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# [Review Article] Review of *Streptococcus pyogenes*

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## Abstract

*Streptococcus pyogenes*, commonly known as group A *Streptococcus* (GAS), is a bacterium that causes a wide range of clinical diseases. Its ability to cause superficial, invasive, and even life-threatening infections makes it an important pathogen that requires prompt diagnosis and treatment. It is a Gram-positive bacterium. These infections involve the bloodstream and can lead to sepsis, toxic shock syndrome, pneumonia, and necrotizing fasciitis. These infections require immediate medical attention and treatment with high doses of antibiotics and aggressive supportive care.

*S. pyogenes* is a bacterium that causes a wide range of clinical diseases. Its ability to cause superficial, invasive, and even life-threatening infections makes it an important pathogen that requires prompt diagnosis and treatment. With the appropriate use of antibiotics and appropriate infection control measures, the incidence of *S. pyogenes* infections can be significantly reduced. The main objectives of this review are to know the causes of *Streptococcus pyogenes*.

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## Introduction

*Streptococcus pyogenes* is a Gram-positive bacterium that is a member of the *Streptococcus* genus [1]. It is a pathogenic bacterium that can cause a wide range of infections in humans, ranging from mild to life-threatening. Some of the common diseases caused by *S. pyogenes* include strep throat, impetigo, cellulitis, necrotizing fasciitis, and rheumatic fever [2][3].

*S. pyogenes* can be easily transmitted from one person to another through contact with infected individuals or contaminated objects [4]. The bacterium is typically found in the upper respiratory tract and can be transmitted when an

infected person coughs, sneezes, or talks. It can also be transmitted through direct contact with infected skin <sup>[5]</sup>. Once the bacterium enters the body, it can quickly spread and cause infections in different parts of the body. The bacteria typically attach to the host cells and produce a variety of virulence factors, which help them to invade and evade the host's defense mechanisms <sup>[6]</sup>.

The most important virulence factor produced by *S. pyogenes* is the M protein. This protein is essential for the bacteria to evade the host's immune system. The M protein allows the bacteria to attach to the host tissues, which helps to prevent phagocytosis by the host's immune cells. The M protein also helps the bacteria to move around the body by binding to special receptors found on the host's cells <sup>[7][8][9]</sup>.

Another important virulence factor produced by *S. pyogenes* is streptokinase. This enzyme helps the bacteria break down blood clots, which enables the bacteria to spread to different parts of the body <sup>[10]</sup>. The clinical manifestations of *S. pyogenes* infections can vary depending on the site of infection. Infections of the upper respiratory tract typically present as strep throat or tonsillitis. Skin infections caused by *S. pyogenes* can range from mild impetigo to severe necrotizing fasciitis, which is a life-threatening infection that can rapidly spread and lead to tissue and organ damage <sup>[11][12]</sup>.

Rheumatic fever is a serious complication that can occur after an *S. pyogenes* infection. This condition is an autoimmune disorder that occurs when the body's immune system attacks its own tissues, particularly the heart, joints, and central nervous system. Rheumatic fever can cause permanent damage to the heart valves and can result in heart failure <sup>[13]</sup>.

*Streptococcus pyogenes* is a significant human pathogen that can cause a wide range of infections, ranging from mild to severe. The bacterium has several virulence factors that enable it to invade and evade the host's immune system. The clinical manifestations of *S. pyogenes* infections can vary, and complications can occur, particularly rheumatic fever. Therefore, prompt diagnosis and treatment of *S. pyogenes* infections are essential to prevent them <sup>[14][15]</sup>.

#### Scientific classification <sup>[11]</sup>

- Domain: Bacteria
- Phylum: Bacillota
- Class: Bacilli
- Order: Lactobacillales
- Family: Streptococcaceae
- Genus: *Streptococcus*
- Species: *S. pyogenes*

## General characteristics of microorganism (*S. pyogenes*)

### Morphology and Identification

A-Typical organism:

*Streptococcus pyogenes* is a commonly found bacterium that belongs to the group of Gram-positive cocci. This bacterium is also known as group A *Streptococcus* (GAS) and is often associated with various bacterial infections, ranging from mild infections such as pharyngitis or skin infections to severe ones such as necrotizing fasciitis or sepsis [16].

Morphologically, *S. pyogenes* appears as small spherical-shaped cells that are arranged in chains. These chains can be observed under the microscope after performing a Gram stain, which yields a positive purple color, indicating that the bacterium is a Gram-positive organism. The chromosomal DNA of *S. pyogenes* is composed of about 1,900 genes, which contain several virulence factors that contribute to the pathogenesis of this bacterium [17].

One of the key characteristics of *S. pyogenes* is the presence of a thick outer capsule composed of hyaluronic acid, which is also found in human connective tissues. The capsule plays a vital role in pathogenesis by reducing the phagocytosis of the bacterium by immune cells. This bacterium also produces an array of virulence factors, including surface proteins, toxins, and enzymes, that contribute to the destruction of host tissues and immune evasion [15][16][17][18][19].

Some of the surface proteins produced by *S. pyogenes* include M protein, fibrinogen-binding protein, and fibronectin-binding protein. These proteins are critical in the adhesion of the bacterium to host tissues and evasion of the host immune system [10][13][20][21].



Figure 1. Chains of *S. pyogenes*[5]



Figure 2. Scanning electron microscope image of *Streptococcus pyogenes*<sup>[10]</sup>

#### B-Culture:

The culture of *S. pyogenes* requires a selective medium, as the bacterium is part of the normal flora of the human throat, skin, and genital tract, and can easily be confused with other streptococcal species [22]. The most commonly used medium is blood agar, which contains tryptic soy agar enriched with 5% sheep or horse blood. The blood provides essential nutrients for bacterial growth, while the agar provides a solid surface for colony formation [23]. The blood agar also facilitates the detection of beta-hemolysis, a characteristic of *S. pyogenes* which indicates the production of streptolysin O, a cytotoxin that causes the lysis of red blood cells [24].

To obtain a *S. pyogenes* culture, a specimen such as a throat swab, skin lesion, or blood sample is collected from the patient and inoculated onto blood agar. The specimen must be properly collected and transported to the laboratory to prevent contamination and reduce the risk of false-negative results. Once the inoculated plate is incubated at 35-37°C in a humid environment with 5-10% CO<sub>2</sub>, the growth of colonies can be observed after 24-48 hours as small, gray, beta-hemolytic colonies with a characteristic disc of clear hemolysis around them [25].

To confirm the identity of *S. pyogenes*, several tests can be performed. The bacitracin susceptibility test is one of the most commonly used tests, as *S. pyogenes* is highly sensitive to bacitracin. A small disc impregnated with bacitracin is placed on the blood agar, and if there is a zone of inhibition around the disc, it indicates that the bacteria are sensitive to bacitracin and are likely *S. pyogenes* [26].

Another test is the pyrrolidinyl arylamidase (PYR) test, which detects the presence of the enzyme pyrrolidinyl arylamidase produced by *S. pyogenes*. A disc impregnated with PYR reagent is placed on the blood agar, and if there is a color change from yellow to red, it indicates a positive result for *S. pyogenes* [27].

Furthermore, the culture of *S. pyogenes* is an important diagnostic tool for the identification and management of diseases caused by this bacterium. The use of selective media, proper specimen collection and transportation, and confirmation tests help ensure accurate diagnosis and appropriate treatment [28].

### C- Growth Characteristics

The growth characteristics of *S. pyogenes* are crucial to understanding its ecology and pathogenesis. The optimal growth conditions for *S. pyogenes* include a temperature range of 35°C to 37°C and a pH range of 7.2 to 7.5. The bacterium grows aerobically but does not require atmospheric oxygen for growth. It prefers an environment that is slightly acidic, and as such, it will grow better in acidic conditions than in neutral pH. *S. pyogenes* is a fastidious bacterium, and thus it requires complex media that are rich in nutrients [20][22][23]. Blood agar is the most commonly used medium for *S. pyogenes* isolation, and it is an excellent source of nutrients for the bacterium [29].

*S. pyogenes* is capable of fermenting various carbohydrates, including glucose, lactose, maltose, and sucrose, to produce lactic acid. The bacterium also produces several extracellular enzymes like streptokinase, hyaluronidase, and DNase that are responsible for its pathogenesis. These enzymes help the bacterium evade the host immune system, spread through the tissues, and cause tissue destruction. The production of these enzymes is dependent on the growth phase of the bacterium, and thus, they are not produced throughout the bacterial growth cycle [21][26][29].

The growth rate of *S. pyogenes* is relatively slow, and it takes 10 to 20 hours for the bacterium to double in number. This characteristic makes it an excellent indicator for monitoring changes in the microbial community [29][30]. As the bacterium grows, it produces a capsule that helps it evade the host's immune system. The capsule also protects the bacterium from phagocytosis by the host's white blood cells, making it difficult for the immune system to clear the infection. This bacterium has a narrow host range, and it primarily infects humans. The bacterium is highly communicable, and transmission occurs through contact with infected individuals or contaminated objects. Crowded conditions, poor sanitation, and suboptimal living conditions increase the risk of *S. pyogenes* infection [31][32].

*S. pyogenes* is a fastidious bacterium that requires optimal growth conditions for its survival. This bacterium produces several extracellular enzymes that are critical for its virulence, and it has a slow growth rate when compared to other bacteria. The narrow host range of *S. pyogenes* makes it a perfect point for monitoring changes in the microbial community. Understanding the growth characteristics of *S. pyogenes* is essential for the effective management of the infections caused by this pathogen [33].

### D- Variation:

One key factor in the genetic variation of *S. pyogenes* is the presence of plasmids. Plasmids are small, circular pieces of DNA that can replicate independently of the bacterium's chromosomal DNA. They can carry genes that confer virulence or antibiotic resistance, making them an important factor in the evolution of *S. pyogenes* [34]. Some plasmids carry genes for toxins, such as the streptococcal pyrogenic exotoxins (SPEs), which can cause severe diseases such as toxic shock syndrome and necrotizing fasciitis. Another source of variation in *S. pyogenes* is its ability to acquire DNA from other



bacteria through horizontal gene transfer. This process involves the transfer of genetic material between different bacterial species, which can introduce new virulence factors or antibiotic resistance genes into the *S. pyogenes* genome. This mechanism has been implicated in the rise of antibiotic-resistant strains of *S. pyogenes* in recent years [35]. One notable example of horizontal gene transfer in *S. pyogenes* involves the acquisition of a prophage, a piece of DNA that is integrated into the bacterium's chromosome. This prophage carries genes for the M-protein, which is a major virulence factor in *S. pyogenes*. The M-protein helps the bacterium evade the immune system by changing its surface antigens, making it difficult for the host's immune system to recognize and eliminate the pathogen [36].

In addition to these mechanisms of genetic variation, *S. pyogenes* also exhibits variability in its adherence and colonization properties. This variability is due in part to differences in the expression of various adhesion molecules, which allow the bacterium to attach to different host tissues. For example, some strains of *S. pyogenes* express the fibronectin-binding protein, which allows the bacterium to adhere to epithelial cells in the respiratory tract, while others express the M protein, which allows the bacterium to attach to host tissues such as the heart valves or the joints [37]. The genetic variation of *S. pyogenes* is a critical factor in the pathogenesis of this bacterium. Plasmids, horizontal gene transfer, and variability in adherence and colonization properties all contribute to the evolution of virulence and antibiotic resistance in this pathogen. Understanding these mechanisms of variation can help us develop more effective treatments and prevent the emergence of new, resistant strains of *S. pyogenes* [38].

#### E- Antigenic Structure:

The pathogenicity of *S. pyogenes* is primarily attributed to its complex antigenic structure, which allows the bacterium to evade the host's immune system and cause disease. The cell wall of *S. pyogenes* is composed of peptidoglycan, lipoteichoic acid, and capsule polysaccharides, which confer structural integrity and protect the bacterium from host defense mechanisms [39]. The capsule polysaccharides are the major virulence factors of *S. pyogenes*, as they inhibit phagocytosis and cause tissue damage. The capsule is formed by repeating units of the sugar hyaluronic acid, which is identical to the host's own connective tissue. This molecular mimicry allows the bacterium to evade recognition and destruction by the host's immune system [40].

*S. pyogenes* also possesses a variety of surface proteins, known as M proteins, which are encoded by the EMM gene family. The M proteins are the most studied and extensively characterized antigens of *S. pyogenes* and play a crucial role in the pathogenesis of GAS infections. The M protein is a surface-anchored protein that extends from the cell surface and interacts with host immune receptors, such as Toll-like receptors and complement regulators. The M protein is highly variable, with over 220 distinct serotypes identified to date, and is classified based on its N-terminal sequence [41][42].

Another important protein of *S. pyogenes* is the streptococcal pyrogenic exotoxin (SPEs), which are secreted by the bacterium and act as superantigens. SPEs are potent activators of T cells and can elicit an overwhelming immune response, leading to toxic shock syndrome and other severe complications. *S. pyogenes* produces at least three distinct SPEs, designated A, B, and C, with each toxin exhibiting a unique antigenic structure [43].

Apart from M proteins and SPEs, several other antigens have been identified in *S. pyogenes*, such as lipoteichoic acid,

fibronectin-binding proteins, and streptolysin O. These antigens contribute to the virulence of *S. pyogenes* and provide new targets for vaccine development [44].

In summary, *S. pyogenes* possesses a complex and diverse antigenic structure, which allows the bacterium to evade host immune defenses and cause disease. The identification and characterization of these antigens have provided a better understanding of the pathogenesis of GAS infections and facilitated the development of new diagnostic tests and vaccines. Future research should focus on elucidating the mechanisms of antigenic variation and immune evasion [45].

#### F- Toxins and Enzymes:

The virulence of *S. pyogenes* is mediated by a variety of toxins and enzymes that play critical roles in colonization, invasion, and evasion of host defense mechanisms. One of the most important toxins produced by *S. pyogenes* is streptolysin O (SLO), a pore-forming hemolysin that causes damage to host cells, leading to tissue destruction and inflammation. SLO is synthesized as a precursor, which is then activated by the insertion of a single cholesterol molecule [45][46]. Once activated, SLO forms large transmembrane pores that disrupt the integrity of host cell membranes, leading to the release of cytoplasmic contents and the activation of the host immune response. Another important toxin produced by *S. pyogenes* is streptococcal pyrogenic exotoxin A (SPEA), a superantigen that stimulates the immune system in an uncontrolled manner, leading to the release of large amounts of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha) [47]. This can result in a number of serious complications, including toxic shock syndrome, sepsis, and multiple organ failure. In addition to toxins, *S. pyogenes* also produces a number of enzymes that play important roles in pathogenesis [48]. One such enzyme is hyaluronidase, which breaks down hyaluronic acid, a major component of connective tissue, thereby facilitating the spread of *S. pyogenes* through host tissues. Another enzyme produced by *S. pyogenes* is streptokinase, which activates plasminogen, leading to the breakdown of blood clots and facilitating the spread of *S. pyogenes* through the bloodstream [48][49]. Finally, *S. pyogenes* also produces a number of proteases, including streptococcal pyrogenic exotoxin B (SPEB), which cleaves the C3 component of the complement system, a key component of the host immune response. By cleaving C3, *S. pyogenes* can evade the host immune response and colonize host tissues. *S. pyogenes* produces a wide range of toxins and enzymes that play critical roles in colonization, invasion, and evasion of host defense mechanisms. Understanding the mechanisms of action of these virulence factors is essential for the development of effective treatments and vaccines for *S. pyogenes* infections [39][50].

#### G- Pathogenesis and Clinical Findings

The pathogenesis of *S. pyogenes* is complex and involves the interaction of multiple virulence factors with the host immune system. In this essay, we will explore the pathogenesis and clinical findings of *S. pyogenes* infections. *S. pyogenes* infections can be classified into two main categories based on the site of infection: skin and soft tissue infections (SSTIs) and invasive infections. SSTIs are the most common type of *S. pyogenes* infections and include impetigo, erysipelas, and cellulitis [50][51]. These infections are typically localized and limited to the skin and subcutaneous tissues. Invasive infections, on the other hand, are more serious and can involve deeper tissues such as the fascia, muscle, and

bone [51]. Examples of invasive infections include necrotizing fasciitis, myositis, and streptococcal toxic shock syndrome. The pathogenesis of *S. pyogenes* infections begins with the colonization of the host. *S. pyogenes* expresses several surface proteins that aid in adherence to epithelial cells, including M protein, F protein, and lipoteichoic acid. Once attached to the host, *S. pyogenes* produces a variety of virulence factors, including streptolysin O, streptolysin S, and pyrogenic exotoxins. These factors aid in immune evasion and promote tissue destruction by damaging host cells and tissues. One of the most important virulence factors of *S. pyogenes* is the M protein [52]. The M protein is a surface protein that inhibits phagocytosis by neutrophils and blocks complement deposition on the bacterial surface. The M protein also elicits a strong immune response and is responsible for the characteristic rash seen in scarlet fever. Another important virulence factor of *S. pyogenes* is pyrogenic exotoxins. These toxins are responsible for fever, rash, and shock in severe infections such as streptococcal toxic shock syndrome. Pyrogenic exotoxins also act as superantigens, which trigger an excessive immune response and can lead to systemic inflammation and tissue damage [53].

Clinical findings of *S. pyogenes* infections depend on the site of infection. Skin and soft tissue infections typically present as localized erythema, warmth, and tenderness. Invasive infections can present as severe pain, fever, and systemic toxicity. Necrotizing fasciitis, a rare but serious complication of *S. pyogenes* infections, can present with bullae, crepitus, and pain out of proportion to physical exam findings. *S. pyogenes* is a pathogenic bacterium that causes a wide range of infections in humans. The pathogenesis of *S. pyogenes* depends on the interaction of multiple virulence factors with the host immune system [54].

#### H- Diagnostic Laboratory Tests:

*Streptococcus pyogenes* is a bacterium that mainly causes strep throat or pharyngitis, skin infections, and invasive diseases such as sepsis, necrotizing fasciitis, etc. Thus, timely diagnosis and treatment are crucial in preventing morbidity and mortality [55]. The following are some of the diagnostic laboratory tests used for the detection of *S. pyogenes*:

##### 1. Throat Swab:

The gold standard test for diagnosing pharyngitis caused by *S. pyogenes* is a throat culture. In this test, a sterile swab is rubbed over the tonsils, posterior pharynx, and the back of the throat. These swabs are then inoculated into culture media containing sheep blood and incubated at 35-37 degrees Celsius in a carbon dioxide-enriched environment for 24-48 hours. Colonies of *S. pyogenes* will appear as small, grayish-white, and beta-hemolytic on the agar plates [55].

##### 2. Rapid Antigen Detection Test (RADT):

RADT is a point-of-care test that detects *S. pyogenes* antigen directly from throat swabs in about 15-20 minutes. This test detects the presence of group A streptococcal carbohydrates called Lancefield antigens using specific monoclonal antibodies. The sensitivity of this test ranges from 70 to 90% compared to culture, but its specificity is high (around 98%-100%), hence it can be used as a confirmatory test [55].



### 3. Serological Tests:

Serological tests are blood tests that detect the presence of antibodies against *S. pyogenes* antigens. They are useful in diagnosing post-streptococcal complications like rheumatic fever and glomerulonephritis. Examples of serological tests include the ASO (Anti-streptolysin O) assay and the Anti-DNase assay, etc. These tests usually require 2-4 weeks after the onset of the disease before they become positive [56].

### 4. PCR (Polymerase Chain Reaction):

PCR is a rapid and sensitive lab test that can detect *S. pyogenes* DNA from throat swabs or blood within a few hours. This test uses primers specific to *S. pyogenes* DNA to amplify it and detect it through fluorescent probes. PCR is more sensitive than culture or RADT, especially for detecting low bacterial loads, but it is not recommended for routine diagnosis due to its relatively high cost compared to other tests [56].

A combination of various laboratory tests like throat culture, RADT, serological tests, and PCR is needed for accurate diagnosis and prompt treatment of *S. pyogenes* infections. Clinicians should consider the patient's medical history, clinical presentation, and other factors when selecting the best test for diagnosis. Prompt and appropriate antibiotic administration is important to prevent complications, especially in high-risk groups [57], [58].

## Conclusion

*Streptococcus pyogenes* is a dangerous bacterial pathogen that can cause a variety of illnesses, ranging from minor infections to life-threatening conditions. Prevention and prompt treatment of infections are essential to preventing the spread of this bacterium and minimizing the severity of illness. Ongoing research may eventually lead to the development of a vaccine against *S. pyogenes*, but in the meantime, vigilance and good hygiene practices are essential in managing this bacterium. This bacterium is an infrequent but pathogenic part of the skin flora, with the most common infection being acute pharyngitis.

By following the tips below, it is possible to limit the spread and infection of *Streptococcus pyogenes*:

Reducing the spread of droplets coming out of the mouth.

Avoiding direct contact. In some cases of burns, inflammation of this type of bacteria is observed, and these burns are not covered during treatment. Therefore, it is advised to avoid direct contact with people with second-degree burns.

Maintaining general hygiene and adhering to work conditions. Members of the medical staff or cleaning workers inside the hospital can contribute to the transmission of these bacteria, so they must adhere to all general hygiene and safety guidelines to avoid the transmission of infection between patients inside the hospital or people outside the hospital.

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