Streptococcus pyogenes: A review of the combination of virulence and versatility

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ABSTRACT

Streptococcus pyogenes is also known as group A β-hemolytic streptococcus (SAG). Man is its only reservoir in nature, and is found asymptomatically colonizing the skin, mucous membranes of the throat, nose, nasopharynx, anus, and scalp. This bacterium affects more children, adolescents and the elderly due to poor hygiene, low immunity and secondary infections. It also has the ability to cause various forms of clinical infections and post-infectious sequelae, the most common being streptococcal pharyngitis. The main virulence factors presented by S. *pyogenes* are adhesion; hyaluronic acid capsule; M protein; DNAse, C5a peptidase, hyaluronidase and streptokinase enzymes; fumed exotoxins; streptolysis. Through the study of these factors it is possible to understand the versatility of this microorganism.

Keywords: *Streptococcus pyogenes*, Virulence, Versatility, Virulence factors.

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INTRODUCTION

The first description of a streptococcal infection occurred in 1874, attributed to Theodor Billroth, an Austrian surgeon, who reported erysipelas and the infection of a wound. He described the presence of small microorganisms found in pairs, in chains, or even in isolation. But it only became important in 1879, when Louis Pasteur isolated the microorganism in a sample from the uteruses and blood of women who had puerperal fever, demonstrating that streptococcus was the main agent responsible for the highly mortality disease in women and newborns (FERRETI; STEVENS; FISCHETI, 2013).

The *genus Streptococcus* belongs to the order *Lactobacillales* and the family *Streptococcaceae.* It is composed of Gram-positive bacteria, which usually grow in chains or can be observed in pairs, being nutritionally demanding, catalase-negative microorganisms and facultative anaerobes. Some species can be found in soil, plants, water, dairy, food, humans, and animals. *Clinically important Streptococci* are homofermenters, capable of obtaining lactic acid through glucose fermentation without the production of gas (GOLIŃSKA *et al*., 2016).

Its cell wall is synthesized and repaired continuously, formed mainly by several layers of peptidoglycans, consisting of N-acetylglucosamine and N-acetylmuramic acid. Carbohydrates, teichoic acids, lipoproteins, and surface antigens of protein origin are fixed in this matrix (PROCOP *et al*., 2017).

Species of clinical importance to humans can be divided, by means of serology, into seven groups based on the composition of the antigenic carbohydrate, known as the Lancefield group. First, the species were divided according to their ability to lyse the erythrocytes present in sheep's blood. Streptococci β-hemolytics are able to generate a transparent halo around the colony, representing complete lysis of the red cell; On the other hand, the α-hemolytics, generate a partial hemolysis of the red blood cells, by means of hydrogen peroxide, resulting in the greenish color around the colony, when in medium with the presence of oxygen; and species that fail to generate hemolysis are classified as C-hemolytics. Lancefield's classification was able to subdivide these microorganisms based on their reaction to pools containing antisors, capable of recognizing surface carbohydrates of the bacterium. They are grouped antigenically from A to H and from K to V. The most associated with human diseases are group A, B, C, D, and G streptococci (HASLAM; GEME III, 2018).

Or *S. pyogenes* it is also known as group A β-hemolytic streptococcus (SAG). Man is its only reservoir in nature, usually found asymptomatically colonizing the skin, mucous membranes of the throat, nose, nasopharynx, anus and scalp. Still, it is a pathogen of great clinical importance, as it can be spread from person to person; be transmitted by droplets or nasal secretions, by direct contact with infected people and surfaces, by sharing fomites and contaminated food, increasing the chances when contact is greater than 24 hours with the infected individual. It affects more children, adolescents and

the elderly, due to poor hygiene, low immunity and secondary infections. It has the ability to cause various forms of clinical infections and post-infectious sequelae. The most common infection is strep throat. SAG also colonizes the skin, and for this reason is capable of causing superficial infections such as pyoderma (KEMBLE *et al*., 2013; BROUWER *et al*., 2016; DUPLOYEZ *et al*., 2017).

Within the risk group are the elderly and children, where the number of cases in males was more prevalent, however, pregnant and postpartum women are also part of the risk group. The main sites related to SAG infections are schools, daycare centers, hospitals, shelters, and military training centers. This may be associated with factors such as poor ventilation, temperature, crowding, and sharing of personal items; in hospitals, it can occur associated with cross-contamination in the interaction between patient and health professional (ALVIRE; WHILEY; ROSS, 2021).

Within the gender group *Streptococcus*, SAG were the most studied, and one of the reasons is the fact that the skin and mucosa of men are its only reservoir. In addition to acute infections caused by the pathogen, there are also rheumatic fever and streptococcal glomerulonephritis, two non-suppurative sequelae. The main virulence factors presented by the *S. pyogenes* they are those of adhesion; the hyaluronic acid capsule; the M protein; the enzymes DNAse, C5a peptidase, hyaluronidase, streptokinase; fumed exotoxins; streptolysins (LINO, 2010; PROCOP *et al*., 2017).

VIRULENCE MECHANISMS

ADHESION AND INVASION

Lipoteicoic acids are attached to the bacterial cell membrane and expand to the cell wall, stabilizing it, in addition to participating in the process of initial adhesion of the bacterium to the pharyngeal region. In addition, SAG has other adhesins, such as fibronectin binding proteins (PBF), F1, F2, FPB54, and PFBP, which allow adhesion to cells in the pharynx and other tissues. Protein F is a surface protein with high affinity for fibronectin bindings, which can bind to the extracellular matrix or cells, very effective in adhesion and also helps in internalization. The expression of F1 and F2 proteins can be affected at the transcriptional level by environmental conditions, such as the presence of oxygen and the potential reduction, which may be an indication that most SAG adhesins respond in the same way, and that, when invading a tissue rich in carbon dioxide and poor in oxygen, inhibition of these adhesins, facilitating the spread of the microorganism (HAŃSKI; CAPARON, 1992; GOLIŃSKA *et al*., 2016; JAFFE *et al*., 1996; OZERI *et al*., 1998; WALKER *et al*., 2014).

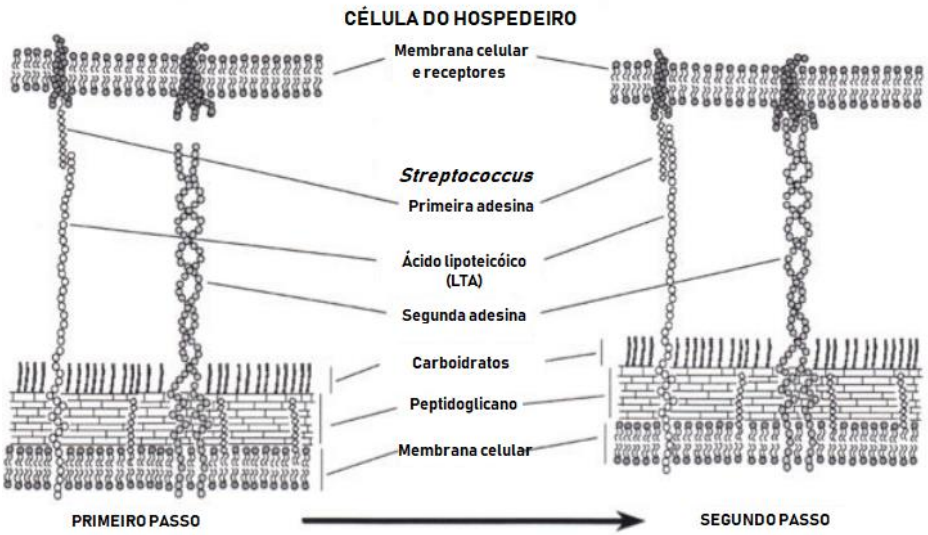
There are also multifunctional surface proteins capable of binding to fibronectin, such as some M protein serotypes; it can participate in the adhesion to keratinocytes, present in the skin, due to its interaction with the CD46 cofactor present in the keratinocyte membrane. The Shr protein is responsible for capturing hemoglobin on the cell surface, so that iron uptake and bacterial proliferation occur. Its uptake mechanism has not been elucidated and is currently being studied.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) protein is capable of binding to plasminogen and has strong binding to fibrinogen, fibronectin and other extracellular matrix proteins (MACDONALD *et al.*, 2018; Pancholi, 2017; Walker *et al.*, 2014).

SAG has collagen-binding adhesins (Cpa) and collagen-like proteins (Scl), such as Scl1 and Scl2. Eukaryotic cells become susceptible as they interact with collagen. The presence of Cpa, Scl1 and Scl2 may favor autoimmunity, as they are very immunogenic, leading to the production of antibodies that will cause cross-reaction to the host proteins (CHAUDHARY *et al.*, 2017).

In 2005, the presence of pili, consisting of fimbriline, capable of binding to the host's cells and assisting in the formation of biofilm, was discovered. Studies suggest that the adhesion process occurs in two stages: lipoteicoic acid provides initial adhesion through a weak hydrophobic interaction between the bacterial cell and the host cell, avoiding electrostatic repulsion and allowing an irreversible second stage to occur, when there is an increase in strength and affinity, protein-to-protein interaction, or carbohydrate-lectin interaction, as adhesion by means of the pili (Figure 1) (WALKER *et al.*, 2014).

Figure 1: Adhesion model.



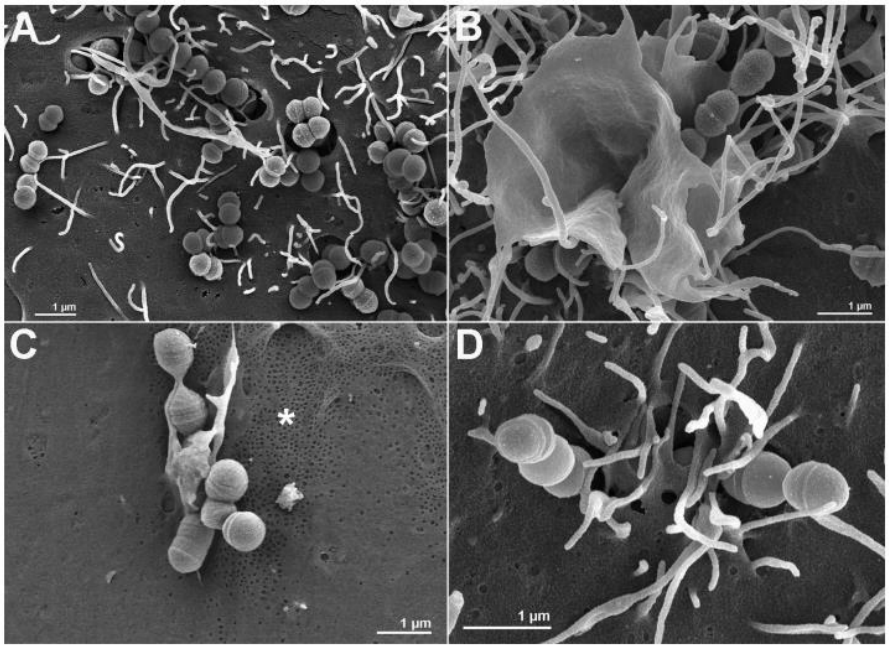
Source: adapted from FERRETI; STEVENS; FISCHETI, 2013.

SAG has several ways of invading a cell, one of which is through the absorption of long chains of streptococci through the cell's microvilli. Absorption begins when the microvilli and the middle of the streptococcal chain interact (Figure 2, D). Or *S. pyogenes* It can also internalize in the cell through endocytosis via *caveolae*, a plasma membrane invagination (Figure 2, C). When the *S. pyogenes* Once the cell enters the cell, a new compartment called caveosome1 is formed, which does not interact with the lysosome. There are invasins distributed along its surface or diffuse proteins that promote the rearrangement of actin present in the cytoskeleton, which leads to membrane derangement (Figure 2, B). Among the most studied adhesins are the M protein and SfbI (SfbI).

Streptococcus pyogenes fibronectin-binding protein), but studies indicate that GAPDH, the superantigens SPE A and SPE E, and C5a peptidase are associated with invasion of host cells, but the mechanism has not been clarified (FERRETI; STEVENS; FISCHETI, 2013; KISS; BOTOS, 2009).

When Sfbl interacts with fibronectin, the latter alters its quaternary structure and exposes the RGD (Arginine, Glycine, and Aspartate) region of the molecule, allowing α5β1 integrin to couple (Figure 2, A). In one study, it was shown that the adhesion protein SfbI, which binds to fibronectin in eukaryotic cells, triggers the internalization of the bacterium by non-phagocytic cells, when it is neutralized by specific antibodies, there is no adhesion or internalization of SAG (FERRETI; STEVENS; FISCHETI, 2013; MOLINARI *et al.*, 1997).

Figure 2: Mechanisms of Invasion in Field Emission Scanning Electron Microscope (FESEM)



Fonte: FERRETI; STEVENS; FISCHETI, 2013.

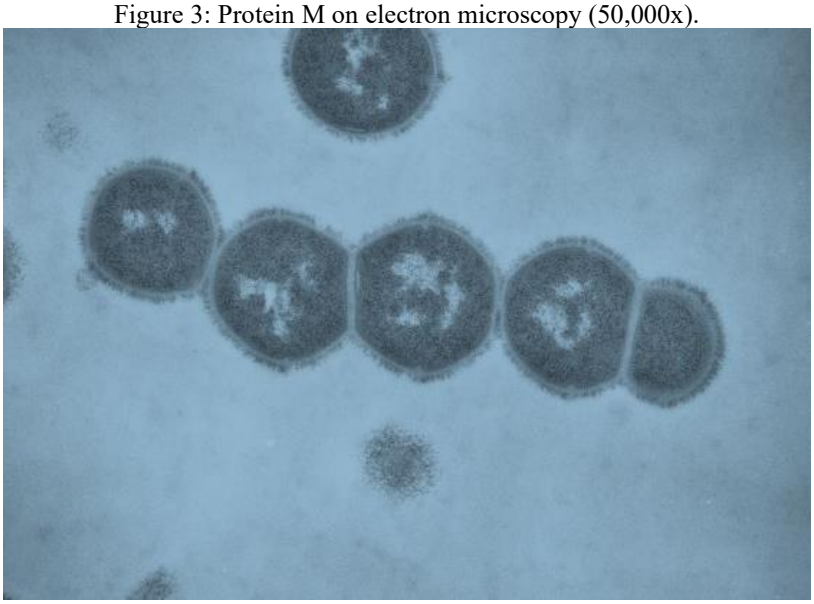
The opacity factor (FO) is a substance produced by SAG, which is responsible for making serum more cloudy. It acts on the fraction of lipoproteins present in the serum, by binding to high-density lipoproteins (HDLs), displacing apolipoprotein A-I, disrupting the HDL structure, releasing large lipid particles, resulting in the clouding of the serum. It has the ability to induce the immune response in humans and bind to several host proteins, such as fibronectin and fibrinogen (COURTNEY; POWNALL, 2010).

PROTEIN M

Discovered by Rebecca Lancefield, the M protein is the most studied virulence factor and is considered the main virulence factor of SAG. It is a surface fibrillar protein (Figures 3 and 4) encoded by the *emm* gene, whose hypervariable N-terminal region has the potential to induce

autoimmunity, while other regions are generally non-immunogenic. Currently, serological classification has been replaced by emm gene typing; its classification occurs by the sequencing method, through the terminal 5' end of the *emm* gene. About 250 types of *emm* have been identified by this methodology. Its expression is regulated by the concentration of carbon dioxide in the environment, and its genetic variability is used as an epidemiological tool (JAFFE *et al*., 1996; FERRETI; STEVENS; FISCHETI, 2013; WALKER *et al*., 2014; ZHU *et al*., 2015; WANG et al., 2023).

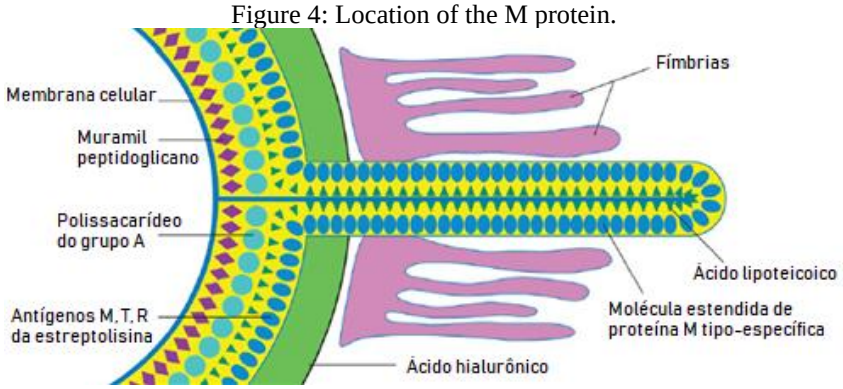
Figure 3: Protein M on electron microscopy (50,000x).



Fonte: FERRETI; STEVENS; FISCHETI, 2013.

Protein M is stable in acidic media, thermostable and labile in trypsin, present on the outer surface of the cell wall. Studies indicate the participation of the M protein in the adhesion of epithelial cells and in the invasion of keratinocytes, as previously mentioned. Strains rich in M proteins are resistant to phagocytosis by polymorphonuclear cells, allowing the bacterium to remain in the infected tissue, while those that do not are easily phagocytosed. It is able to interact with antimicrobial molecules such as LL-37, found in the skin, preventing it from being able to reach your cell membrane and puncture it. The M protein unwinds its superhelix and exposes a hydrophobic region, capturing LL-37 (PROCOP et al., 2017.; KOLESINSKI et al., 2022)

Figure 4: Location of the M protein.



Font: Adaptada by PROCOP et al., 2017.

Its antiphagocytic action prevents the opsonization of SAG, inhibiting the classical and alternative pathways of the complement system. Add to this the fact that M proteins have the ability to form complexes with fibrinogen; These bind to β2 integrins of neutrophils, triggering the release of inflammatory mediators. Some are very antigenic, acting as superantigens, and induce the proliferation of T cells as well as the release of cytokines. Others are capable of triggering the formation of antibodies, causing cross-reacting with host proteins (PROCOP et al., 2017).

In 1992, the term "M-type protein" was first used by Bessen and Fischetti. Little can be said about them (MRP and Enn protein), as there is still little study, only that they are possibly involved with the maintenance of lipoteicoic acid present on the surface of the bacterium and assisting in the formation of biofilms (FROST et al., 2018).

Studies have shown similarities between the types of *emm* in developed countries, as well as the difference in worldwide distribution. Among the strains studied best known for their ability to invade cells are M1, M3, M5, M6, M12, M18 and M49, with M18 being the least invasive, due to the size of its capsule, which interferes with the initial adhesion process. The M1 protein can bind to fibronectin and laminin with lower affinity than SfbI, but it can be efficient.

Serotype 28 is more isolated in urogenital infections, puerperal sepsis, and neonatal infections. This serotype has a region in its genome that carries virulence factors present in *Streptococcus agalactiae* or Group B *Streptococcus* (CHUA *et al*., 2017; KACHROO *et al,* 2019).

Recently, an inverse correlation has been evidenced between the diversity of strains and the development of a country. The more developed the country, the lower the diversity of SAG strains (SMEESTERS *et al*., 2024).

Exotoxins

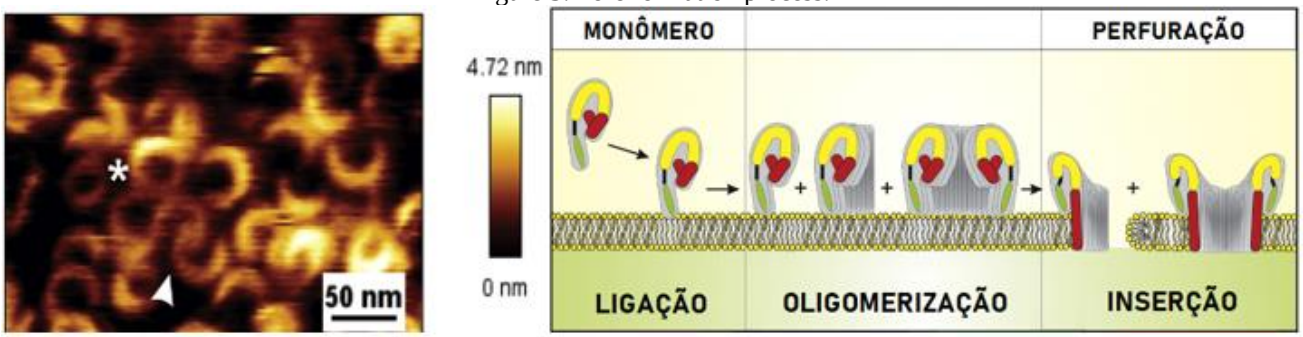
SAG secretes two well-known enzymes: Streptolysin O (EsO) and Streptolysin S (EsS). EsO is oxygen-labile, is able to induce pore formation, is antigenic, and is produced by all *S. pyogenes*. It also has the ability to lyse erythrocytes, in addition to being toxic to various cells, such as leukocytes, endothelial cells, fibroblasts, lysosomes, cardiomyocytes and even platelets. It is mainly responsible

for the formation of β-hemolysis, present around the colonies on sheep blood agar (PROCOP *et al*., 2017).

It exists in two active forms and their cleavage, during secretion, generates the active form of EsO. The lysis process occurs due to the interaction of EsO monomers with cholesterol present in the cell membrane (Figure 5), resulting in a change in the conformation of the molecule, forming a coaggregation of more monomers and resulting in the formation of complete and incomplete pores. Its interaction with polymorphonuclear cells stimulates its degranulation and lysis; It also inhibits the process of phagocytosis of macrophages; It has the ability to compromise the proliferation of lymphocytes and stimulates the production of cytokines. The titration of antibodies against EsO, also known as antistreptolysin O titers (ASLO), is used to evaluate recent infections, especially pharyngitis, because skin infections induce a low response of ASLO antibodies, due to the presence of cholesterol in the tissue, responsible for inactivating the antigen (FERRETI; STEVENS; FISCHETI, 2013; STEWART *et al*., 2014).

NADase is a cytotoxin secreted by SAG. Translocated to the host cell, it generates depletion of NAD+ present inside the cell. It is interconnected with EsO, and some lines of study suggest that it would interact physically: NADase would require the pore formation triggered by EsO to translocate, and NADase binding to the cell membrane would increase the cytotoxic and hemolytic activity of EsO (ZHU *et al*., 2017).

Figure 5: Pore formation process.

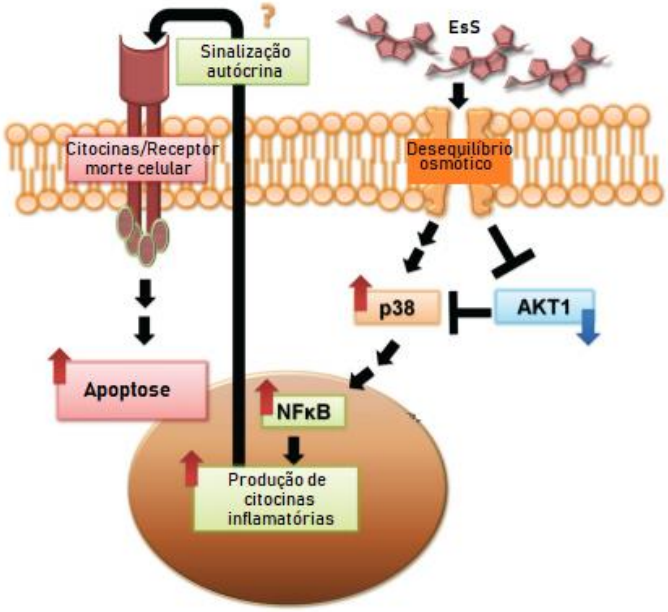


Fonte: Modificado de STEWART *et al*., 2014.

EsS is stable in the presence of oxygen; it can be found in intracellular form, or bound to the intracellular or cellular surface; it is not antigenic, but it is toxic to many cells, just like EsO. It is usually associated with carrier molecules such as albumin, α-lipoprotein, or ribonucleic acid (RNA). The level of EsS expression occurs in the final logarithmic phase, and the presence of iron is necessary for this increased production to occur. By interacting with phospholipids, EsS has its toxic effects, erythrocytes undergo swelling, accompanied by lysis, due to the disruption of the osmotic barrier and the extravasation of ions from the cell. Its presence in keratinocytes generates for a certain time the inactivity of Akt, a cytoprotective factor, consequently activating the cascade of the

p38 MAPK (Mitogenic Protein Kinases) pathway, the activation of this pathway promotes inflammatory signals through the nuclear factor kappa B (NF-κB) and triggers EsS-dependent programmed cell death in keratinocytes (Figure 6). Its hemolytic action can be inhibited by interaction with simple phospholipids and serum lipoproteins (CUENDA; ROUSSEAU, 2007; FLAHERTY *et al*., 2015; PROCOP *et al*., 2017).

Figure 6: Action of EsS on keratinocytes.



Source: Modified from FLAHERTY *et al*., 2015.

Streptococcal fumed exotoxins (SPE) stimulate increased T cell proliferation, generating exacerbated release of interleukins (IL) IL-1, IL-2 and IL-6, as well as tumor necrosis factor (TNF-α) and other cytokines. In this way, there is vasodilation and the movement of serum fluid and proteins present in intravascular and extravascular environments (CHO; FERNANDO, 2012; MCCORMICK; YARWOOD; SCHLIEVERT, 2001).

Three SPEs have been described, which are distinct from the immunological point of view; among them are Spe types A, B and C. The genes responsible for the expression of these exotoxins are *speA*, *speB* and *speC*. *SpeA* and *speC* are encoded in a lysogenic bacteriophage, which may or may not be present in some strains, while *speB* has a chromosomal origin and is present in all SAGs.

SpeB, a C5a peptidase, coupled to the cell surface, has the ability to cleave human immunoglobulins and proteins present in the individual's cells, forming small and active peptides, such as IL-1, histamine and other cytokines. In addition, it inactivates the C5a component of the complement pathway, impairing chemotaxis and polymorphonuclear recruitment.

SpeA and C induce fever and act as superantigens, i.e., they are molecules with a high capacity to induce T lymphocytes by binding to type 2 Major Histocompatibility Complex (MHC) molecules and releasing pro-inflammatory cytokines.

About eleven (11) superantigens have been described in SAG strains: SpeA, SpeC, SpeG, SpeH, SpeI, SpeJ, SpeK, SpeL, SpeM and the streptococcal superantigen (SSA). SpeB is considered a cysteine protease and not a superantigen (PROCOP *et al.*, 2017).

SpeB is also known to induce the process of Gasdermin A-dependent pyroptosis (GSDMA). GSDMA, belonging to the gasdermin family (GSMD), is present in large quantities in the skin, and plays an important role in the defense against invasive cutaneous infections by SAG, acting as a surveillance protein. A study conducted in mice showed that those infected with strains carrying SpeB had greater tissue damage, neutrophil infiltration, and lactate dehydrogenase (LDH) release. It was also observed in different studies that other bacteria are capable of causing skin infections, such as *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* No Clivam GSDMA (Deng et al., 2022; Zhao; Kirkby; Mann, 2022; Lark et al., 2022).

Other exotoxins secreted are DNAses A, B, C, or D enzymes, which are capable of degrading deoxyribonucleic acid (DNA) and DNA-based extracellular neutrophil traps (NETs). In addition, antibodies against B DNA can be used to check for previous SAG infection along with ASLO. The enzyme hyaluronidase, which degenerates hyaluronic acid, present in connective tissues, through the depolarization of the fundamental substance found in this tissue, allows the spread of the bacteria. The enzyme streptokinase, on the other hand, hydrolyzes fibrin clots, preventing the formation of fibrin barriers at the wound edge, allowing the lesion to spread; SpyCEP or chemokine streptococcal protease can inactivate interleukin 8 by catalyzing its C-terminal region, preventing neutrophil recruitment (FERRETI; STEVENS; FISCHETI, 2013; ZINGARETTI *et al.*, 2010).

The streptococcal histidine-rich glycoprotein interacting protein (sHIP) is secreted in high amounts by invasive strains when compared to non-invasive strains. It is able to bind to HRG (Histidine-rich glycoprotein) with high affinity. It is present in large quantities in plasma and has antimicrobial potential, and its action is blocked when this binding occurs (DIEHL *et al*., 2016).

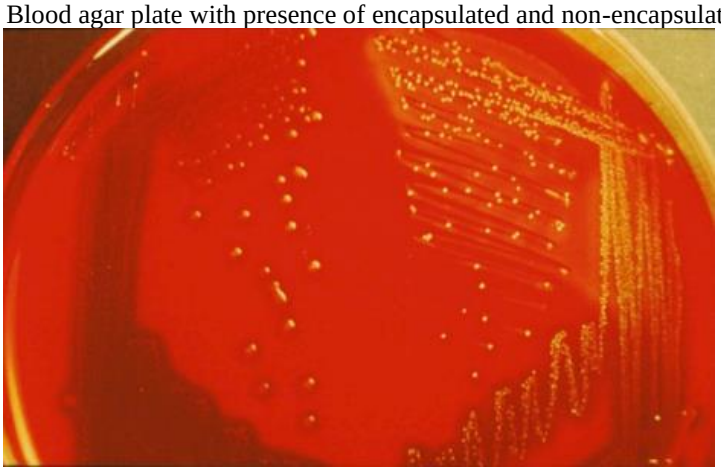
CAPSULE

The capsule is formed by hyaluronic acid, a polysaccharide, which has numerous functionalities, such as physical and chemical protection of the bacteria, including the interaction with heavy metals, superoxide radicals and other toxic elements, preventing its dehydration and also the action of the immune system, through evasion of the complement system and contributing to invasive infection of soft tissues, as observed in a study conducted on animals. It is not considered immunogenic, being indistinguishable from the material found in connective tissue, from a chemical point of view. Genes *Hasa*, *hasB* and *hasC* They are responsible for the expression of the enzymes that generate the polysaccharide. There is variation in the expression of this virulence among SAG strains, controlled by two gene products known as CrsS and CrsR, which enables the expression of

the gene to increase or decrease *has*. In studies *in vitro*, it was possible to observe the peak of capsular production during logarithmic growth, and its loss occurred during the stationary phase, probably due to the production of hyaluronidase in its final phase. Its participation in the adhesion process occurs due to its ability to adhere to epithelial cells, through the modulation of the interaction between the M protein and the surface molecules, acting as a ligand to the CD44 receptor present in the membrane of the epithelial cells (PROCOP *et al.*, 2017).

For some years, the presence of large, mucoid, translucent colonies on blood agar from newly collected samples of pharyngitis and invasive infections has been noted. As the incubation time passed, the colonies began to lose their mucoid characteristic and became small and opaque. In symptomatic samples, there was the presence of colonies with both types of characteristics (Figure 7). Studies indicated that mucoid and opaque characteristics were related to virulence in rats and resistance to phagocytosis by leukocytes in human blood. The presence of the mucoid colony represents the production of the hyaluronic acid capsule and the opaque aspect represents the production of the M protein (FERRETI; STEVENS; FISCHETI, 2013).

Figure 7: Blood agar plate with presence of encapsulated and non-encapsulated SAG.



Fonte: FERRETI; STEVENS; FISCHETI, 2013.

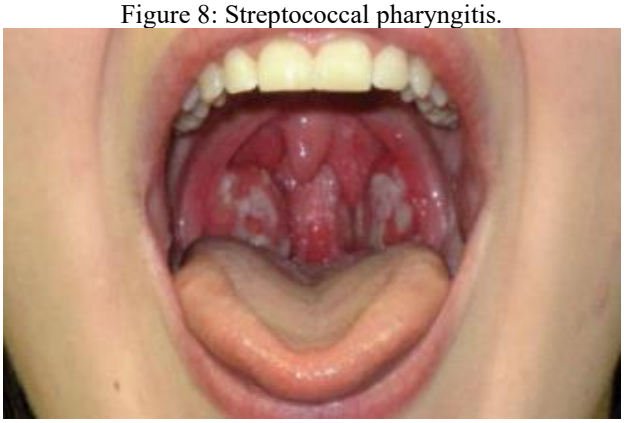
MAJOR STREPTOCOCCAL INFECTIONS

The degree of pathogenicity of a microorganism is called virulence, in which it depends on factors of the microorganism itself, the host and the interaction between them. The difference between pathogenic and non-pathogenic species is the expression of genes responsible for encoding factors that facilitate colonization, infection and disease severity, generating signs and symptoms and, thus, defining the disease. Virulence factors can be components of the bacterial structure, and can be an accidental virulence factor, as they can only be part of the composition of the bacterium, or products of the microorganism (FERRETI; STEVENS; FISCHETI, 2013).

Pharyngitis (Figure 8) is the most common form of manifestation, presenting edema of the tonsils, erythema, presence of pus, pain when swallowing, abdominal pain, and the presence of

vomiting is common. It is a rapid-course, insidious onset, arising two to four days after contact with the infected individual. It tends to be very symptomatic, and the symptoms depend on the virulence factors present in the strain. When there are no complications, it is self-limiting; Symptoms such as fever may disappear in three to five days and sore throat in seven to ten days without the use of treatments. However, the individual who presents symptoms usually seeks diagnosis and treatment, and, for these cases, the ideal is to perform the culture and antibiogram of the infection sample. Of these individuals, 10 to 15% may become asymptomatic carriers after treatment. Treatment can be done with penicillin G or V, or erythromycin for patients allergic to penicillin, as the bacterium is still sensitive to the drug. Two suppurative complications can occur due to streptococcal pharyngitis, rheumatic fever (RP), and acute glomerulonephritis (AGN). The first is more associated with previous pharyngitis, and the second can occur after skin infections or pharyngitis (FERRETI; STEVENS; FISCHETI, 2013; PROCOP *et al.*, 2017).

Figure 8: Streptococcal pharyngitis.



Fonte: FERRETI; STEVENS; FISCHETI, 2013.

Rheumatic fever (RF) is a systemic inflammatory disease, triggered by SAG infections, usually rich in M protein, cross-reactions occur with antigenic epitopes of the heart tissues and joints, its onset occurs after two to five weeks, after a streptococcal pharyngitis. The most relevant clinical manifestations are cardiac, involving the endocardium, myocardium, pericardium, mitral and aortic valves, which can be chronic and cause sequelae. The patient may have heart murmurs, heart failure accompanied by cardiac enlargement, cardiac arrests, and death. Painless and firm subcutaneous nodules tend to appear along with the manifestations of carditis, affecting more the bony regions of the hands and feet. There may also be manifestations of migratory arthritis with involvement of multiple joints and usually regresses spontaneously. The presence of chorea is also reported. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and a history of previous SAG infection are laboratory findings of RF. When RP is suspected, it is advisable to perform ASLO, anti-DNAse B, and anti-hyaluronidase. Therapy consists of the use of analgesics,

corticosteroids, and supportive therapy to prevent heart failure (PEREIRA; BEAUTIFUL; SILVA, 2017).

GNA comprises the presence of lesions in the renal glomeruli; it may occur due to the deposition of preformed immune complexes, and these contain SAG antigens and antibodies from the host or from the binding of streptococcal products (especially SPE B) to the glomerulus. It should be noted that streptococcal products interact with C3 and activate the alternative complement pathway or the mannose-binding lectin pathway directly, without the need for the antibody and damaging the glomeruli, presenting in a more prolonged and progressive manner (PROCOP *et al.*, 2017).

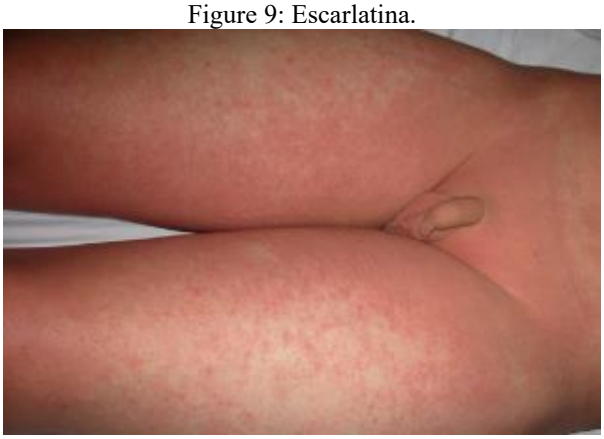
It can occur within ten days after strep throat, or three to six weeks after SAG skin infections. Its main clinical manifestations are anorexia, malaise, weakness, headache, edema, encephalopathy and hypertension. In AGN, there is a decrease in glomerular filtration, which may present oliguria or anuria, as well as an increase in serum creatinine and urea levels. Hematuria occurs due to the migration of red blood cells through the lesions formed in the glomeruli, decreased membrane permeability, causing proteinuria. Other laboratory findings are increased ESR, increased CRP, presence of anemia, decreased C3 of the complement system pathway. For diagnosis, it is necessary to perform a culture of the pharynx and skin lesions to evidence the presence of the bacterium and to observe the titration of anti-DNAse B antibodies against hyaluronidase, since ASLO is not reliable in skin infections (COUSER, 2016; SOARES, 2018).

In general, the main virulence factors involved in cutaneous infections are lipoteicoic acid, M protein, and fibronectin-ligand proteins such as F1, which are initially responsible for adhesion. SAG uses F1 to adhere to the surface of the skin, because this factor is amplified by the presence of oxygen and, if it is found in deeper tissues, the M protein will be the amplified factor responsible, due to the presence of carbon dioxide. EsO works by lysing erythrocytes, platelets, endothelial cells, fibroblasts, and cardiomyocytes. SAG has the ability to liquefy pus and propagate through the tissue, through DNAs, which degrade DNA and prevent NETs, in addition to interrupting the recruitment of plasma cells through the reduction of Interferon type 1 (IFN-1); hyaluronidase, responsible for degrading the hyaluronic acid found in connective tissue, allowing the spread of the bacteria; streptokinase, which dissolves clots by converting plasminogen to plasmin; and SPE B, which acts as a potent protease (FERRETI; STEVENS; FISCHETI, 2013; KELLER *et al.*, 2019).

Scarlet fever may appear as a complication of strep throat one to two days after the onset of pharyngitis. It occurs through the release of SAG toxins, which spread through the hematogenous route. Some studies point to erythrogenic toxin as the culprit, while others cite pyrogenic toxins. According to PROCOP *et al.* (2017), SPE A and SPE B are responsible for the manifestation of the rash. Erythema appears (Figure 9), which does not itch, and usually begins in the region of the

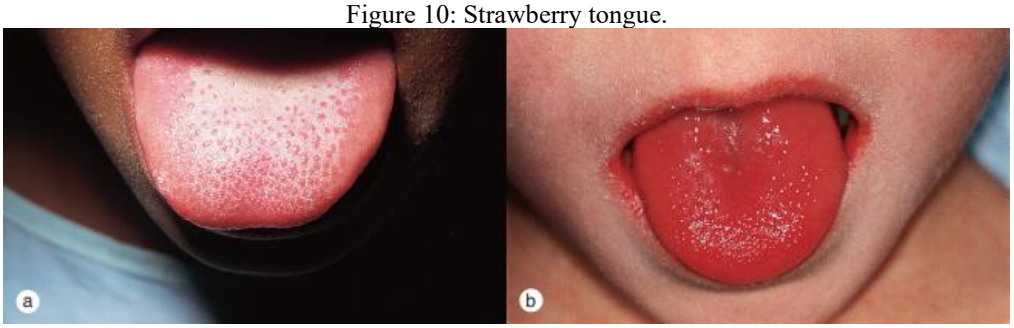
thorax and upper limbs, spreading downwards, not affecting the hands and feet. There is also the presence of a high fever that is difficult to subside. The following week, the tongue may be swollen and yellowish (Figure 10 A), later becoming red, which is called "strawberry tongue" (Figure 10 B). In the convalescence phase, the palms of the hands and soles of the feet peel off. (BONATTI; LEITE, 2017; FERRETI; STEVENS; FISCHETI, 2013;).

Figure 9: Escarlatina.



Fonte: Modified from COHEN; POWRDERLY; OPAL, 2017.

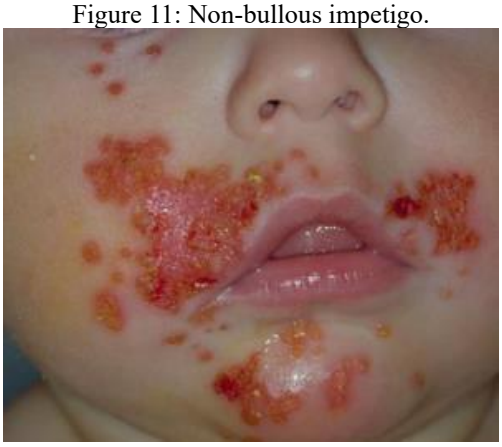
Figure 10: Strawberry tongue.



Fonte: Modified from COHEN, 2013.

Non-bullous impetigo (Figure 11), an infection in the keratinous superficial layer, is another common streptococcal infection, especially in children living in developing countries with poor hygiene and a tropical climate. Impetigo occurs mainly in exposed regions, usually on the face. The lesion is well localized, but usually appears in large numbers. Lymphadenitis may be present, but systemic symptoms are not present. Impetigo is highly contagious, which can occur by self-inoculation, when the individual is colonized by the bacteria and touches a skin wound with a contaminated hand, or by invasion of pre-existing fissures and lesions, and can affect any segment of the skin. There is the formation of papules that develop into vesicular lesions and, finally, into pustules, which rupture within 5 to 7 days, forming a thick, melliceric crust (FERRETI; STEVENS; FISCHETI, 2013; PROCOP *et al.,* 2017).

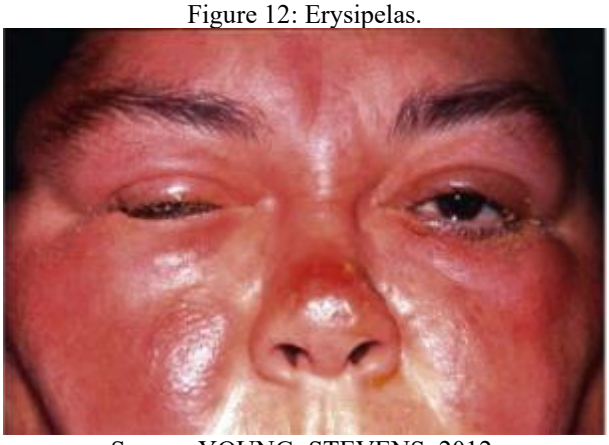
Figure 11: Non-bullous impetigo.



Fonte: CHICAGO UNIVERSITY, 2019.

Erysipelas (Figure 12) is an acute infection with involvement of the soft tissues, skin and lymphatic vessels. The lesions have a raised and well-defined border, with the presence of erythema and edema. It is most common in infants, young children, and the elderly. It usually occurs after a strep throat. Skin lesions start localized but spread to the periphery. Skin inflammation may be accompanied by fever and chills. When left untreated, it can progress to necrotizing fasciitis, with abscess formation and sepsis. Streptococcal cellulitis, on the other hand, is an acute inflammation of the skin and subcutaneous tissues; In general, they are the result of pre-existing injuries such as burns, wounds, and surgical incisions. Manifestations are systemic and include fever, chills, malaise, associated with lymphagitis and/or bacteremia. Unlike erysipelas, the lesions are not as well demarcated. Two causes that may predispose to streptococcal cellulitis are the use of illicit injectable drugs and individuals with lymph node occlusion or drainage problems, such as filariasis, or even women who have undergone mastectomy with axillary nodule removal (COHEN; POWRDERLY; OPAL, 2017; FERRETI; STEVENS; FISCHETI, 2013; JONG; STEVENS, 2012; PROCOP *et al.,* 2017).

Figure 12: Erysipelas.



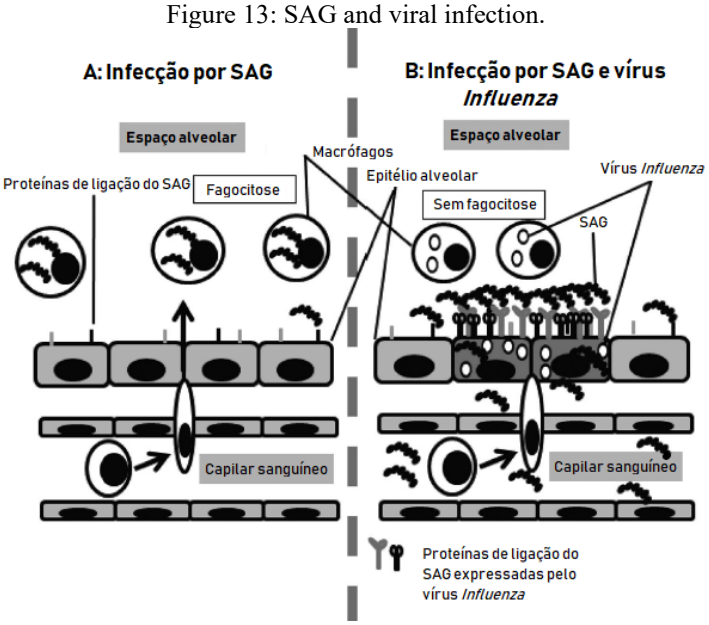
Source: YOUNG; STEVENS, 2012.

INVASIVE *S. PYOGENES INFECTIONS*

S. pyogenes has the ability to pass through physical barriers and cause several invasive infections (SARS) with high morbidity and mortality. The most common are bacteremia and cellulitis, and in some cases it can also cause necrotizing fasciitis, septic arthritis, pneumonia, meningitis, abscess, osteomyelitis, endocarditis, peritonitis, and other infections in focus. In the worst case, it can progress to toxic shock syndrome (TSS) (LINDEGREN *et al*., 2016; WALKER *et al*., 2014).

iSAGs were frequent before the introduction of antibiotic therapy, but their incidence decreased after the use of antimicrobials. However, cases have been reported during the last ten years, mainly in children (mostly lactating women) and healthy males in the age group of 20 to 50 years, due to the increased colonization of the population with invasive strains of SAG. They occur more frequently in winter, and may be related to the increase in viral respiratory infections and, consequently, make the host more vulnerable to the disease; The use of nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit neutrophil function increases the chances of TSS and, consequently, a more severe complication of SAG. The increased risk of chickenpox should be noted, as the skin and mucosa are not intact and the virus generates immunosuppression. In children, SAGIS was associated with varicella zoster infections, influenza virus (Figure 13), or streptococcal pharyngitis. (KOJIĆ *et al.*, 2015; NÓBREGA; GEORGE; BRITO, 2012).

Figure 13: SAG and viral infection.



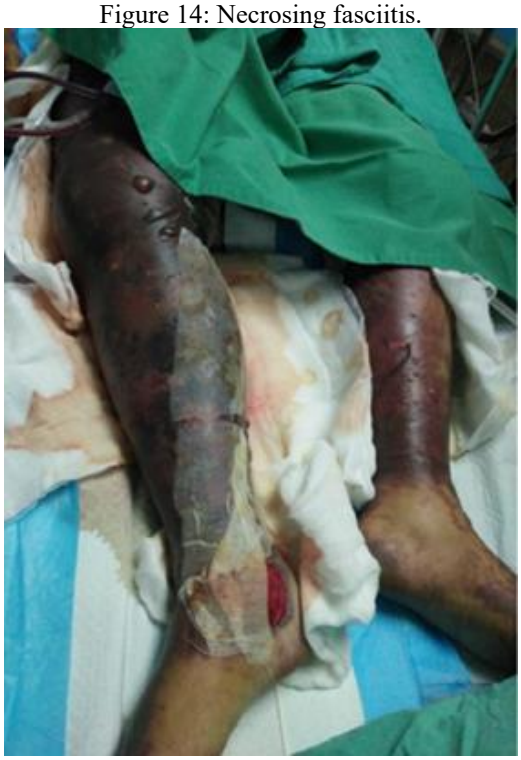
Source: Adapted from OKAMOTO; NAGASE, 2018.

Streptococcal necrotizing fasciitis (NEF) causes high morbidity and high mortality; it has a low incidence, but its progression is very rapid, requiring immediate intervention. Infection involves systemic toxicity, extensive tissue destruction, necrosis, and thrombosis of the fascia, muscle, and

dermis. The terms fasciitis, myositis, and cellulitis are related to the degree of tissue involvement. Age is a predictor of a low survival rate, and older patients tend to die more easily. Other important factors are the presence of immunocompromise (diabetes, cirrhosis, HIV, and AIDS) and the presence of TSS, mortality rises from 30% to 80, and can reach 100% in patients who present the associated condition (GRAHAM, 2019; KHAMNUAN *et al*., 2015).

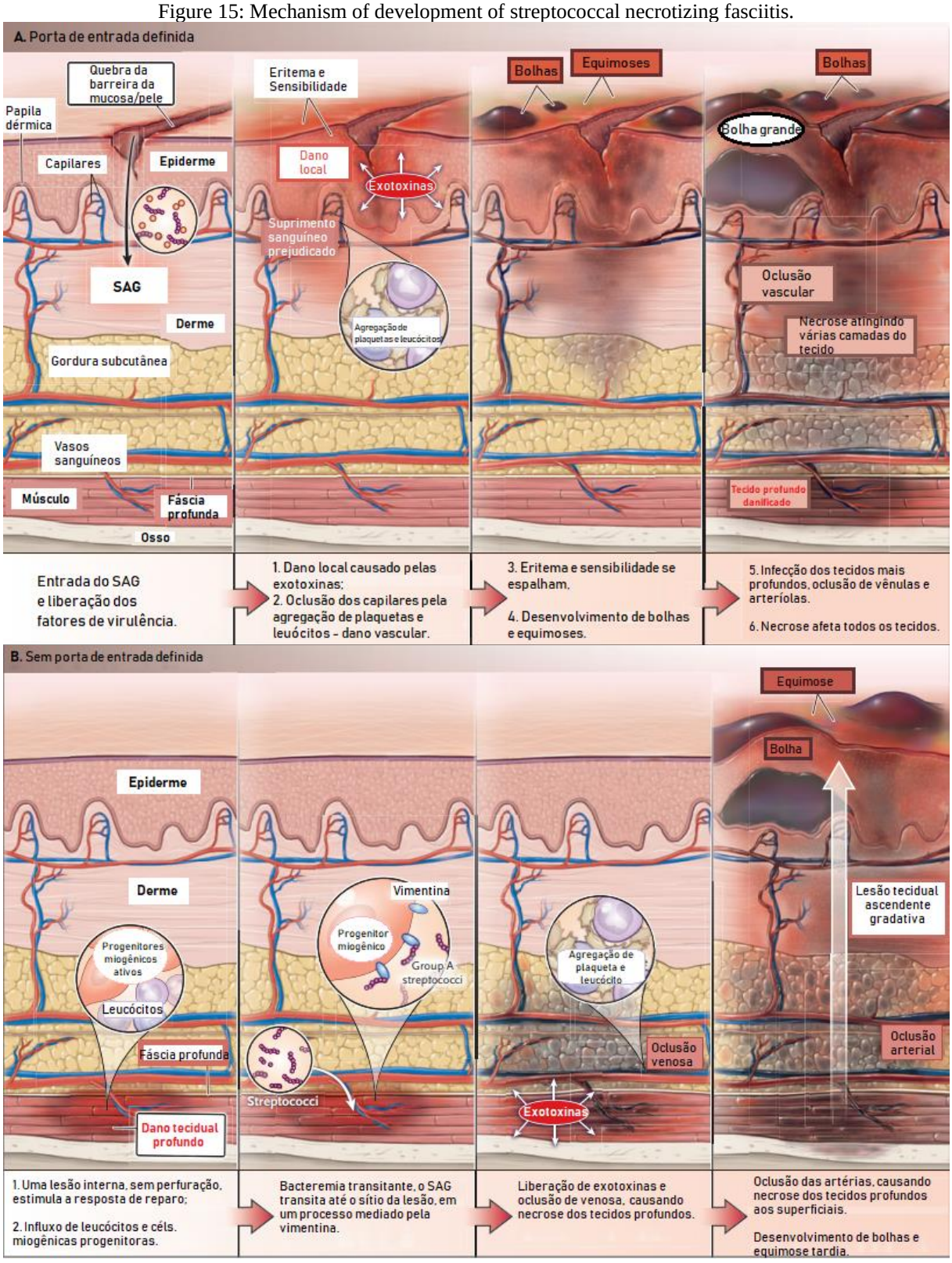
It is usually caused by SAG alone, but S. *aureus* may be present as this bacterium normally colonizes the skin. Cutaneous symptoms are usually not present initially, usually the patient complains of malaise, myalgia, diarrhea, and anorexia (Figure 15 B). The disease begins after a trauma (Figure 15 A) or a small lesion (injectable illicit drugs, insect bites, lacerations, chickenpox, streptococcal pharyngitis, contusions, gynecological procedures or after surgery), with direct inoculation, rapidly developing erythema, swelling, presence of grayish exudate, tenderness, absence of pus. After a few days, the site presents purple blisters, which may be hemorrhagic, which become gangrenous lesions (Figure 14). This lesion becomes more delimited, with separation of dead tissue from normal tissue. In fulminant cases, there are signs of hemodynamic instability, shock, and multiple organ failure. The presence of bacteremia is frequent and metastatic infections may occur. Surgical debridement is the most indicated action in case of suspicion of FNE, when there is the presence of severe disease and changes in the skin (STEVENS; BRYANT, 2017; KOJIĆ *et al.*, 2015).

Figure 14: Necrosing fasciitis.



Cast iron: CHUA *et al*., 2017.

Figure 15: Mechanism of development of streptococcal necrotizing fasciitis.



Source: Modified from STEVENS; BRYANT, 2017.

TSS is an invasive tissue infection resulting from the potent fumed exotoxins released by SAG. These are very antigenic (such as SpeA, SpeC and SpeB, SpeF and SSA), capable of mediating fever, tissue lesions and shock. Pyrogenic exotoxins bind to MHC class 2 and T lymphocyte receptors, stimulating proliferation, increasing the secretion of pro-inflammatory cytokines, leading

to shock and organ failure. Other factors associated with high mortality are the development of necrotizing fasciitis; late diagnosis, due to the lack of specific symptoms; delay in empirical treatment and surgical intervention; as well as the aggressiveness present during the evolution of the disease. TSS can be divided into three phases: the first phase consists of flu-like symptoms, with the presence of fever, myalgia, nausea, vomiting and diarrhea, lowering blood pressure. The second phase presents persistent fever, tachycardia, tachypnea, a lot of pain at the site of infection, and may develop necrotizing fasciitis and myonecrosis, when pain increases according to the severity of the infection and usually occurs after the development of hypotension. The last phase is represented by sudden organ failure and shock. Progression of the phases can happen in the period of 24 to 48 hours (AL-AJMI *et al*., 2012; CHUA *et al.*, 2017).

TSS caused by SAG is characterized by the presence of hypotension and two other signs, including renal damage, liver damage, coagulopathies, respiratory failure syndrome, generalized rash, or soft tissue necrosis (KOJIĆ *et al.*, 2015).

Poor circulation and thrombosis in the blood vessels present in infected tissues may be one of the reasons why antibiotic therapy is not sufficient after the development of more severe symptoms, so there is a need for surgical intervention, which includes debridement of the affected regions, and, in some cases, amputation of the infected limb (MCCORMICK; YARWOOD; SCHLIEVERT, 2001).

STRAINS PREVALENT IN INVASIVE INFECTIONS

Among the most prevalent virulent strains of *S. pyogenes* observed in studies are the presence of the genes *emm* type 1, 3, 49, 77 and 87; however, the M1 and M3 strains are more prevalent mainly in Europe and the United States. There are studies in several regions of the world that demonstrate the presence of differences between SAG strains in invasive infections in developed and developing countries. It was also found that there is no predominance of a single type. A study carried out in Japan showed that of 249 SAG, isolated during the years 2010 and 2012, 22 genotypes *emm* have been identified; Of these, the dominant one was also the *emm1* (60.6%), followed by *emm89* (12,0%), *emm12* (7,6%), *emm28* (5,2%), *EMM3* (2.4%) and *EMM90* (2,4%) (TERAO, 2012; WALKER et al., 2014; IKEBE et al., 2015; REGLINSKI; SRISKANDAN; TURNER, 2019).

According to Gherardi, Vitali, and Creti (2018), the gene *EMM1* continues to be prevalent in Europe and North America, followed by the *EMM28*, *EMM89*, *EMM3*, *EMM12*, *EMM4*and *emm6*, corresponding to 50-70% of the isolates analyzed.

The severity of the disease does not depend exclusively on the strain, there are other factors such as the virulence of the microorganism and the immune response of the host (LUCA-HARARI *et al*., 2009).

RESISTANCE PROFILE OF *STREPTOCOCCUS PYOGENES*

Regarding resistance, SAG has maintained a remarkable susceptibility to most antimicrobial agents, such as most β-lactams, since the 1940s. However, it is important to highlight that, in some isolated clinical cases, a tendency to develop some tolerances has been recorded, especially in relation to macrolides (CATTOIR, 2022).

Initially, with regard to β-lactams, studies conducted by Markowitz, Gerber and Kaplahn (1993) explained that, between 1953 and 1993, in the United States, the efficacy of β-lactams in the treatment of streptococcal pharyngitis proved to be ineffective in 12% of cases. In addition, Brook (2013), in an analysis covering the period from 1998 to 2013, found that failure in penicillin therapy increased by 40% in several regions of the world.

In this context, some of the important adaptations of *S. pyogenes* pointed out as the main factors that contribute to the aforementioned phenomenon and that possibly intensify the virulence of the bacterium are: i) the protection conferred *on S. pyogenes* by the presence of β-lactamase produced by bacteria of the oral microbiota; and ii) the association between *M. catarrhalis*, a bacterium commonly present in the upper respiratory tract (CEES M. *et al*, 2002), with *S. pyogenes,* which may favor its adherence to human epithelial cells, increasing their colonization capacity (PICHICHERO; CASEY, 2007; SCHAAR; UDDBÄCK; NORDSTRÖM; RIESBECK, 2014, *apud* CATTOIR, 2022).

Regarding macrolides, which constitute a class of drugs used in the treatment of bacterial infections, such as azithromycin, clarithromycin and erythromycin, (PATEL; HASHMI, 2023), significant resistance has been observed on the part of *S. pyogenes* (CATTOIR, 2022). In this vein, the first record of inefficacy of this antibiotic occurred in the United States in 1968 (SANDERS; FOSTER; SCOTT, 1968), and, subsequently, some European countries indicated rates of tolerance to erythromycin that reached figures above 20% (SEPPÄLÄ, *et al*., 1997; HAIL *et al.*, 2000; BINGEN, *et al.*, 2004; SILVA-COSTA; RAMIREZ; MELO-CRISTINO, 2005; CRETI, *et al*., 2007; RICHTER, *et al*., 2008, *apud* CATTOIR, 2022).

In addition, it is worth noting that the highest rate of resistance of *S. pyogenes* to macrolides was recorded in China, where, as documented by Silva Costa, Friães, Ramizes and Melo-Cristino (2015) reached a number between 80% and 95%. From this perspective, this is correlated with the significant consumption of this type of antimicrobial agent in the country, added to changes in the clonal composition of the bacterium (MONTES *et al*., 2014; SILVA-COSTA; FRIONS; RAMIREZ; MELO-CRISTINO, 2012, Silva-Costa *et al.*, 2015, *apud* CATTOIR, 2022).

Indeed, it is important to note that macrolide tolerance is entirely linked to virulence factors (CATTOIR, 2022). Such an association, according to Facinelle *et al*. (2001) and Haller *et al.* (2005),

is related to a significant increase in the expression of the prtF1 gene, often found in macrolide-resistant bacterial strains, which encodes the fibronectin binding protein F1.

In addition, new bacterial strains of *Streptococcus pyogenes* with decreased susceptibility to antimicrobials have been analyzed. In fact, recent studies have shown that a mutation in the penicillin-binding protein (PBP2x) gene reduces the bacteria's resistance to β-lactams, such as ampicillin, amoxicillin, and cefotaxime, drugs commonly used in the treatment of infections caused by GAS (COCHUA *et al.,* 2017; MUSSER *et al.,* 2020; VANNICE *et al*., 2020). In this sense, one of these studies used 7,025 genomic sequences of *S. pyogenes* of the emm1, emm28 and emm89 variants to identify mutations that alter amino acids in PBP2x and detected that "some of the strains with amino acid substitutions in PBP2x [...] showed reduced susceptibility to some β-lactam antibiotics, including penicillin G" (MUSSER *et al.,* 2020).

POST-COVID-19 SCENARIO

Following the SARS-CoV-2 virus pandemic, regions such as the United Kingdom, Spain, and France have witnessed an increase in the numbers of infections caused by *Streptococcus* group A. Accounting for a significant number of child deaths in the UK in early 2023 (LU; YU; YANG, 2023).

Firstly, as mentioned by Venkatesan (2022), the increase in the incidence of infections caused by SAG may be associated with the fact that during the COVID-19 pandemic, confinement restriction measures, combined with the frequent use of masks, caused the so-called immune deficit. This means that there was possibly a reduction in contact with bacteria of the *Streptococcus* A group, delaying the natural formation of the level of immunity against it, increasing the susceptibility of individuals and leading to a higher proportion of people susceptible to infection (BILLARD et al., 2022).

Second, according to *The Lancet Microbe* (2022), group A *Streptococcus* infection may be associated with co-infection with some seasonal viruses, such as influenza and respiratory syncytial virus (RSV). This is because infection with one pathogen possibly increases the chances of colonization by the other (HERRERA; HUBER; CHAUSSEE, 2016), in which case the virus can break through the respiratory barrier to allow SAG to enter. In fact, this is an aspect to consider, because with the relaxation of restrictive measures related to COVID, people have become less attentive to safety and personal hygiene practices, which has facilitated the spread of respiratory viruses, as well as group A *Streptococcus* (HODJAT et al., 2021).

REPORTS OF STRAINS IN BRAZIL

Streptococcus pyogenes is a bacterium that can colonize individuals without showing symptoms. Some studies have already been carried out in Brazil to investigate this occurrence and reveal the presence of asymptomatic carriers. As an example, a study conducted in 2003 in two public schools in Recife-PE identified the existence of the bacterium in 6 people in a sample of 753 students aged between 5 and 19 years (MACIEL *et al.,* 2003). Also, in another study conducted in the city of Araraquara-SP, in 1981, 160 swabs were collected from a group of 80 children, of which 19 of these had group A *Streptococcus* isolates (FRACALANZZA; BENCHETRIT, 1981).

From this point of view, the concern undoubtedly emerges when the bacterium transitions from an asymptomatic to a symptomatic state. In fact, it is important to mention that the most striking outbreak of *Streptococcus pyogenes* in Brazil occurred in 2011 in the country's capital, Brasília-DF, resulting in 26 deaths. This occurrence was extremely worrisome, being considered "the first record of this type of outbreak in South America" (FERNANDES et al., 2017).

In addition, in October 2023, the city of São João del Rei was the scene of another episode of concern due to three suspected cases of death of children associated with *Streptococcus pyogenes infection* (PASSOS, 2023). However, detailed information about the situation is still limited. Therefore, these events underscore the continued importance of epidemiological surveillance and the prompt response of health authorities in the face of possible outbreaks by the bacterium *S. pyogenes*.

EMERGING CHALLENGES: *STREPTOCOCCUS PYOGENES OUTBREAK* IN JAPAN IN 2024

Since the beginning of 2024, Japan has observed a worrying outbreak of *group A Streptococcus pyogenes* infections. With a mortality rate of 30%, the Japanese National Institute of Infectious Diseases (NIID) recorded a total of 422 occurrences of the disease between January 1 and March 17. This number is alarming, given that in just three months the country has already recorded almost half of the total cases of the previous year, which was 941. This rapid spread of the bacterium has resulted in red alerts being issued in 27 of Japan's 47 prefectures (MESMER; LEMAIGNEN, 2024).

Indeed, although the reasons behind the increase in *S. pyogenes* infections are not yet fully understood, the Japanese authorities link the recurrent epidemic to a change in the classification of COVID-19 from "category 2 of contagious diseases, which includes tuberculosis, to category 5, on an equal footing with seasonal influenza" (MESMER; LEMAIGNEN, 2024). This adjustment resulted in the weakening of sanitary protocols, compromising hygiene practices, which are extremely important to contain the spread of the bacterium (EFSTRATIOU; LAMAGNI, 2022).

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