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# Virulence factor, pathogenesis and Laboratory diagnosis technique of *Streptococcus pyogenes*: Review

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## Abstract

*Streptococcus pyogenes* is a gram-positive bacterial pathogen which responsible for a wide ranges of clinical conditions, including pharyngitis, severe invasive infections, and necrotizing fasciitis. This species' organisms are notable for the wide diversity of their virulence factors and surface antigens. As pathogens, they evade host defense mechanisms and exhibit a group of virulence determinants to avoid host defense mechanisms, and express extracellular toxins such as streptokinase, proteinases, esterase, the hemolysins, DNases, hyaluronidases, complement inhibitor, superoxide dismutase, and immunoglobulin degrading enzymes which correlates to this organism's ability to be a successful pathogen. Many of these presumed virulence factors may also function as digestive enzymes that provide the bacteria with nutrients from the host. GAS bacteria are common causes of bacterial pharyngitis, scarlet fever or impetigo, streptococcal toxic shock syndrome, and necrotizing fasciitis, which involves destruction of the skin and soft tissues in severe cases. *Streptococcus pyogenes* is distinguished from other non-group A β -hemolytic streptococci by its increased bacitracin sensitivity. Because other β -hemolytic streptococci that may contain the group A antigen are resistant to bacitracin, the bacitracin test, along with the Lancefield antigen A test, is used to increase specificity in the identification of *S. pyogenes*. The bacitracin test is also used to differentiate S. pyogenes from other PYR-positive a-hemolytic streptococci, such as *S. iniae* and *S. porcinus*. The other technique such as bacterial culture, serology and molecular detection were used for laboratory diagnoses of *S. pyogenes*. This review was aimed to discuss the virulence factor, pathogenesis and diagnostic technique of the *S.pyogenes*.

**Keywords:** Diagnostic technique, pathogenesis, *Streptoccocus pyogenes*, Virulence factor

## 1. Introduction

*Streptococcus pyogenes* is an important gram-positive bacterial pathogen that causes a wide variety of clinical conditions, ranging from pharyngitis to severe invasive infections and necrotizing fasciitis (Canningham, 2000). It is the most prevalent bacterial pathogens causing human disease worldwide, ranging from the fairly mild to highly severe. Streptococci with human reservoirs, such as *S. pyogenes* and *S. pneumoniae* can occasionally be transmitted to animals. These reverse zoonoses can cause human illness if an infected animal, such as a cow, comes into

contact with them. *S. pyogenes* colonized the udder and transmits the organism back to humans. Some Streptococcus spp. are human-adaptedhave no natural reservoirs in animals, but can be passed on to them (reverse zoonoses). Animals that have colonized can then spread the infection to humans (Center, A. O. C. 2005).

Organisms of this species are remarkable for the extensive diversity in their spectrum of virulence factors and surface antigens. Importantly, those variant features can be used to organize GAS strains into subgroups that, in turn, correlate with distinct clinical features. The primary ecological niche of GAS is the superficial epithelium of the oropharynx or skin (Carapetis *et al*., 2005). S. Pyogenes usually colonizes the throat or skin epithelial surfaces and causes a wide variety of clinical manifestations, such as non invasive pharyngitis, dermatitis, and scarlet fever (Bisno, 2000). However, this pathogen is also responsible for deadly invasive systemic infections such as necrotizing fasciitis and streptococcal toxic shock syndrome.

The role of the environment in facilitating the spread of *S. pyogenes* is potentially under recognized, despite well-documented accounts that suggest a key environmental role in facilitating disease transmission. *S. pyogenes* are shed in the immediate environment of infected, untreated individuals in large numbers with viable bacteria cultivated from clothing and bedding belonging to the infected person, as well as in accumulated dust. Similarly, food can become inoculated and may facilitate the spread of infection to numerous recipients of foods prepared by infected kitchen staff (Efstratiou and Lamagni., 2016).

Today, culturing bacteria from clinical specimens is still used extensively in the laboratory diagnosis of group A streptococcal infections. To detect streptococci in clinical samples (particularly *S. pyogenes*), the material is typically cultured on blood agar plates, which allows for an easy preliminary screen for -hemolytic colonies. Following confirmation of suspicious colonies as *S. pyogenes*, several simple, quick laboratory tests can be used, which are still widely used in clinical microbiology despite the increasing use of automated identification systems. In contrast to acute *S. pyogenes* infections, the determination of specific antibodies is required for the diagnosis of poststreptococcal diseases such as glomerulonephritis, acute rheumatic fever, and cerebral disorders (Spellerberg, and Brandt, 2016). Antibiotic treatment is recognized as an effective means to reduce transmission of the organism particularly for respiratory and coetaneous infections (Steer *et al*., 2012). This review is aimed to discuss the *streptococcus pyogens* virulence factor, pathoginesis, and is laboratory diagnostic techniques.

## 2. Virulence factors of *Streptococcus pyogenes*

*Streptococcus pyogenes* has a number of virulence factors that act as assault weapons, allowing it to attack and destroy host cells while evading the immune system. Wide ranges of virulence factors contribute to *Streptococcus pyogenes'* success by increasing its ability to colonize, multiply, evade host immune response, and spread in its host. This review discusses the exotoxins, structural components, and enzymes that contribute to its virulence.

### 2.1. Hyaluronic acid capsule.

The group A streptococcal capsule is composed of a polymer of hyaluronic acid containing repeating units of glucuronic acid and N-acetylglucosamine . The hyaluronic acid capsule is required for resistance to phagocytosis .The ability to infect a host requires resistance to the host's immune system and capsules have been shown to facilitate survival of the organism by interfering with antibodies, complement, and phagocytosis-mediated host defense mechanisms (Crater *et al.*, 1995). Capsules are major virulence factors of many pathogenic bacteria as they are anti-phagocytic in nature. The hyaluronic acid capsule of *S. pyogenes* is **non-antigenic** because of its chemical similarity to host connective tissue. The capsule of *S. pyogenes* thus assists the bacterium

to hide its own antigens and going unrecognized as antigenic by its host. The hyaluronic acid capsule also prevents opsonized phagocytosis.

## 2.2 Adherence

Bacterial attachment is thought to be a two-stage process that begins with weak and/or long-range interactions and progresses to more specific, high-affinity binding. Lipoteichoic acid (LTA), a membrane-bound amphiphilic polymer of glycerol phosphate containing glucose and D-alanine substitutes, may help S*treptococcus pyogenes* adhere to host surfaces at first by establishing weak hydrophobic interactions between bacterial cells and host components ( Nobbs *et al*., 2009). The backbone and accessory pilin proteins of *Streptococcus pyogenes* spontaneously form covalent intramolecular isopeptide bonds, promoting mechanical stabilization to counteract shearing forces during bacterial adherence to the host epithelium ( Young *et al*., 2014). A more recent, significant breakthrough is the discovery that internal thioester bond formation leads to covalent linkage of GAS adhesins to host ligands, allowing GAS adhesins to act as 'chemical harpoons.' Surface streptococcal ligands bind to specific receptors on host cells, resulting in host-pathogen interactions. The most important initial step in colonization of the host is attachment of group A streptococci to pharyngeal or dermal epithelial cells. Group A streptococci could not attach to host tissues without strong adherence mechanisms and would be removed by mucous and salivary fluid flow mechanisms, as well as epithelial exfoliation. A site of previous damage may be important in overcoming the dermal barrier in skin attachment and colonization by group A streptococci. Specific adhesion allows normal flora and group A streptococci to compete for tissue sites occupied by normal flora. The study of adherence determinants in both streptococcal and host cells is critical for understanding pathogenic mechanisms in disease and developing anti-adhesion therapies or vaccines to prevent colonization. Immunization or exposure to microbial adhesins in humans or animals may induce antibodies that concentrate in the mucosal layer and inhibit adherence and colonization at the mucosal epithelium (Rohde and Cleary, 2016).

## 2.3 M Protein

M proteins are one of the key virulence factors, due to their involvement in mediating resistance to phagocytosis and their ability to induce potentially harmful host immune responses via their superantigenicity and their capacity to induce host-crossreactive antibody responses (Robinson and Kehoe, 1992). The M protein coats group A streptococci (GAS) and serves as the primary antigen and type-specific immune determinant. M is required for GAS virulence, as it provides antiphagocytic functions required for survival in human tissues and fluids. Cross-reactivity between these epitopes and human proteins may be the source of autoimmune sequelae such as rheumatic heart disease. M proteins offer active protection against phagocytosis and thereby allow the pathogen to persist in infected tissues (Metzgar and Zampolli, 2011). It is a major surface protein and virulence factor of group A streptococci, with diffirent serotypes identified are considered virulence factors conferring antiphagocytic properties upon the streptococcal cell. Several functional domains within M proteins, and their predicted binding motifs, strongly correlate with emm clusters, including plasminogen-binding in emm cluster D4 and fibrinogen-binding in most A–C clusters within clade. Despite advances on M protein-based GAS–host interactions, precisely how differential modulation of the coagulation–fibrinolysis pathways (Loof *et al*., 2014) may translate into bacterial tissue tropisms remains elusive. The antiphagocytic behavior of group A streptococci is also mediated by the binding of fibrinogen to the surface of M protein (Bessen *et al*., 1996)**.**

## 2.4 Hemolysins

*Streptococcus pyogenes* secretes two well-known hemolysins, streptolysin O and streptolysin S, which have a wide range of effects on different cell types (Hynes and Sloan, 2016).

### 2.4.1 Streptolysin S

Streptolysin S(SLS) is a 2.7 kDa ribosomally synthesized (Molloy *et a*l., 2011), non-immunogenic haemotoxin that is deposited upon the surface of target cells via direct GAS contact. SLS possesses cytotoxic effects against a broad spectrum of eukaryotic cells including myocardial cells, epithelial cells, neutrophils, lymphocytes and platelets. SLS is responsible for the characteristic beta-haemolytic phenotype of GAS, and contributes to pathogenesis through inhibition of neutrophil opsonophagocytosis and modulation of the host immune response during early infection which encoded 9-gene operon in GAS, designated *sag* (for SLS-associated genes), that was necessary and sufficient for SLS production (Wessels, 2005). The transposons disrupted the promoter for a gene, designated *sagA* (SLS-associated gene), that encodes the 53-amino acid SLS precursor, SagA that is enzymatically processed and exported by the downstream *sag* genes (Molloy *et al*., 2011 ; Reglinski and Sriskandan, 2015). The mature SLS haemolytic moiety is highly unstable, and the molecule requires the association of a carrier molecule, such as LTA, RNA-core, or serum albumin, to maintain its cytolytic activity. The separation of SLS from its carrier molecule results in the molecule's irreversible inactivation. SLS-mediated activation of cellular calpain (a host cysteine protease) during invasive pathogenesis promotes degradation of the transmembrane protein E-cadherin and partial disruption of the mucosal epithelium. GAS translocation across the epithelial cell monolayer is thus facilitated by SLS-mediated activation of cellular calpain (Reglinski and Sriskandan, 2015).

### 2.4.2 Streptolysin O

Streptolysin O (SLO) is a cholesterol-dependent, oxygen-labile, thiol-activated cytotoxin with pore formation. A variety of other pathogens produce similar types of hemolysins, and the structure of SLO is similar to these other cholesterol-dependent cytolysins, but there are some differences. One distinction is in the binding of the cytolysins to cholesterol-rich membranes, where there is a structural difference between SLO and perfringolysin O's membrane-binding interface (Farrand, et al., 2015). The SLO hemolysin is 69 kDa in size and is cleaved at the N-terminus by cysteine proteinase. In addition to cholesterol, the membrane-binding domain of SLO suggests the involvement of a glycan (galactose) receptor in binding and pore formation. These pores disrupt the integrity of host cell membranes and cause apoptosis (Hynes and Sloan, 2016)

## 2.5 Pyrogenic exotoxins of *Streptococcus pyogenes* (SPEs) types A,B and C

These toxins act as superantigens (not requiring processing by antigen-presenting cells ) **(**McCormick *et al*.**,** 2000). Streptococcal pyrogenic exotoxins A (SpeA) and C (SpeC) are members of a family of superantigens produced by group A streptococci that appear to play a key role in the pathogenesis of streptococcal toxic shock syndrome.They are produced by lysogenized strains of *S. pyogenes* (bacteria carrying an integrated phage i.e. prophage) (Christ and English, 1997). The streptococcal pyrogenic exotoxin B (SpeB) is the most common cysteine protease secreted by GAS. SpeB cleaves or degrades host serum proteins like human human extracellular matrix, immunoglobulins, complement components, and even GAS surface and secreted proteins. A bacterial chromosome encodes streptococcal pyrogenic exotoxins (SpeB). These toxins exert their pyrogenic (fever-producing) properties directly on the hypothalamus, resulting in the scarlet fever rash. Streptococcal toxic shock syndrome is another disease caused by the production of potent SPE. It is characterized by multi-system involvement, including renal and respiratory failure, rash, and diarrhea (Chiang and Wu, 2008; Wood *et al*., 1993).

## 2.6 Spreading factor

These are enzymes that aid streptococci in their invasion of tissues by dissolving tissue clots and destroying connective tissue. This category of enzymes includes, Streptokinase (fibrinolysin)

Hyaluronidase and deoxyribonucleases (streptodornase DNase) (Hynes *et al*., 2000; Hynes and Sloan, 2016)

## 3. Pathogenesis of *Streptococcus pyogenes*

### 3.1. Adherence and colonization

Streptococcus pyogenes or group A streptococci are Gram positive extracellular bacterial pathogens which colonize the throat or skin and are responsible for a number of suppurative infections and non-suppurative sequelae (Raeder *et al*., 1998). Surface streptococcal ligands bind to specific receptors on host cells, resulting in host-pathogen interactions. The most important initial step in colonization of the host is attachment of group A streptococci to pharyngeal or dermal epithelial cells. Group A streptococci could not attach to host tissues without strong adherence mechanisms and would be removed by mucous and salivary fluid flow mechanisms, as well as epithelial exfoliation. A site of previous damage may be important in overcoming the dermal barrier in skin attachment and colonization by group A streptococci. Specific adhesion allows normal flora and group A streptococci to compete for tissue sites occupied by normal flora. The study of adherence determinants of both streptococcal and host cells is critical to understanding pathogenic of bacteria (Cunningham, 2000). Streptococci pyrogen contains multiple surface components that have been identified as potential adhesions to the host receptors as described in table1

Table1: Group A streptococcal adhesins and their host cell receptors

| Adhesis | Receptor | Reference |
|---|---|---|
| LTA, | Epithelial cell/fibronectin receptor | Beachey *et al*. ,1976; Simpson and Beachey,1983 |
| M protein | HEp-2 cells | Ferretti *et al* 2016; Courtney *et al*.,1997 |
| Protein F/SfbI, | Epithelial cell/fibronectin/CD46 receptor on keratinocytes | Ellen and Gibbons,1972; Okada *et al*,1995 |
| Fibronectin-binding protein (FBP54) | Fibronectin/fibrinogen | Courtney *et al.,*1994 |
| Serum opacity factor, | Fibronectin | Kreikemeyer et al.,1995; Rakonjac et al,1995 |
| Hyaluronic acid capsule, | Keratinocyte/CD44 (hyaluronate receptor | Schrager et al.,1998; Wessels and Bronze,1994, Ferretti *et al*., 2016 |
| Glyceraldehyde-3-phosphate dehydrogenase, | Pharyngeal epithelium/fibronectin/cytoskeletal proteins/plasminogen-plasmin | Pancholi and Fischetti 1992; Winramand Lottenberg, 1997 |
| Fibronectin-binding protein (29 kDa), | Fibronectin | Cunningham, 2000 |
| Vitronectin-binding protein, | Vitronectin | Cunningham, 2000 |
| 70-kDa galactose-binding protein, | Galactose | Cunningham, 2000 |
| Collagen-binding protein | Collagen | Cunningham, 2000 |

### 3.2. Intracellular invasion

The reason for invasion of host cells is not entirely clear, although the streptococci may find the intracellular environment to be a good place to avoid host defense mechanisms. Therefore, internalization of streptococci may lead to carriage and persistence of streptococcal infection (Cunningham, 2000). The invasins and pathways used by Streptococcus pyogenes to enter the intracellular state, as well as the link between intracellular invasion and human disease are discussed. Intracellular invasion is dependent on at least two types of surface proteins, M proteins and Fn-binding proteins. Invasins are a type of bacterial adhesin molecule that is required for host cell ingestion. Invasion proteins are typically proteins expressed on the surfaces of bacterial cells that recognize specific host cells directly or indirectly. The internalization by a zipper mechanism is mediated by interactions between surface invasins, ligands, and host cell receptors (Wang *et al*., 2006). The classical intracellular pathogens not only efficiently invade epithelial cells, but they also survive macrophage ingestion by blocking intracellular armaments in various ways. Some evade phagosomes and multiply in the cytoplasms of these and other cells. The first line of cellular defense against invading streptococci is composed of resident macrophages and polymorphonuclear neutrophils (PMNs). Despite long-held beliefs that virulent streptococci are immune to phagocytosis in blood, some strains of S. pyogenes can evade the intracellular killing mechanisms of polymorphonuclear neutrophils (Rohde and Cleary, 2016). As pathogens they evade host defense mechanisms and exhibit a group of virulence determinants and common cause of bacterial pharyngitis, scarlet fever or impetigo, streptococcal toxic shock syndrome and necrotizing fasciitis which involves destruction of the skin and soft tissues in severe cases (Raeder *et al*., 1998).

## 4. Laboratory diagnosis technique of Streptococcus pyogenes

### 4.1. Culturing techniques

Streptococci are generally grown on agar media supplemented with blood. This technique allows the detection of β-hemolysis, which is important for subsequent identification steps, and enhances the growth of streptococci by the addition of an external source of catalase. Selective media for culturing Gram-positive bacteria (such as agar media that contains phenylethyl alcohol, or Columbia agar with colistin and nalidixic acid) also provide adequate culturing conditions for *S. pyogenes*. When properly performed and interpreted, culturing throat swabs on a 5% sheep blood agar with trypticase soy base incubated in air remains the gold standard and reference method for the diagnosis of *S. pyogenes* acute pharyngitis ( Shulman *et al*., 2014). Culture based screening relies on the detection of βhemolytic colonies and subsequent identification steps. However, clinical nonhemolytic *S. pyogenes* isolates that carry deletions of SLS genes have been published (Yoshino *et al*., 2010). Moreover, nonhemolytic *S. pyogenes* strains have repeatedly been implicated as causing pharyngitis, as well as invasive infections (Cimolai *et al*., 2002). Standard throat cultures will not detect these strains and it is currently unknown if there is a true burden of disease caused by nonhemolytic S. *pyogenes* strains. To identify Morphology of *S. pyogenes* in clinical samples, blood agar plates are screened for the presence of β-hemolytic colonies. The typical appearance of *S. pyogenes* colonies after 24 hours of incubation at 35-37°C is dome-shaped with a smooth or moist surface and clear margins. They display a white-greyish color and have a diameter of > 0.5 mm, and are surrounded by a zone of β-hemolysis that is often two to four times as large as the colony diameter. Microscopically, *S. pyogenes* appears as Gram positive cocci, arranged in chains (Spellerberg, 2016).

### 4.2. PYR test

Pyrrolidonyl Arylamidase (PYR) testing is a rapid test used to identify group A beta-hemolytic streptococci and enterococci based on the activity of the enzyme pyrolidonyl arylamidase (Aryal, 2020). The PYR test is a rapid colorimetric method that is frequently used to differentiate S. pyogenes from other hemolytic streptococci with similar morphology (such as *S. dysgalactiae* subsp. *equismilis*) and looks for the presence of the enzyme pyrrolidonyl amino peptidase. Within a few minutes, the test can be performed on paper strips containing dried chromogenic substrates for pyrrolidonyl aminopeptidase (Spellerberg and Brandt, 2016). PYR positive β-hemolytic streptococci that display the typical morphology of *S. pyogenes* can be presumptively identified as *S. pyogenes.* To avoid false positive reactions caused by other PYR positive bacterial species, which may be present in mixed cultures, this test should only be performed on pure cultures. The PYR test has been found to be very simple to use and thus may be regarded as a rapid, reliable, and cost-effective method for presumptive identification of group A streptococci and enterococci in the clinical laboratory (Chen *et al*., 1997).

### 4.3. Bacitracin susceptibility

Bacitracin test are used to differentiate *Streptococcus pyogenes* Bacteria from other non-group A β-hemolytic streptococci by their increased sensitivity to bacitracin. The bacitracin test, along with the Lancefield antigen A test, is used for greater specificity in the identification of *S. pyogenes,* since other β-hemolytic strains of streptococci that may contain the group A antigen are resistant to bacitracin. The bacitracin test is also used to distinguish *S. pyogenes* from other β hemolytic streptococci that are PYR-positive, such as *S. iniae* and *S. porcinus.* The strain being tested is streaked with several individual colonies of a pure culture on an sheep blood agar plate and a disk containing 0.04 U of bacitracin is placed on the SBA plate. After overnight incubation at 35°C in 5% CO2, a zone of inhibition surrounding the disc indicates the susceptibility of the strain. (Malhotra-Kumar *et al*., 2003; Mihaila-Amrouche *et al*., 2004).

### 4.4. Nucleic acid detection techniques

One of the methods introduced for direct *S. pyogenes* diagnosis from clinical throat swabs was nucleic acid detection. The GAS Direct test uses a single-stranded rRNA sequence to identify specific *S. pyogenes* rRNA sequences in pharyngeal specimens. *Streptococcus pyogenes* (group A streptococci) chemiluminescent nucleic acid probe diagnosis in the laboratory (Spellerberg 2016). The GAS Direct test is suitable for batch screening of throat cultures and can be used for primary testing. It has also been used as a backup test to negative antigen tests (Nakhoul & Hickner, 2013*). S. pyogenes* genome sequences revealed that the putative transcriptional regulator gene spy1258 is unique to this species (Zhao *et al*., 2015), making it an ideal target for specific identification in clinical and epidemiological studies.

### 4.5. Serological tests

Serological tests are frequently used to help diagnose *Streptococcus pyogenes* infections, especially when non-suppurative sequelae are suspected. Antibody levels are typically measured to various combinations of the extracellular group A Streptococcus (GAS) antigens streptolysin O (SLO), DNase B, streptokinase, and hyaluronidase. In response to GAS infections, antibodies to the extracellular cysteine proteinase streptococcal pyrogenic exotoxin B (SPE B) and its precursor zymogen are also produced (Batsford *et al*., 2002). Antibodies directed against extracellular products of group A streptococci, particularly anti-streptolysin O (ASO) antibodies, have been extremely useful in establishing the diagnosis of acute poststreptococcal disease for several decades. Of course, because acute rheumatic fever develops three weeks after infection, culture methods are far less effective than serological methods. Aside from their clinical utility, serological tests have proven invaluable in research into the epidemiology and pathogenesis of streptococcal

infections. Anti-streptolysin-O (ASO), anti-deoxyribonuclease B (ADN-B), and anti-hyal bodies are the most commonly used methods in clinical laboratories for detecting anti-streptococcal antibodies. Streptolysin-O (SLO) is an oxygen-labile toxin that can lyse a wide variety of mammalian cells but not bacteria (Burdash *et al*., 1986). The ability of streptolysin O to bind only to membranes containing cholesterol explains this differential effect. Free cholesterol (also known as non-esterified or protein-bound cholesterol) interacts with SLO and inhibits its lytic activity. Although serum cholesterol is not in a state that allows for SLO inhibition, the beta lipoprotein fraction of normal human sera shows a slight in hitions. Streptolysin-O is produced by streptococcal strains from groups A, G, and C, but not by other streptococcal strains (Wannamaker, 1983).

## Conclusion

*Streptococcus pyogenes* is a major global human pathogen that causes a wide range of acute infections, including soft tissue infections and pharyngitis, as well as severe life-threatening infections like streptococcal toxic shock syndrome and devastating postinfectious sequelae like rheumatic fever. It has A number of virulence factors that act as assault weapons, allowing it to attack and destroy host cells while evading the immune system that contribute to *Streptococcus pyogenes* success by increasing its ability to colonize, multiply, evade host immune response, and spread in its host. Patients admitted with GAS infections should be subjected to strict isolation procedures. Avoid close contacts whose primary cases of severe invasive GAS infections pose a higher risk of colonization than the general population, and all cases must be started on antibiotics as soon as possible, even if their symptoms are mild, to prevent further disease spread.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## 5. References


Aryal .S. *(2020).* PYR Test- Principle, Uses, Procedure and Result Interpretation

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