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Virulence Factors and Clinical Features of *Streptococcus Pyogenes* : Overview

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Abstract:

The aim of our review is to know the virulence factors for a gram-positive coccus that appears to grow in chains is *Streptococcus pyogenes*. The cause of many serious human diseases, ranging from pharyngitis and mild superficial skin infections to life-threatening systemic diseases, is *S. pyogenes*. Usually, infections begin in the throat or the skin. Pharyngitis (strep throat) and localized skin infections include Mild *S. pyogenes* infections (impetigo). Erysipelas and cellulitis are characterized by *S. pyogenes* multiplication and lateral dissemination in deeper skin layers. Invasion and fascial involvement of *S. pyogenes* can lead to necrotizing fasciitis, a life-threatening condition. In children with fever, scarlet fever is characterized by a sandpaper-like rash and is caused by a streptococcal toxin. High mortality is associated with severe infections which lead to septicemia or toxic shock syndrome. Characteristic syndromes including rheumatic fever and nephritis are caused by autoimmune reactions. The disease of *S. pyogenes* is readily treatable because penicillin is invariably responsive to the organism. Significant mortality and morbidity are associated with delayed treatment of this widespread childhood pathogen.

Key words: Group A Streptococci, β- hemolytic, Virulence genes, Streptococcal disease

Introduction:

The pathogenic streptococci have several characteristics that contribute to their virulence. The virulence mechanisms of the *S. pyogenes*, in particular, have been studied most extensively. This bacteria continues to be an extremely significant human pathogen, and human skin and mucous membranes are the only known reservoirs of Group A streptococci in nature. The WHO estimates that over 500,000 people die each year from severe group A streptococcal infections, particularly invasive disease and the sequelae of acute rheumatic fever and consequent rheumatic heart disease [1,2]. Twenty-five to 35 million cases of group A streptococcal pharyngitis occur each year in the United States [3]. In the United States, group A streptococcal infections occur at an annual rate of about 3.5 cases per 100,000 population, resulting in over 9,600 cases and 1,100 to 1,300 fatalities per year [4]. In addition to acute infections, the group A *Streptococcus* is also associated with two nonsupperative sequelae−acute rheumatic fever and acute post streptococcal glomerulonephritis−that continue to occur particularly in developing countries. More than 95% of the estimated 294,000 fatal cases of rheumatic heart disease worldwide occur in developing countries, which also bear the overwhelming number of other invasive group A streptococcal diseases [1, 5].

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A: Virulence Factors

1. Lipoteichoic acids (LTAs)

The cell wall of group A β-hemolytic streptococci consists of a thick peptidoglycan along with integral Lipoteichoic acids (LTAs) and other surface associated molecules. LTAs are thought to play an important role in promoting group A streptococci's initial adherence to pharyngeal epithelial cells, other forms of cells, and to host proteins such as fibronectin [6]. In addition to LTAs, several other group A streptococcal adhesions have been described, including several fibronectin-binding proteins (e.g., protein F1 [SfbI, streptococcal fibronectin-binding protein], protein F2 [SbfII], FPB54, and PFBP) [7,8,9]. These proteins that are surface-binding facilitate adherence to all forms of pharyngeal and cutaneous cells. M proteins play a role in skin adherence to keratinocytes by association with the CD466 cofactor of the keratinocyte membrane [10]. The major group A cell wall antigen is a complex polysaccharide consisting of L-rhamnose and *N*-acetyl-D-glucosamine in a 2:1 ratio[11]. The antigen is covalently attached to the peptidoglycan. The role of the cell wall grouping antigen as a virulence factor is not known, although the peptidoglycan material itself has biologic activity, including the induction of fever, dermal and cardiac necrosis in animals, lysis of erythrocytes and platelets, and enhancement of nonspecific resistance.

2. Capsule

Some group A strains possess a capsule composed of hyaluronic acid, which is a high molecular weight linear polymer composed of β (1-4)-linked disaccharide repeating units of D-glucuronic acid and (1-3)-β-D-*N*- acetylglucosamine [12,13]. This material is the product of enzymes encoded by a three-gene cluster consisting of *hasA*, *hasB*, and *hasC*. These three genes encode a hyaluronic acid synthase, a UDPglucose dehydrogenase, and a glucose pyrophosphorylase, respectively [14]. These genes are highly conserved among group A streptococcal strains, and variations in the degree of capsular gene expression likely reflect differences in regulation of gene transcription. Strains that maximally express these genes appear mucoid when grown on sheep blood agar (SBA) [15]. Two gene products, CrsS and CrsR, appear to function as a two-component regulatory system that is able to increase or decrease the degree of encapsulation by up- or downregulation of *has* gene expression [16]. Chemically, this capsular hyaluronate material is indistinguishable from the ground substance of connective tissue, which may explain the lack of immunogenicity of this substance in the infected host. In vitro, capsule production is maximal during logarithmic growth, and the organisms shed their capsules as they enter the stationary phase of growth; this loss is probably due to the elaboration of hyaluronidase during the latter stages of the logarithmic growth phase. The hyaluronic acid capsule functions to help the organisms resist complement-dependent killing by phagocytic cells. In animal models, the hyaluronic acid capsule has been shown to contribute to the capacity of group A streptococci to produce invasive soft tissue infections [17]. The capsule also influences the ability of group A streptococci to adhere to epithelial cells by modulating the interaction of M protein and other surface molecules and by serving as a ligand for binding to the CD44 receptor on epithelial cell surfaces [18,13].

3. M protein

The major virulence factor of the group A *Streptococcus* is a cell surface antigen designated M protein [11,19,20]. M proteins are acid- and heat-stable, trypsin-labile, fibrillar proteins associated with the outer surface of the cell wall. M proteins are composed of two polypeptide chains complexed together in an α-

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helical coiled-coil configuration [21]. In the cell membrane, the M protein is anchored, spreads through the peptidoglycan layer, and projects from the bacterial cell surface (Figure 1). The amino acid sequence and structure of the carboxy-terminal end of the molecule is located within the cell membrane and cell wall of the organism and is highly conserved among group A strains. The *N*-terminus extends beyond the cell surface and terminates with a sequence of about 11 amino acid residues. This terminal sequence varies among clinical isolates and constitutes the basis for the Lancefield serologic classification of group A streptococci. Strains that are rich in M protein are resistant to phagocytosis and intracellular killing by polymorphonuclear cells, thereby allowing the organisms to persist in infected tissues; cells lacking demonstrable M protein are readily phagocytosed and killed [11].

M protein apparently exerts its anti-phagocytic effects by interfering with opsonization of the bacterial cells via inhibition of both the classical and the alternate complement pathways. M proteins are also able to form complexes with fibrinogen that consequently bind to β 2 integrins of neutrophils. Binding triggers release of inflammatory mediators that induce vascular leakage, a pathologic component of streptococcal toxic shock [22]. Some M proteins can act as super antigens, causing T-cell proliferation and release of cytokines, and M proteins from classically "rheumatogenic" M types elicit the formation of antibodies that cross react with several mammalian host cell proteins, including myosin, laminen, and keratin [19]. Eventually, antibodies against the more prevalent M types emerge, and with development of herd immunity, these types disappear and new M types appear and expand through increased transmission.

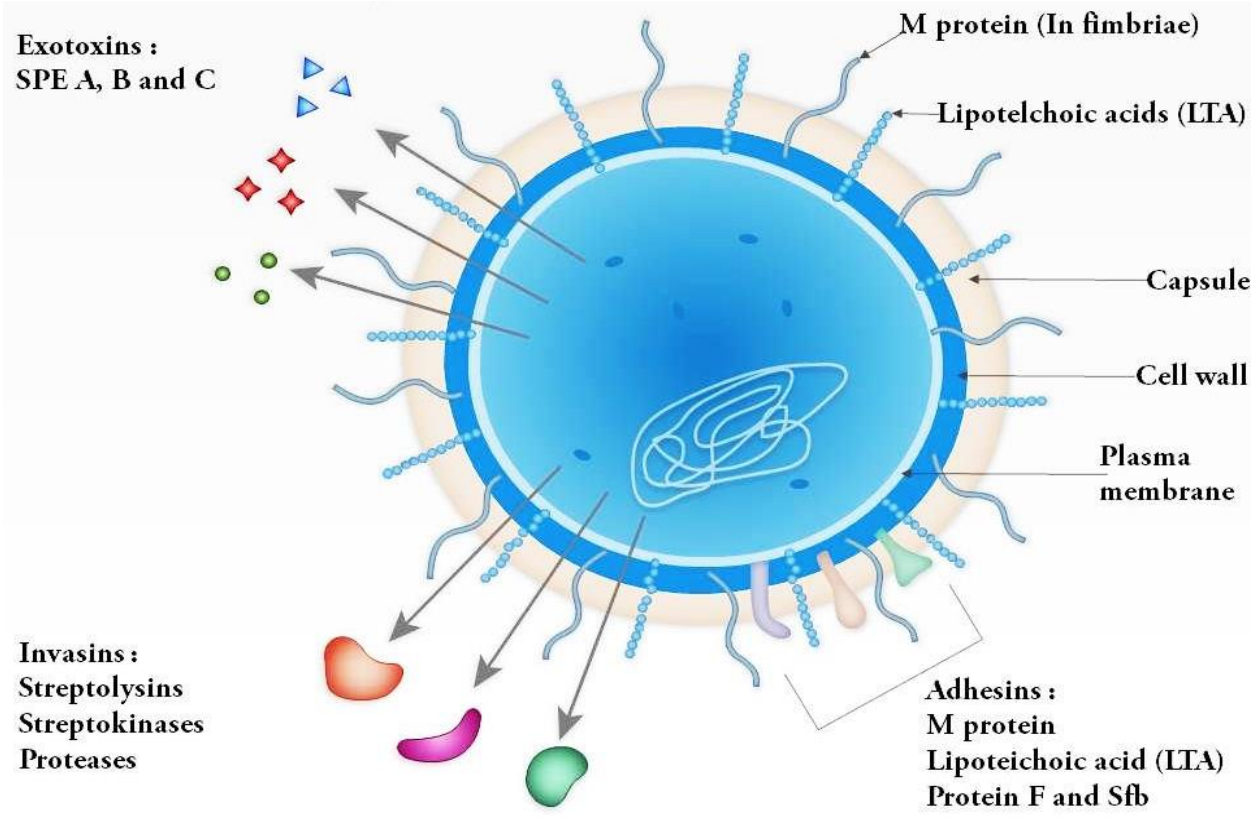

Figure 1: surface of the *Streptococcus pyogenes*

Serologic M typing is usually performed on hot acid extracts of group A streptococci using capillary precipitin or agarose gel immunodiffusion techniques. Only a single M-type antigen is expressed by group A

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strains, and 93 different M serotypes have been identified using these methods [23]. Cloning of the M protein gene, called the *emm* gene, has resulted in the expansion and standardization of *emm* typing to replace the conventional serologic method. Consequently, there are now over 200 known *emm* types. The *emm* typing system is performed by sequence analysis of the NH2-terminal nucleotide residues and has resulted in the identification of over 124 recognized *emm* genotypes [24].

In addition to M protein, several other M-related cell surface proteins have been identified on group A streptococci, and the genes encoding these molecules (e.g., *enn*, *mrp*, *arp*, *fcrA*, *protH*) have been grouped together as members of the "*emm* gene superfamily [25]." In addition to M protein, some streptococci have other "M-like" proteins (e.g., the Spa protein of M-type 18 group A streptococci) that have been shown to contribute to and augment group A streptococcal virulence [26]. These molecules apparently work in concert with M proteins to help the organisms resist phagocytosis. M-protein-like molecules are also able to bind to several host proteins such as plasminogen and fibrinogen, and, via this interaction, also exert anti-opsonic effects.

4. Opacity factor (OF)

Opacity factor (OF) is another M-protein-associated cell surface antigen of group A streptococci that is a virulence factor. OF is an α-lipoproteinase that is able to opacity media containing mammalian serum. Antibodies directed against OF are specific in inhibiting the opacity reaction of the M-type producing it; so OF typing can be used as a supplementary or complementary typing reaction. OF is produced by strains that belong to 29 different M types and can be detected in those M types even if M-type-specific reactivity is lost or undetectable (i.e., the presence of OF is associated only with specific M types). Therefore, OF positive and OF-negative reactions are consistently associated with specific M types. OF is primarily associated with strains of group A streptococci isolated from skin infections [27].

5. Streptolysin O & Streptolysin S

Two hemolysins are developed by Group A streptococci: streptolysin O and streptolysin S. Streptolysin O (SLO) is oxygen-labile, cholesterol-inhibited, antigenic, and toxic to a range of types of cells, including leukocytes, monocytes, and cultured cells. Streptolysin O is primarily responsible for the β-hemolysis seen around subsurface colonies of group A streptococci in pour plates or in the stabbed areas of surface-inoculated SBA plates because of its oxygen lability. Some group C and group G streptococci are also provided by Streptolysin O. SLO causes the formation of pores in the membrane of susceptible cells by initial binding of SLO monomers to cholesterol in the cell membrane. Streptolysin S (SLS) is oxygen-stable, non-antigenic, and, like SLO, is toxic to a variety of cell types. SLS exists in intracellular, cell surface bound, and intracellular forms and is usually associated with some type of carrier molecule, such as serum albumin, RNA, or α-lipoprotein. SLS, a small molecule having a molecular weight of about 1,800 Da, is maximally produced during the late logarithmic and early stationary phases of growth, and requires iron for maximal production. SLS is believed to interact with membrane phospholipids in exerting its toxic effects. Erythrocytes exposed to SLS undergo swelling, followed by lysis due to the disruption of the osmotic barrier and leakage of ions from the cell. Unlike SLO, no slits or pores are observed on affected erythrocyte cell membranes by electron microscopy. SLS is active in both surface and subsurface hemolysis when the organisms are grown on SBA. The hemolytic activity of SLS is inhibited by serum lipoproteins and other simple phospholipids. Like SLO, SLS is able to damage the membranes of polymorph nuclear cells, platelets, and internal subcellular organelles [28].

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6. Streptococcal pyrogenic exotoxins (SPEs)

Group A streptococci also produce several extracellular products; many of these play real or theoretical roles in virulence of group A streptococci. Streptococcal pyrogenic exotoxins (SPEs) (particularly SPE A and SPE B) are responsible for the rash of scarlet fever and are also the principal virulence determinants in the pathogenesis of the streptococcal toxic shock-like syndrome. Three immunologically distinct SPEs, designated SPE types A, B, and C, have been well described, and the genes that encode them have been identified and characterized. The genes for SPEs A and C (*speA* and *speC*) are encoded on a streptococcal lysogenic bacteriophage, whereas the gene for the type B exotoxin (*speB*) is chromosomal. The *speB* gene is found in all group A streptococci, whereas the other two genes may or may not be present. SPE B, the product of the *speB* gene, is actually a cysteine protease enzyme that is able to cleave human immunoglobulin, fibronectin, vitronectin, and other host cell proteins, resulting in the formation of small, biologically active peptides, including interleukin-1, histamine, and kinins [29]. Expression of cysteine protease SPE B and other virulence determinants is regulated by the *CovR/S* gene system, which mediates the group A streptococcal stress response and regulates the repression and de-repression of major virulence genes [30]. Following colonization with group A streptococci, mutations in *CovR/S* genes cause upregulation of several virulence factors, including capsule production and the secretion of several virulence factors, including the newly described serine protease SpyCEP [31].

7. C5a peptidase

Group A β-hemolytic streptococci also produce several other products that contribute to virulence. As mentioned, SPE B is actually a C5a peptidase that is bound to the cell surface. This molecule contributes to disease because of its peptidase activity rather than as a super antigen. C5a peptidase inactivates C5a, the chemotactic complement component, resulting in limiting recruitment and chemotaxis of polymorph nuclear leukocytes. This peptidase also cleaves immunoglobulins, fibronectin, vitronectin, and other proteins with the generation of biologically active peptides. These organisms also produce four immunologically and electrophoretically distinct deoxy-ribonucleases, designated DNase A, B, C, and D. Antibodies against DNase B (anti- DNase B) are helpful, along with ASO titers, for serologic documentation of prior group A streptococcal pharyngeal or skin infections [30].

8. Hyaluronidase & Streptokinase

Hyaluronidase produced by group A streptococci depolymerizes the ground substance of connective tissue, resulting in contiguous spread of the organism. Streptokinase produced by group A streptococci hydrolyze fibrin clots and may function in virulence by preventing the formation of fibrin barriers at the periphery of spreading streptococcal lesions. The contribution of these enzymes and toxins to infection is uncertain. Many of these factors are produced by other β-hemolytic streptococci as well [30].

B: Clinical Spectrum of Group A Streptococcal Disease

Humans are the natural reservoir for group A, β-hemolytic streptococci, and the organism is transmitted from person to person by the respiratory route. The most common infection caused by group A streptococci is streptococcal pharyngitis [32]. Group A streptococci are responsible for 5% to 15% of pharyngitis in adults and 20% to 30% of cases in children. Most cases of pharyngitis are seen in school aged children (5 to 15 years old) during the winter or spring. Following an initial incubation period of 2 to 4 days, onset is

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generally abrupt, with fever, sore throat, headache, malaise, and abdominal pain. The posterior pharynx is usually inflamed and swollen, and a grayish white exudate may be present on the tonsils. The anterior cervical lymph nodes are usually tender and swollen. The presence of rhinorrhea, hoarseness, cough, or diarrhea speaks against group A streptococcal infection, instead suggesting a viral or mycoplasmal etiology. Infection with strains that elaborate pyrogenic exotoxins A, B, or C may also cause a scarlatiniform rash (i.e., classic scarlet fever). Complications of group A streptococcal pharyngitis may be suppurative (i.e., peritonsillar abscess, retropharyngeal abscess, suppurative cervical adenitis, otitis media, sinusitis, mastoiditis, bacteremia), nonsuppurative (i.e., acute and chronic rheumatic fever, glomerulonephritis), or toxin-mediated (streptococcal toxic shock-like syndrome) [33].

In the absence of complications, streptococcal pharyngitis is self-limited. Fever usually resolves in 3 to 5 days and throat pain resolves in 7 to 10 days without therapy. The "nonsuppurative" complications of group A streptococcal infections include acute rheumatic fever and glomerulonephritis. Acute rheumatic fever (ARF) is associated with prior group A streptococcal pharyngitis, while glomerulonephritis usually occurs after prior pharyngeal or skin infections. ARF is a multisystem disease characterized by major manifestations of carditis, polyarthritis, subcutaneous nodules, erythema marginatum, and chorea. Onset usually occurs 2 to 5 weeks after streptococcal pharyngitis and is not usually initiated by cutaneous group A streptococcal infections [34,28,35].

Cardiac pathology involves the endocardium, myocardium, pericardium and, oftentimes, the mitral valves. Clinically, the patient develops characteristic heart murmurs, cardiac enlargement, congestive heart failure, or intractable cardiac arrest and death. ARF-associated arthritis is migratory, involves multiple joints, and usually resolves spontaneously. Painless, firm, subcutaneous nodules appear simultaneously with carditis and occur around the bony areas of the hands and feet. Erythema marginatum appears as inflamed eruptions with raised, serpiginous borders and central areas of clearing that usually appear on the trunk, arms, and legs. Chorea is a neurologic condition characterized by muscle spasms, incoordination, and weakness that develop simultaneously with or several months after the appearance of ARF [36]. Attacks of ARF generally last 3 to 6 months. Because of the protean clinical manifestations of ARF, the differential diagnosis is diverse and includes rheumatoid arthritis, systemic lupus erythematosus, sickle cell disease, rubella, septic arthritis, disseminated gonococcal infection, Lyme disease, bacterial endocarditis, and myocarditis. Laboratory findings of ARF include elevated sedimentation rates and Creactive protein, and evidence of antecedent streptococcal infection, as determined by a positive throat culture, a positive direct antigen test for group A streptococci, and/or elevated anti-streptolysin O (ASO), anti-DNase B, and anti-hyaluronidase titers. All three of these antibody tests should be performed if ARF is suspected. Therapy for ARF includes analgesics, salicylates, and corticosteroids for treatment of fever and inflammation, in addition to supportive therapy for prevention of cardiac failure [37].

Acute glomerulonephritis (AGN) is associated with glomerular lesions, hypertension, hematuria, and proteinuria. Glomerular lesions contain deposits of complement component C3, properdin, and immunoglobulin, and these deposits can be demonstrated by immunofluorescence techniques. Glomerulonephritis may occur as soon as 10 days following pharyngitis or 3 to 6 weeks after cutaneous infections. Disease manifestations include malaise, weakness, anorexia, headache, edema, and circulatory congestion, as evidenced by hypertension and encephalopathy. The mechanism by which group A streptococci induce ARF and AGN is not clear, but the prevailing theories are that streptococcal infection results in production of antibodies against various streptococcal components (e.g., capsular materials, cell

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wall carbohydrate and protein antigens, cell membrane antigens) that cross-react with antigenic epitopes of heart tissues, including myocardial, endocardial, and valvular heart tissues, myocardial sarcolemma, skeletal muscle, and joints [38].

Group A β-hemolytic streptococci that are responsible for ARF are usually rich in M protein, and M types M1, M3, M5, M16, M18, M19, M24, and a few others are known to be "rheumatogenic"; they have an increased capacity to trigger non supperative sequelae. Isolates with these M types have a mucoid colony morphology, are usually OF negative, are associated with pharyngitis, and evoke a strong type-specific immune response. These M types share antigenic determinants with cardiac muscle, sarcolemma membrane proteins, and synovial membranes. A similar mechanism is believed to operate in the pathogenesis of poststreptococcal glomerulonephritis. In addition to pharyngitis, group A β-hemolytic streptococci cause a variety of cutaneous infections, puerperal sepsis, and post-partum infections. Impetigo is usually seen in children and constitutes the most common skin infection in this age group worldwide, particularly in developing countries with tropical climates [39].

Pyoderma usually occurs in children ages 2 to 15 years, with peak incidence in the 2- to 5- year age group. This skin infection is characterized by the development of papules that develop into vesicular lesions that evolve into pustules. These pustules break down over the next 5 to 7 days to form thick scabs. These lesions are usually on the lower extremities and may also involve other pathogens, such as *Staphylococcus aureus*. Interestingly, the *emm* types of strains causing pyoderma are distinct from pharyngitis strains. As mentioned, cutaneous infection with nephritogenic group A streptococcal strains may give rise to poststreptococcal glomerulonephritis. In pyoderma patients, the ASO titer may not be elevated, but DNase B titers will be elevated [40]. Erysipelas is an acute infection that is associated with soft tissue involvement and cutaneous lymphatics, resulting in systemic evidence of infection (i.e., fever) **(Figure 2)[41].**

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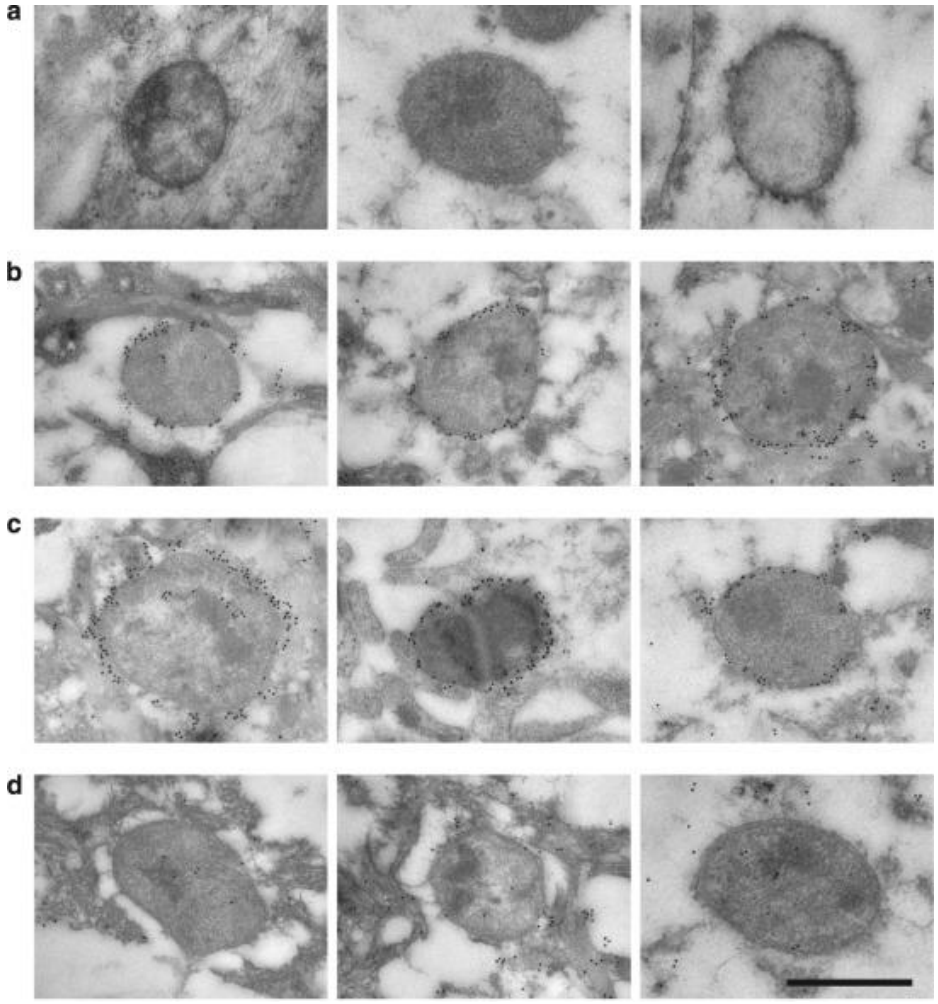

Figure 2: Thin-section transmission electron microscopy of three patients with erysipelasis taken from the skin. (**a**) In the dermis, spherical bacteria-like structures are sometimes seen. A particular antiserum against the carbohydrate group A of Lancefield was incubated with parts (**b**) Or an antiserum raised against the M1 protein region's conserved C-terminal region (**c**), Detection is accompanied by gold-labelled secondary antibodies. Group-A-specific carbohydrate and M protein colocalization with bacterial cell surfaces is visible. (**d**) Gold-labelled fibrinogen was also incubated in sections. [42].

The lesions present as areas of edema and erythema that spread rapidly and have a raised, well-demarcated margin. Lesions of erysipelas are frequently on the face and patients often have accompanying streptococcal pharyngitis [43]. Lesions of erysipelas on other body sites start as areas of redness and swelling, with rapid spread and a raised, well-demarcated border. Complications of erysipelas include necrotizing fasciitis, abscess formation, and septicemia [41]. Cellulitis usually results from streptococcal infection of preexisting lesions, such as wounds, burns, or surgical incisions. This infection presents as a spreading inflammatory process that may involve larges areas of the skin and subcutaneous tissues, along with fever, chills, lymphangitis and, occasionally, bacteremia. Cellulitis is usually seen in intravenous drug users and may be complicated by bacteremia and other sequelae (e.g., osteomyelitis, deep tissue infection, endocarditis) [44]. Puerperal sepsis is seen in women following delivery (either vaginal or abdominal) or abortion [45,46]. Organisms colonizing the genital tract or from obstetrical personnel invade the upper genital tract, causing endometritis, lymphangitis, bacteremia, necrotizing fasciitis, and streptococcal toxic shock syndrome [47,48,49]. Genital tract infection may be complicated by pelvic cellulitis, peritonitis, and abscess formation. Intrapartum transmission of group A streptococci, leading to severe and often fatal group A streptococcal

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disease in the neonate has also been observed. Manifestations in the neonate include stillbirth, septicemia, jaundice, and cellulitis. Necrotizing fasciitis describes infection of deep subcutaneous tissues that results in progressive devitalization and destruction of the fascia. This infection sometimes presents with erythema at a site of localized trauma or previous surgery, or via hematogenous seeding of subcutaneous muscles and soft tissue. The infection spreads very rapidly, resulting in cutaneous bullous lesions containing serosanguinous fluid [50,51].

Streptococcal toxic shock syndrome (STSS) first appeared in the United States during the late 1980s and is now a well-recognized clinical entity associated with group A β-hemolytic streptococci [52,53]. Patients who develop invasive group A streptococcal infections often have comorbid diseases, especially diabetes mellitus, congestive heart failure, malignancies, and immunosuppression.68 Some patients present with a viral-like prodrome of fever, chills, and myalgias; diarrhea and vomiting may also be prominent features. Soft tissue infection, indicated by swelling, tenderness, erythema and/or pain, may be evident if the primary infection is cutaneous, but infection may not be apparent in up to 50% of cases and may already have progressed to severe cellulitis or necrotizing fasciitis by the time the patient seeks emergency medical care [54]. These individuals may develop several severe complications and disease manifestations, including myocarditis, hepatitis, peritonitis, septic arthritis, endophthalmitis, puerperal sepsis, meningitis, and overwhelming toxemia [55,56,57,58]. Pulmonary symptoms include cyanosis, tachypnea, and respiratory failure. Renal involvement occurs in over 80% of patients and often persists despite aggressive treatment with antibiotics and intravenous fluids. The disease is characterized by the sudden onset of overwhelming shock and organ system failure. Patients become hypotensive with little or no response to albumin and electrolyte administration. The acute respiratory distress syndrome develops in more than half of patients, requiring intubation and mechanical ventilation. In fulminant, ultimately fatal infections, the Waterhouse−Friderichsen syndrome and disseminated intravascular coagulation may occur [59]. Almost 80% of these patients have bacteremia with group A streptococci, and the organism may also be isolated from surgical specimens, tissue, peritoneal fluid, pleural fluid, and rarely CSF. If soft tissue infection is present, surgical procedures may be necessary to remove infected, devitalized and necrotic tissues. This syndrome characteristically results in shock and multiorgan system failure shortly after the onset of symptoms and may have a mortality rate of 30% to over 80% [60].

Group A β-hemolytic streptococci cause a variety of other infections, including pneumonia, meningitis, osteomyelitis, endocarditis, peritonitis, and nosocomial infections. Pneumonia due to group A streptococci usually occurs in debilitated hosts with other conditions, including influenza or other intercurrent respiratory virus infections, chronic obstructive pulmonary disease (COPD), alcoholism, and neoplastic disease. Pneumonia may also be a part of the clinical presentation of invasive group A streptococcal diseases, such as STSS. Streptococcal pneumonia often presents with an abrupt onset of fever, chills, malaise, dyspnea, and chest pain. Chest films usually show basilar infiltrates with pleural effusions [61].

Conclusion:

S. pyogenes is a gram-positive bacteria that is responsible for mild neck and skin infections. It has also been confirmed, more recently, that *S. pyogenes* are capable of causing significant invasive infections. Bacterial adhesion to and invasion of human epithelial cells via Fn is the first stage of infection with *Streptococcus pyogenes*. *Streptococcus pyogenes* Fn-binding proteins have been identified and we have investigated their function in epithelial cell invasion. The mechanisms by which *Streptococcus pyogenes* escapes from human immunity and how it develops in human blood and tissues, however, have remained unclear. The aim of our

research and this review was to identify the virulence factors of *Streptococcus pyogenes* more clearly and to better understand the mechanisms associated with the development of serious infections with *Streptococcus pyogenes*. *Streptococcus pyogenes* must evade human innate immunity, which acts as the initial protective barrier against pathogens, in the process after bacterial invasion of human tissues. In innate immunity, neutrophils and complement play major roles, and in complement immunity, the complement activation products C3b and C5a play central roles. Our studies have made a greater contribution to understanding how serious invasive infections are caused by *Streptococcus pyogenes*. The mechanisms associated with invasive infections should continue to be explained in further research of *Streptococcus pyogenes* virulence factors.

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