multi-domain surface-exposed molecule that forms a coiled-coil secondary structure with significant irregularities that in the B-repeat region are essential for the fibrinogen binding properties (86). Binding of complement factors, fibrinogen and inhibition of C3b deposition on the bacterial surface are mechanisms by which the M-protein can inhibit opsonization of the organism by the alternative complement pathway, thus evading the host's nonspecific immune defense mechanism.

Several M-like proteins have been identified in group C and G streptococci. Protein MG1, the first group G streptococcal M-like protein characterized on the molecular level (87), exhibits typical structural and biological features of M proteins, such as coiled-coil structure and the ability to generate type-specific opsonizing antibodies. Protein MG1 shares highly homologous sequences with the C-terminal repeat region of class I M proteins, which are frequently associated with rheumatic fever. M proteins of group G streptococci are also responsible for conferring resistance to phagocytosis (88).

In human strains of group G streptococci, FOG is critical for bacterial pathogenesis through its antiphagocytic action of binding fibrinogen (89). It also has the ability to bind IgG subclasses IgG1 and IgG2, although FOG-bound IgG1 can actually trigger the complement cascade through C1/C1q activation. It is unclear as to whether this is then detrimental to the bacteria as FOG remains protective against phagocytosis (90).

The antiphagocytic protein SeM (FgBP) appears to be the most predominant M-like protein on the surface of S. *equi*, capable of binding fibrinogen and IgG4 and IgG7 subclasses (91-93). SeM confers resistance to phagocytosis but this also requires the presence of the hyaluronic acid capsule (94). Like the M protein of *S. pyogenes*, SeM is variable at the N-terminal region suggesting selective pressure (95). Interestingly this does not appear to be the case for two other M-like proteins expressed by *S. equi*; Se18.9 and SzPSe (95). The antiphagocytic protein Se18.9 is commonly found in strains of *S. equi,* but rare for strains of *S. zooepidemicus* (72), and acts by binding to fibrinogen and the complement regulatory protein, Factor H (96). SzP proteins are also antiphagocytic and are expressed by both *S. equi* and *S. zooepidemicus*. Whole genome sequence analysis of *S. zooepidemicus* strain H70 identified a potential M-protein homologue in SzM which resembles SeM in secondary structure that consists of a predicted C-terminal coiled-coil (72, 97). The N-terminal of SeM is unique to *S. equi* and binds fibrinogen (93, 98). SzM can also bind fibrinogen but cannot bind IgG (99). The M protein of *S. canis* specifically binds the Fc region of IgG in a non-opsonic manner (100).

DemA is a *S. dysgalactiae* protein with homology to FgBP identified by screening of a phagemid expression library (101). The mature DemA protein is 54kDa in size, contains a signal sequence, cell wall binding domain and is predicted to have a coiled coil secondary structure. DemA shows greatest homology to the FgBP at the C-terminal end in a region that does not participate in fibrinogen binding. The amino acid motif VSKDLADKL is present

with the repeat units of both DemA and FgBP suggests the sequence may have an important biological function. DemA is able to bind IgG from various animal sources, reminiscent of type IIa Ig-binding proteins of *S. pyogenes* in a domain distinct from the fibrinogen binding domain. Nucleotide sequencing of the *demA* locus identified an open reading frame upstream of *demA* homologous to *mga*, a positive regulator of M-protein expression in *S. pyogenes* (101).

C5a peptidase of *S. pyogenes* (ScpA) is well known to specifically cleave and inactivate the chemoattractant C5a, but it has also recently been shown to cleave the complement factor C3 and the chemoattractant C3a (102), expanding its impact on immune evasion. ScpA has also been identified as an adhesion factor enabling bacteria to adhere to endothelial and epithelial cells (102). Homologues of ScpA have been identified in group B *Streptococcus* (ScpB) and group C and G streptococci isolated from humans but not group G streptococci from animals (103, 104). Both *S. equi* and *S. zooepidemicus* also carry homologous C5a peptidase genes (*scpE* and *scpZ* respectively). Unlike in *S. pyogenes*, where *scpA* is located within the *mga* regulon that includes the *emm*-gene, the *scp* genes of group B, C and G streptococci are associated with a transposon, suggesting lateral genes transfer between these species (103, 105).

The *S. pyogenes* cell wall envelope proteinase, SpyCEP is another protease that contributes to the prevention of phagocytosis through the specific cleavage of interleukin-8 and other chemokines to prevent the activation and migration of neutrophils (106, 107). Similar enzymes have been identified in *S. equi* (SeCEP) and *S. zooepidemicus* (SzoCEP) which share 98% identity to each other and 59% identity to SpyCEP (108). SeCEP has been shown to cleave both human and equine IL-8 and vaccination with a recombinant portion of SpyCEP prevented bacterial dissemination in a murine model of *S. equi* invasive infection, suggesting an important contribution to disease (108).

IMMUNOGLOBULIN BINDING AND INACTIVATING PROTEINS

Streptococcal protein G is a surface molecule associated with the majority of group C and G streptococcal isolates of human origin. Protein G interactions with immunoglobulins and other host proteins have been the subject of detailed reviews (109-111). Protein G is defined as a type III IgG Fc receptor and interacts with a wide species range of immunoglobulins, as well as human serum albumin, kininogen, and α_2-macroglobulin. Protein G exhibits a modular structure in which the binding sites for IgG are located within the C-terminal repeat region (110-112). The central A/B-repeat region constitutes the binding domain for serum albumin, and the N-terminal E region is responsible for interacting with the native form of α_2-macroglobulin (78). In contrast to human pathogenic strains of group G streptococci that exclusively bind to the native (slow) form of α_2-macroglobulin via protein G, animal-derived isolates of bovine and equine origin bind the proteinase-complexed (fast) form of the molecule. The B1 domain of protein G involved in immunoglobulin binding consists of an α-helix and 4 β-strand sheets. This domain has been used a model structure in numerous biochemical studies examining protein folding, protein interaction and synthetic protein design (113-115).

Two protein G-related proteins from a mastitis-causing *S. dysgalactiae* strain, MIG (116) and MAG (117, 118), as well as ZAG (119) from *S. zooepidemicus*, have been characterized on the molecular level. Like protein G, MAG and ZAG exhibit serum albumin and type III Fc receptor activity, whereas protein MIG lacks albumin-binding activity. However, MAG is able to bind to immunoglobulins from a greater number of animal sources than protein G. MAG, ZAG and MIG also bind to the fast form of α_2-macroglobulin. The α_2-macroglobulin binding region in MIG is not homologous to those of protein G, MAG, ZAG and GRAB. In

phagocytosis assays a MIG isogenic mutant strain of *S. dysgalactiae* are not as resistant to opsonization by bovine neutrophils as the parental strain (120). MIG has also recently been shown to bind to bovine immunoglobulin A (121) and can inhibit bacterial internalization into host cells (122).

As well as IgG binding proteins, group C and G streptococci can express variants of the *S. pyogenes* IdeS and EndoS, which are IgG-degrading enzymes. While IdeS cleaves the hinge-region of IgG (123), EndoS removes core IgG glycans (124). Both *S. equi* and *S. zooepidemicus* express two forms of IdeE and IdeZ, respectively, that are capable of cleaving IgG from several different mammalian species (125), although IdeE2/IdeZ2 cleave horse IgG with greater efficiency than IdeE/IdeZ (126). EndoS homologues have also been identified in *S. equi* (EndoSe) and *S. zooepidemicus* (EndoSz) and they share 86-89% sequence identity to each other and 70% identity to EndoS of *S. pyogenes* (127). EndoSd has also been found in *S. equisimilis* with IgG hydrolyzing activity (128) and IdeP was identified in the group C *S. phocae* subsp. *phocae* that affects marine animals, although its function has not been confirmed (129).

ENZYMES AND TOXINS

After colonization, adherence and evasion of host immune responses, the dissemination of pathogenic streptococci in tissues is regarded to be an important step for the onset and development of an invasive disease. One of the factors involved in this process is streptokinase, a protein found in groups C, G, and A streptococci (130). The formation of a streptokinase/plasminogen complex results in the exposure of the plasminogen active site which then catalyses the conversion of other plasminogen molecules into plasmin (131). Plasmin is a key serine protease in the fibrinolytic system that is able to break down tissue barriers, thereby enabling the dissemination of streptococci. M proteins co-ordinately interact

with the secreted streptokinase by binding either fibrinogen (132) or plasminogen (133). A high level of variation exists within the streptokinase gene, *ska*, and alleles of *ska* have been associated with tissue trophisms and differing levels of plasminogen activation (134). There is some overlap of alleles between human strains of group C and G streptococci and group A *Streptococcus* (135). Streptokinases have been isolated from both human and animal group C and group G isolates, and have specificity for the plasminogens of their respective hosts (136). Thus streptokinases from human group A, C and G streptococci isolates have greater homology to each other than to animal isolates of group C and G streptococci. A study by Caballero et al., (57) found that the amino acid homology between streptokinases from a human and animal *S. equisimilis* isolates to be only 35%. Homology between the streptokinase from *S. equisimilis* from equine and porcine origins was only 21%. The ability of streptokinases to cleave plasminogen from specific species may therefore be a critical factor in determining the host range of individual streptococcal strains (137). Invasive human strains of *S. equisimilis* have been found to express higher levels of streptokinase and this can drive virulence in a murine model of invasive necrotising fasciitis, suggesting an important role for streptokinase in disease (138, 139).

Streptolysin O (SLO) is the prototype of a family of thiol-activated cytolysins produced by the genus *Streptococcus* as well as by other Gram-positive bacteria, including *Bacillus*, *Clostridium*, and *Listeria* species (140). The genes coding for SLO of group C and G streptococci (*S. dysgalactiae*) are almost identical to that of *S. pyogenes* (141). SLO homologues have not been described in *S. equi*. SLO is able to disrupt the cytoplasmic membrane of several different eukaryotic cell types that includes erythrocytes, leukocytes, macrophages, platelets and epithelial cells. Separate to its pore-forming activity, SLO also acts to translocate NADase into host cells (142), which contributes to cytoxicity by depleting energy stores. Other functions of these two streptococcal toxins include limiting neutrophil

responsiveness and potentiating bacterial survival, replication and persistence inside keratinocytes, epithelial cells and macrophages which may protect GAS from the immune response and antimicrobial therapy (143-147).

Streptolysin S (SLS) is another cytolysin secreted by groups A, C and G streptococci, including the animal-pathogenic *S. equi* species (148). Streptolysin S belongs to a distinct group of hemolytic toxins that are characterized by their resistance to oxidation and sensitivity to trypan blue. SLS activity results in damage to membranes of various cell-types as well as subcellular organelles (149). In contrast to the 57kDa SLO, SLS is a small 57 amino acid protein. The gene encoding SLS, *sagA,* is part of a locus containing 9 open reading frames which contain significant homology with genes from bacteriocin loci (150, 151). In *S. equisimilis*, SLS expression is under the control of both the *covRS* and *fasCAX* two component regulatory systems, which in *S. pyogenes* have been shown to be involved in the regulation of multiple virulence factors (152). In a mouse infection model, *S. equisimilis* expressing SLS proliferate and induce necrotic lesions at the site of infection, whereas SLS negative strains do not, suggesting SLS is an important factor in the development of necrotizing fasciitis (150).

Streptococcal pyogenic toxins (spe's) are superantigen genes capable of cross-linking the MHC class II on antigen presenting cells to the T cell receptor, leading to proliferation of T cells and substantial release of inflammatory cytokines. Eleven superantigen genes have been identified in *S. pyogenes* and they are thought to drive the development of scarlet fever and toxic shock syndrome, the latter contributing to high mortality rates following necrotising fasciitis. Recent work has also identified a role for superantigens in upper respiratory tract infection (153). Homologues of the group A streptococcal superantigens have been identified in group C and G streptococci (154). The most commonly found superantigen in *S. equismilis*

is *speG* (*spegg* or *speG*^{dys}) (155, 156) and genomic analysis indicates that *S. pyogenes* and *S. equisimilis speG* genes are orthologues that are direct descendants from a common ancestor gene (157). The gene for *speG* can also be found in *S. canis* (154). The role of S. *equisimilis speG* in humans is unclear as the presence of this gene does not correlate with disease severity and it does not confer mitogenic activity towards human mononuclear cells, although it can stimulate bovine T cells (156, 158, 159). The streptococcal superantigens *speA*, *speC*, *speJ*, *speK*, *speH*, *speL*, *speM* and *ssa* are found infrequently in *S. equismilis* and other human group C and G streptococci (154, 160-162).

Homologues of *S. pyogenes* superantigens *speH* and *speI* can be carried by strains of *S. equi* (163) and homologues of *speK* and *speL* can be carried by both *S. equi* and *S. zooepidemicus*, although confusion with the nomenclature meant *speK* homologous were originally termed *speL*$_{se}$*/seeL/szeL* and *speL* homologous were termed *speM*$_{se}$*/seem/szeM* (154, 164, 165). Three additional superantigen genes, termed *szeN, szeP* and *szeF*, have been identified in *S. zooepidemicus* only, and are capable of stimulating equine peripheral blood mononuclear cells (166). *S. dysgalactiae*-derived mitogen (SDM) shows homology to *speM* of *S. pyogenes* and can stimulate human mononuclear cells (154, 167). The majority of the superantigens found in *S. pyogenes* and group C and G streptococci are associated with prophages which may drive the lateral transfer of these virulence factors between streptococcal species (72, 168).

CONCLUSIONS

Many recent studies have again highlighted the increasing number of systemic infections caused by *S. equisimilis*, particularly amongst immunocompromised individuals and also specific populations and this therefore, suggests that this species will gain even more clinical importance in the future. High nucleotide similarities amongst virulence genes and their

association with mobile genetic elements supports the hypothesis of extensive horizontal gene transfer events between streptococcal species of the pyogenic group. A better understanding of the mechanisms of pathogenesis will hopefully be revealed with whole genome sequencing and this may therefore impact upon more effective clinical strategies for the pyogenic group of streptococci, generally.

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TABLE 1. Pathogenicity factors of group C and group G streptococci

PATHOGENENICITY FACTORS	ORGANISM	REFERENCE
Fibronectin Binding Proteins		
FnbA	*S. dysgalactiae*	(58)
FnbB	*S. dysgalactiae*	(58)
GfbA	*S. dysgalactiae*	(63)
FNZ/FNE	*S. zooepidemicus, S. equi*	(60, 64)
FNZ2/FNE2	*S. zooepidemicus, S. equi*	(65, 66)
SFS	*S. zooepidemicus, S. equi*	(67)
M-like Proteins	*S. dysgalactiae*	(87, 101, 169)
	S. equisimilis	
FOG	*S. dysgalactiae*	(89, 90)
DemA	*S. dysgalactiae*	(101)
SzM/SeM	*S. zooepidemicus, S. equi*	(72, 91-93, 97)
SzPSe/SzP	*S. zooepidemicus, S. equi*	(98)
Se18.9	*S. equi*	(72, 96)
ScM	*S. canis*	(100)
Others		
C5a peptidase	*S. dysgalactiae*	(104, 170)
SeCEP/SzoCEP	*S. zooepidemicus, S. equi*	(108)
Immunoglobulin binding proteins		
Protein G	*S. dysgalactiae*	(112)
MIG	*S. dysgalactiae*	(116)
MAG	*S. dysgalactiae*	(118)
ZAG	*S. zooepidemicus*	(119)
Toxins		
Streptokinase	*S. dysgalactiae, S. equisimilis*	(130)
Streptolysin O	*S. dysgalactiae, S. equisimilis*	(141)
Streptolysin S	*S. dysgalactiae, S. equisimilis*	(148, 150)
	S. equi, S. zooepidemicus	
Superantigens		
$SpeG^{dys}$/Spegg/SpeG	*S. equisimilis, S. canis*	(155) (154)

SpeH	*S. equi*	(163)
SpeI	*S. equi*	(163)
SpeK	*S. equi, S. zooepidemicus, S. equismilis*	(154, 164, 165)
SpeL	*S. equi, S. zooepidemicus, S. equismilis*	(154, 164, 165)
SpeM	*S. equisimilis*	(171)
ssa	*S. equisimilis*	(171)
SDM/SpeM	*S. dysgalactiae*	(167)
SpeA	*S. equismilis*	(160)
SpeC	*S. equismilis*	(160)
SzeN	*S. zooepidemicus*	(166)
SzeP	*S. zooepidemicus*	(166)
SzeF	*S. zooepidemicus*	(166)

TABLE 2. Species within Lancefield group C and group G streptococci (1)

SPECIES	KNOWN SOURCES	LANCEFIELD GROUP
S. dysgalactiae subs. dysgalactiae	Animals	C
S. dygalactiae subs. equisimilis	Humans, animals (rare)	C, G
S. equi subs. equi	Animals	C
S. canis	Animal, humans (rare)	G
S. equi subs. zooepidemicus	Animals, humans	C
S. phocae	Animals (seal)	C
'S. anginosus' group	Humans	A, C, F, G