Review article

Journal Of Clinical & Medical Images Case Reports

Open Access, Volume - 3

Current update of streptococcus pyogene infection or Group A Streptococcus

Behre Dari*

Worabe comprehensive specialized hospital, Worabe city, Ethiopia

Received Date : September 29, 2023
Accepted Date : November 10, 2023
Published Date : November 17, 2023
Archived : www.jcmimagescasereports.org

***Corresponding Author:** Behre Dari, Worabe comprehensive specialized hospital, Worabe city, Ethiopia.
E-mail: enudari30@gmail.com

Introduction

Background

S.pyogenes infections were first described in the 5th century by Hippocrates, who wrote of a scarlet fever epidemic [1]. During the late 19th century, Rosenbach classified this pathogen as Streptococcus pyogenes [2]. In 1919, Brown described the classic streptococcal hemolytic patterns on blood agar plates, including beta (complete) hemolytic, which is seen in S. pyogenes. Classification of streptococcal infections drastically changed in the early 1930's when Dr. Rebecca Lancefield, an American bacteriologist, pioneered a new technique of identifying and typing by streptococcal sero groups [3]. The Lancefield technique classifies hemolytic streptococci based on group-specific antigens in t. Using this method, Dr. Lancefield identified groups A through O.

Streptococcus pyogenes are gram-positive, non-motile, facultative anaerobic cocci [4]. Streptococci are considered one of the predominant flora which colonize the respiratory tract of human. One of these Streptococcus pyogenes is an obligate human pathogen [5]. It is a cause of major human morbidity and mortality worldwide. Streptococcal infections have been documented in all races, sexes and age groups. Group A streptococci (GAS) cause 18 million cases of severe diseases resulting in 517,000 deaths annually worldwide [5]. GAS causes a variety of human diseases, such as mild superficial infections (e.g., impetigo and pharyngitis), invasive diseases (e.g., necrotizing fasciitis and cellulitis), toxigenic diseases (e.g., toxic shock syndrome and scarlet fever), and post infectious autoimmune diseases (e.g., rheumatic fever, rheumatic heart disease, and post streptococcal glomerulonephritis) [6].

The primary infection sites of S. pyogenes are the upper respiratory mucosal epithelium and the superficial layers of the epidermis 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, as well as invasive systemic infections such as Necrotizing Fasciitis (NF) and streptococcal toxic shock syndrome (STSS).Additionally, glomerulonephritis and rheumatic fever are post-streptococcal non-suppurative immune sequelae. In humans, non invasive GAS infections occur most frequently in various age group [7]. The incidence of invasive GAS infections has been increasing globally since the mid-1980s and is associated with high morbidity and mortality. The incidence and severity of the infections are highest in winter. A systematic review of the Medline estimated that 18 million existing cases of severe GAS diseases, with 1.78 million new cases occurring globally each year, lead to 500,000 deaths yearly due to severe acute rheumatic fever, rheumatic heart disease, post-streptococcal glomerulonephritis, and invasive infections [8].

A variety of virulence factors are associated with the severity of GAS infection including streptolysin O and S (hemolytic) [9]. streptokinase, streptodornase, M protein and its related protein, hyaluronic acid capsule, hyaluronidase, the cysteine protease SpeB, superantigen proteins (SAgs), and several phage-encoded exotoxins [10]. M-like protein is a term applied to the surface protein that resembles the M protein in its structure . Virulence factors are equally distributed within S. pyogenes; some are encoded by chromosomes, while others depend on the presence of mobile genetic elements. Confirmation of their presence or absence is considered as a simple clinical diagnosis method [11].

M protein is the most analyzed virulence factor, which can be used in the serotype classification of S. pyogenes. SAgs contribute to GAS pathogenicity based on their immune stimulatory activity. SAgs gene distribution has been used as a method for the detection of genomic heterogeneity, the correlation between gene contents, and the determination of clinical manifestation [12]. GAS possesses various cell-surface components such as hyaluronic acid, M and T proteins, and proteins binding to host components such as Fibronectin (FN), laminin, immunoglobulins (Igs), lipoteichoic acid, and peptidoglycan, which may contribute to pathogenesis [13].

Additionally, GAS produces extracellular enzymes including streptokinase (Ska), proteinases, hyaluronidase, nucleases, and neuraminidase, and toxins such as streptolysins, pyrogenic serotoxins (Spe), and streptococcal super antigens, some of which induce fever and shock [7]. Following adherence of GAS to human host-cell surfaces, these factors may function in invading host tissues/organs, resulting in exacerbation of the

Citation: Behre Dari. Current update of streptococcus pyogene infection or Group A Streptococcus. J Clin Med Img Case Rep. 2023; 3(6): 1583.

disease manifestations. Some of these extracellular products induce the production of specific antibodies in hosts, which protect them from further infection by the same GAS strain [14].

General characteristics

GAS comprises of Lancefield group A Streptococci. It is a Gram positive coccoid-shaped bacterium that grows in chains bacterium, aero tolerant, extracellular bacterium, consisting of non-motile and non-sporing cocci and GAS produces small white to grey colonies with a clear zone of β-hemolysis on blood agar [15]. Rapidly growing gram-positive cocci arranged in chains and it has group-specific carbohydrate (A antigen) and type-specific proteins (M protein) in cell wall) [16].

Toxins and enzymes

S.pyogenes is generally an extracellular pathogen that uses its secreted products, the streptococcal extracellular products, to mediate bacterial invasion of the host. The in vasins and exotoxins interact with host blood and tissue components in ways that kill host cells and result in damaging inflammatory responses [17]. Of the in vasins, streptolysin O and S are leucocidins, meaning they destroy phagocytes. Hyaluronidase digests host connective tissue, and the streptodornases degrade DNA [18]. Hyaluronidase also digests the bacterial capsule, made of hyaluronic acid, which allows the bacterial proteins involved in the internalization process to be readily accessible for interaction with host cell proteins. The streptokinases are involved in fibrin lysis. Fibrin is a critical protein involved in blood clotting, so streptokinase activity can lead to hemorrhaging. Taken together, streptococcal invasins lyse host cells, including blood and immune cells, and allow S.pyogenes to spread among host tissues by dissolving fibrin and other intercellular substances [19].

The exotoxins include the three SPEs, types A, B, and C, which act as super antigens. These SPEs stimulate T cells by binding to the MHC class II molecules. The T cells are thus activated, and release a large amount of cytokines, triggering an inflammatory cascade [20]. The streptococcal pyrogenic exotoxins (Spe), are produced by lysogenic strains of streptococci. Four immunologically distinct heat-labile toxins (Spe A, SpeB, Spe C, have been described in S. pyogenes [21]. The toxins act as super antigens, interacting with both macrophages and helper T cells, with the enhanced release of pro inflammatory cytokines. This family of exotoxins is believed responsible for many of the clinical manifestations of severe streptococcal diseases, including necrotizing fasciitis and streptococcal toxic shock syndrome, as well as the rash observed in patients with scarlet fever. The Streptococcus pyogenes are again produce cytolysin toxin known as Streptolysin O) SLO) and Streptolysin S (SLS) [22].

SLO is a potent cytolysin which has a toxic effect on a variety of cells and has an antigenic and produced by almost all Group A beta hemolytic streptococci [23]. SLS is one of the most potent cytotoxins capable of lysing leukocyte, platelets and subcellular organelles. SLS responsible for Beta- hemolysis characters on blood agar medium .SLS is an oxygen-stable, none immunogenic, cell-bound hemolysin that can lyse erythrocytes, leukocytes, and platelets. SLO is an oxygen-labile hemolysin capable of lysing erythrocytes, leukocytes, platelets, and cultured cells. Enzymes produced by Streptococcus pyogenes streptokinase (A and B) and deoxyribonucleases (DNases A to D) [21]. Streptokinase (A and B) these enzymes mediate the cleavage of plasminogen, releasing the protease plasmin that, in turn, cleaves fibrin and fibrinogen. Thus these enzymes can lyse blood clots and fibrin deposits and facilitate the rapid spread of S. pyogenes in infected tissues. Antibodies directed against these enzymes (anti-streptokinase antibodies) are a useful marker for infection. (DNases A to D) these enzymes are not cytolytic but can depolymerize free deoxyribonucleic acid (DNA) present in pus. This process reduces the viscosity of the abscess material and facilitates spread of the organisms. Antibodies developed against DNase B are an important marker of S. pyogenes infections (anti- DNase B test), particularly for patients with cutaneous infections, because they fail to make antibodies against streptolysin O [24].

Disease

Group A streptococcus pyogene is the causative agent in a wide range of (GAS) infections. GAS-associated diseases are generally divided into three categories. Non-invasive diseases are those in which the infection does not spread to the surrounding healthy tissue [25]. The most well-known of the non-invasive diseases include scarlet fever, pyoderma (impetigo), and pharyngitis (also known as strep throat) and. GAS is the most common bacterial cause of pharyngitis. The clinical symptoms of GAS pharyngitis include a sudden-onset fever accompanying a sore throat, which frequently manifests physically as inflammation of the pharynx and tonsils, often with patchy exudates and cervical lymph node adenopathy. Other

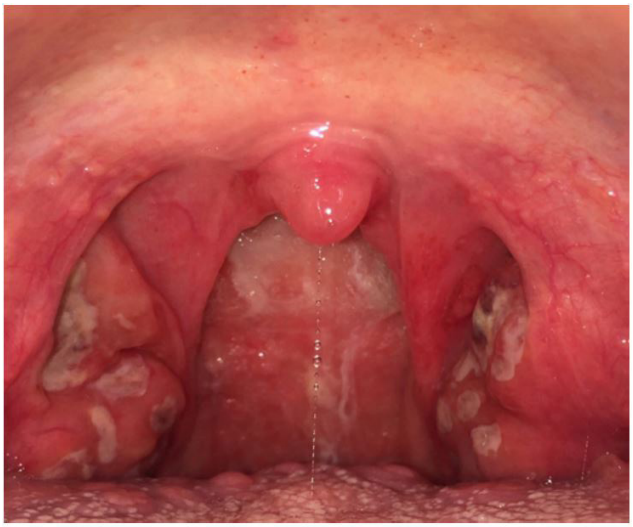

Figure 1: *Tonsillar exudate and palatal petechiae in a patient with group A Streptococcus pharyngitis (Adopte as is) [26].*

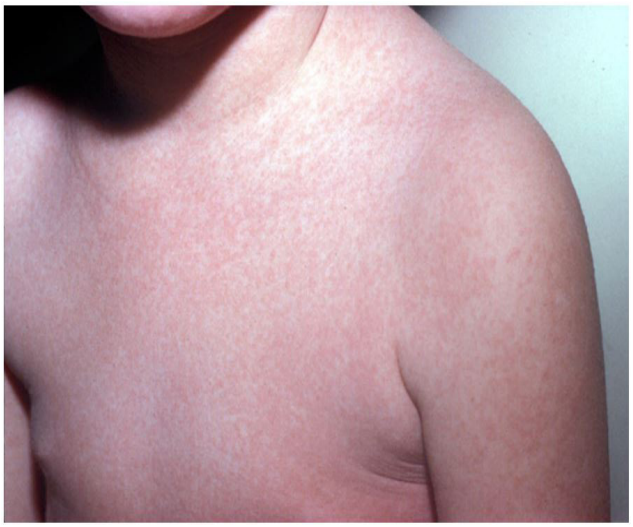

Figure 2: *Diffuse erythematous sandpaper rash of scarlet fever (Adopte as is) [26].*

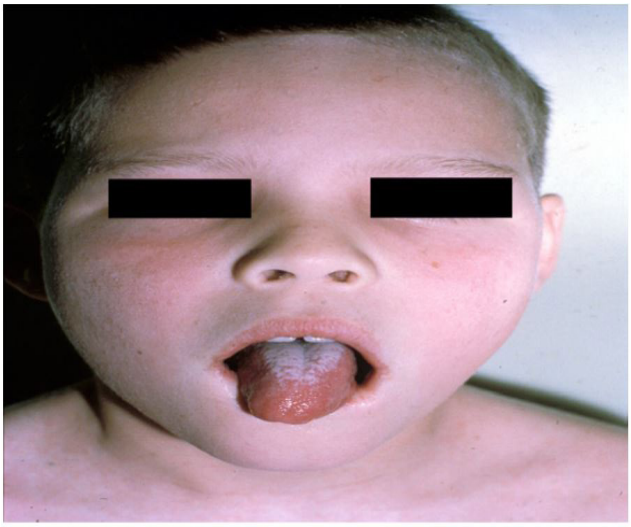

Figure 3: *Circumoral pallor and strawberry tongue in a patient with scarlet fever (Adopte as is) [26].*

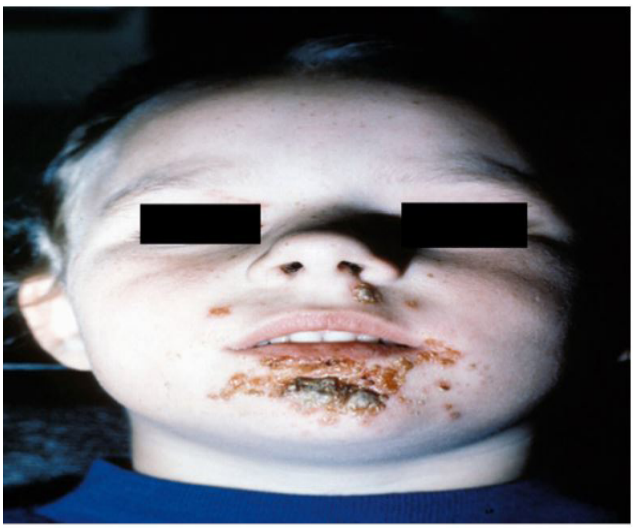

Figure 4: *Impetigo with characteristic honey-colored exudate and thick crusts. (Adopte as is) [26].*

common symptoms include malaise, fever, headache, nausea, abdominal pain, and vomiting [26].

Occasionally, GAS pharyngitis is accompanied by scarlet fever, which is thought to result from pharyngeal infection with a GAS strain that secretes bacteriophage-encoded streptococcal pyrogenic exotoxins, most notably SpeA. Also known as scar Latina, scarlet fever manifests as a deep red, finely popular, erythematous rash; "strawberry tongue"; and exudative pharyngitis.

Impetigo is a contagious infection of the skin that manifests as pustules that gradually enlarge and rupture, forming thick, honey-colored scabs. The disease is spread through direct skin contact and most commonly affects children living in tropical and subtropical climates in areas with poor hygiene and crowded living conditions. The Impetigo is an extremely common superficial infection of the skin described either as bullous or nebulous [26].

Conversely, the invasive diseases are those that do invade the healthy tissue. Therefore, the invasive and post-infectious diseases cause the most morbidity and mortality some of the most well-known invasive infections are Streptococcal Toxic Shock Syndrome (STSS), meningitis, pneumonia, and necrotizing fasciitis. STSS consists of infection with GAS accompanied by hypotension and evidence of multiorgan failure. STSS is usually preceded by skin or soft tissue infections with GAS, but can be seen with GAS infection at any site. In STSS, super antigen toxins trigger massive T-cell proliferation and a subsequent "cytokine storm. Type II Acute Necrotizing Fasciitis (ANF) is an aggressive, rapidly progressing deep tissue infection caused by GAS, usually alone [27].

Acute Rheumatic Fever (ARF) is a systemic disorder that can follow untreated GAS pharyngeal infection. The major manifestations are inflammation of the joints (arthritis) (60 to 80% of cases), inflammation of the heart (carditis) (30 to 45% of cases), and/or neurological symptoms (e.g., Sydenham chorea) (10% of cases). Less common manifestations of the skin include erythema marginatum (2% of cases). Rheumatic fever is a major cause of acquired heart disease in children [28].

Virulence factors

S.pyogenes ability to colonize and rapidly multiply and spread within host tissues while simultaneously evading phagocytosis and confusing the immune system [29]. This organism accomplishes all of these things through use of its virulence factors. The different types of GAS virulence factors include those involved in anti-phagocytosis, adherence to epithelial cells, internalization, invasion/spread throughout host tissues, and systemic toxicity [30]. The bacteria multiply in host tissues, where they secrete toxins and enzymes that contribute to GAS pathogenicity. For example, streptokinase dissolves blood products, and streptolysins O and S are toxic to a variety of host cells, including heart and immune cells [31].

The virulence factors are best described by their contribution to GAS pathogenesis. The M protein, Protein F (a fibronectin-binding protein), and Lipoteichoic Acid (LTA) are all involved in adherence to epithelial cells [32]. The hyaluronic acid capsule functions as an immunological disguise to the host immune system and inhibits phagocytosis [33]. The M protein inhibits

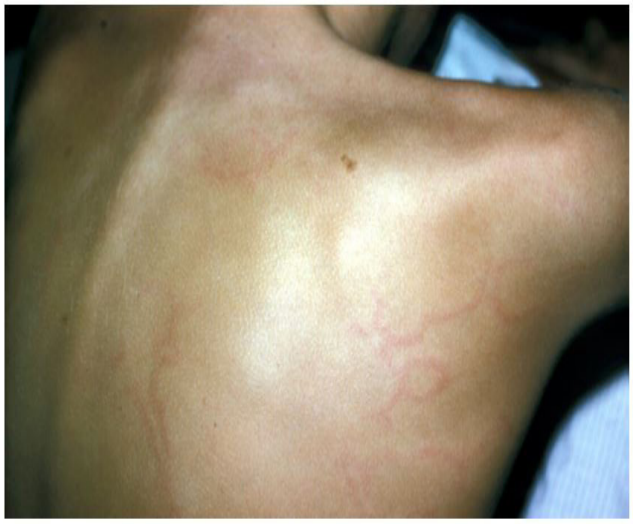

Figure 5: *Erythema marginatum in a patient with acute rheumatic fever. (Adopte as is) [26].*

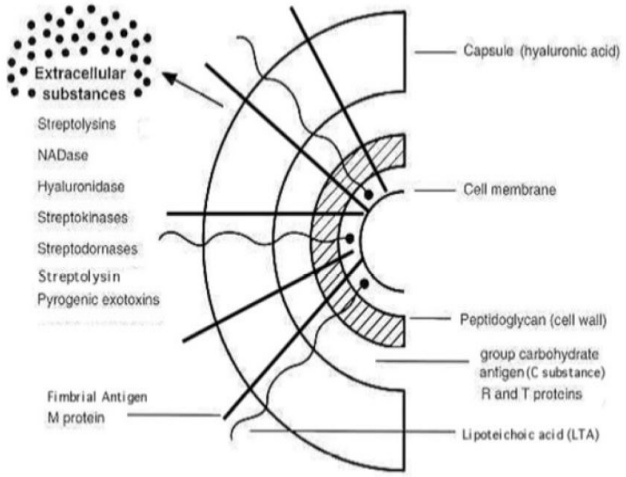

Figure 6: *Cell surface structure of GAS and secreted products involved in Virulence(Adopte as is) [25].*

phagocytosis, as well. The in vasins, such as streptokinase, hyaluronidase, streptodornase, and the streptolysins, all work to facilitate bacterial spread through the host. Lastly, actions of the SPEs result in systemic toxicity [34].

Epidemiology

S.pyogenes causes infections of the skin and pharynx of humans, and is actually part of the normal bacterial flora for 5-15% of the population. Thus, as normal flora, S.pyogenes most frequently infects people when their immune defenses are compromised, or when the bacteria penetrate the body's defenses [35]. Also, this pathogen is spread from person to person generally through direct contact with wounds or skin sores or with mucus from the nose or throat of an infected individual [36]. The bacterial strains that cause skin infections are spread only via skin contact, whereas the strains that cause respiratory infections are spread via respiratory droplets or mucus [37]. While immune compromised people are at a higher risk for bacterial infection, S.pyogenes is otherwise undiscriminating.

Even healthy individuals are at risk, and age, gender, race, and ethnicity do not influence susceptibility. However, the prevalence of infection is higher in children, particularly for the non-invasive diseases like pharyngitis. This prevalence is probably due to the children's lower immunity and higher exposure rate in sites [38]. A five-state laboratory and population-based surveillance study conducted from 1995 to 1999 showed that invasive GAS infections occurred at a rate of 3.6 per 100,000 people in the population annually in the United States [39]. This accounted for 9600-9700 cases and 1100-1300 deaths. Case-fatality ratios were related to the type of infection. Individuals infected with pneumonia, necrotizing fasciitis, and central nervous system infections, slightly over 20% did not survive. Of the cases of streptococcal toxic shock syndrome, approximately 44.5% were fatal [40].

In the United States, upper respiratory infections are most common in northern regions, particularly during the winter and early spring. Conversely, skin infections are most common during the summer or in climates with year-round warmth. In this weather, the skin is most exposed and abrasions or insect bites are more likely to happen, thus providing a portal of entry for skin-residing bacteria [41]. Internationally, GAS infections are seen worldwide, with the prevalence of streptococcal pyoderma (skin infection) being highest in tropical regions. Other than this, there are no geographic barriers that guard against S.pyogenes [42].

Burden of GAS A 2005 WHO study estimated that at least 663,000 cases of invasive GAS disease occur each year, resulting in 163,000 deaths. Similar rates of disease are observed in a number of developed countries (2 to 3 per 100,000), which corresponds to approximately 10,000 cases per year in the United States. GAS diseases, the rates of invasive GAS disease are higher in less developed regions, with the highest rates being observed in indigenous populations in Australia (13.2 to 82.5 per 100,000 , Africa (13.0 per 100,000 , and the Pacific Islands (9.9 to 11.6 per 100,000) [21]. In a 2005 study, the highest rates of ARF were found in sub-Saharan Africa (5.7 cases per 1,000), in the Pacific Islander and indigenous minority populations of Australia and New Zealand (3.5 cases per 1,000), and south central Asia (United Nations regional classification) (2.2 cases per 1,000).

Due to the high rates of impetigo and low rates of GAS pharyngitis in the indigenous Australian population, it has been proposed that ARF can also occur as a complication of impetigo, although this has not been confirmed. In Ethiopia about 60% of all cases of heart morbidity among children are of rheumatic origin [18]. Globally, there are over 470,000 annual cases, resulting in approximately 5,000 deaths worldwide. APSGN rates are highest in children in less developed countries, with incidence rates as high as 94.3/1,000 being reported in the Northern Territory of Australia. Unlike ARF, APSGN tends to occur in outbreaks associated with "nephrogenic" strains of GAS and contributing risk factors such as crowding, poor hygiene, and poverty. With proper supportive care, long-term renal damage as a result of APSGN is rare. Incidence of pharyngitis is highest in places of crowding, such as schools and military training facilities. Approximately 15% of schoolchildren and 4 to 10% of adults may suffer an episode of GAS pharyngitis each year in developed countries., whereas incidence rates in developing countries are 5 to 10 times higher [19].

Transmition

The nasopharyngeal mucosa and skin are the principal sites of GAS asymptomatic colonization. These sites are also the most common sources of infections such as pharyngitis and impetigo. These tissue sites represent the primary reservoirs responsible for the maintenance and transmission of GAS to a new host. The characterized ability of GAS to overcome the innate and acquired immune mechanisms present in saliva allows the bacterium to remain viable for long periods , permitting transmission from infected persons or asymptomatic carriers via respiratory droplets [34].

Similarly, the ability of GAS to colonize and persist in skin tissue permits transmission through person-to-person skin contact. Therefore, family members or close contacts of primary cases are at greater risk than the general population for subsequent infection. Transmission of GAS infection is usually through occurs through inhalation of large droplets from infected patients and direct skin-to-skin contact. with droplets of saliva, nasal secretions or infected lesions of people with the condition [43].

Immunity

S.pyogenes is typically an exogenous secondary invader, following another infection or a disturbance in the normal bacterial flora. Normally, the skin is the first line of defence, providing an effective barrier against streptococcal invasion. Once the pathogen is inside its human host, the second line of defence is the host's phagocytic system. Pathogens can be opsonized by activation of the complement pathway and by anti-streptococcal antibodies present in the serum. In immune individuals, the third line of defence is the IgG antibodies that react with the M protein to promote phagocytosis, killing the bacterium. This M protein-reactive antibody-mediated immune response is the main mechanism by which GAS infections are naturally terminated. The only protective immunity resulting from GAS infections is from the host development of type-specific antibodies to the M protein of the fimbriae [26].

Pathogenesis

Host-pathogen interactions occur due to binding of surface streptococcal ligands to specific receptors on host cells. Attachment of group a streptococci to pharyngeal or dermal epithelial cells is the most important initial step in colonization of the host. Without strong adherence mechanisms, group A streptococci could not attach to host tissues and would be removed by mucous and salivary fluid flow mechanisms and exfoliation of the epithelium [44]. In skin attachment and colonization by group A streptococci, a site of previous damage may be important in overcoming the dermal barrier. Specific adhesion allows competition between normal flora and group A streptococci for tissue sites where normal flora reside.

The virulence of group A streptococci is determined by the ability of the bacteria to avoid opsonization and phagocytosis, adhere to and invade host cells, and produce a variety of toxins and enzymes. S. pyogenes has multiple mechanisms for avoiding opsonization and phagocytosis [45]. The hyaluronic acid capsule is a poor immunogenic and interferes with phagocytosis. The M proteins also interfere with phagocytosis by blocking the binding of the complement component C3b, an important mediator of phagocytosis. C3b may also be degraded by factor H, which binds to the cell surface of the M protein. M-like proteins resemble M proteins in structure and are under the same regulatory control.

These proteins interfere with phagocytosis by binding either the Fc fragment of antibodies or fibronectin, which blocks activation of complement by the alternate pathway and reduces the amount of bound C3b. Finally, all strains of S. pyogenes have C5a peptidase on their surface. This serine protease inactivates C5a, a chemo attractant of neutrophils and mononuclear phagocytes, and protects the bacteria from early clearance from infected tissues [46]. More than 10 different bacterial antigens have been demonstrated to mediate adherence to host cells, with lipoteichoic acid, M proteins, and F protein the most important. The initial adherence is a weak interaction between lipoteichoic acid and fatty acid binding sites on fibronectin and epithelial cells. Subsequent adherence involves M protein, F protein, and other adhesions that interact with specific host cell receptors. S. pyogenes can invade into epithelial cells, a process that is mediated by M protein and F protein and other bacterial antigens [47].

Laboratory Diagnosis

Today, laboratory diagnosis of group A streptococcal infections still largely relies on culturing bacteria from clinical specimens. To detect streptococci in clinical samples (and especially S. pyogenes), the material is most often cultured on blood agar plates, which facilitates an easy preliminary screen for β-hemolytic colonies. Subsequent confirmation of suspicious colonies as S. pyogenes can be achieved by several easy, rapidly performed laboratory tests that are still widely applied in clinical microbiology [37].

Specimen

- Throat Swab, blood.
- Puss.
- Sputum, spinal fluid.

Culturing techniques

Bacterial Throat culture is considered the gold standard for the diagnosis of GAS due to high sensitivity and with 90% to 95% specificity. To isolate GAS (Streptococcus pyogenes), throat swab samples are cultured on sheep blood agar plates and incubated for 18 to 24 h at 37°C. Plating the organism on blood agar results in streptococcal colonies that are grayish-white, and approximately 0.5-1 mm in diameter. There is also a clear pattern of beta-hemolysis, or a complete breakdown and clearing of the cells surrounding the Streptococcus colonies. Most other streptococcal strains do not cause beta-hemolysis [48].

Morphology of culture

To identify 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 colure and have a diameter of > 0.5 mm, and are surrounded by a

Clinical feature/manifestation

Table 1: *Clinical Sign and symptoms of the major group A Streptococcus infections.*

S.No	Disease Type	Disease Signs and/or symptoms
1	**Superficial/ None Invasive GAS infection**	
	Pharyngitis	Sore throat, malaise, fever
	Scarlet fever	pharyngitis Deep red rash, "strawberry tongue," exudative
	Impetigo	Skin pustules that mature into honey-colored Scabs
2	**Post Streptococcal Infection**	
	Acute rheumatic fever	Polyarthritis, carditis, rapid and jerky movements, rash, subcutaneous nodules
	Rheumatic heart disease	Mitral and/or aortic regurgitation with possible stenosis over time
	Acute post streptococcal glomerulonephritis	Edema, hypertension, urinary sediment abnormalities, complement deficiency
3	**Invasive GAS infection**	
	Streptococcal toxic shock syndrome	High fever, rapid-onset hypotension, accelerated multisystem failure
	Necrotizing fasciitis	Fever, exquisitely tender skin lesions, vomiting, diarrhea, toxemia, tissue destruction
	Bacteremia	High fever, nausea, vomiting
	Puerperal sepsis	Fever, chills, abdominal pain in a pregnant or early postpartum woman
	Cellulites	Acute, tender, erythematous, and swollen area of skin

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 [49].

Biochemical identification tests

Catalase Test

To differentiate members of the Staphylococcus, which are catalase positive from Streptococcus species, which are catalase negative after the detection of β-hemolytic colonies displaying a typical S. pyogenes morphology, catalase testing confirms that the isolates represent streptococci.

Pyrrolidonyl aminopeptidase test

Measures hydrolysis L-pyrrolindonyl-β- naphthylamide, releasing β naphthylamine, which, in the presence of p-dimethylaminocinnamaldehyde, forms a red compound. The PYR test is a rapid colorimetric method often used to distinguish S. pyogenes from other β-hemolytic streptococci and tests for the presence of the enzyme pyrrolidonyl aminopeptidase. This enzyme hydrolyzes L-pyrrolidonyl-β-naphthylamide (PYR) to β-naphthylamide, which produces a red colour when a cinnamaldehyde reagent is added [50].

Antibiotic resistance testing

Penicillin remains the drug of choice for the empirical treatment of S. pyogenes infections, [49].

Bacitracin susceptibility test

Streptococcus pyogenes can be differentiated 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. To perform a bacitracin susceptibility test, it is important to make a subculture of the strain to be tested on a Sheep Blood Agar plate (SBA) [98].

Serologic tests

Antigen detection of S. pyogenes (RAD Test)

Rapid diagnostics developed secondary to the long TAT of standard culture methods and led to the development of rapid antigen detection tests (RADTs). The RADTs were designed to be used either within the clinical microbiology laboratory [16].

Latex agglutination assays

Latex agglutination was one of the first rapid antigen detection tests used in the diagnosis of group A streptococcal pharyngitis . With TATs as short as 10 min, the test allowed rapid screening of pharyngeal swab samples for the presence of GAS carbohydrate antigen. The presence of agglutination, graded 1_ through 4_, was interpreted as a clinically significant infection with GAS [16].

Lateral Flow Immunoassays (LFIAs)

Lateral flow immunoassays (LFIAs) have been available for testing for the presence of GAS carbohydrate antigen. Similar to latex agglutination LFIAs are point-of-care tests that are run in two steps, an extraction step and a testing step. The overall endpoint of the test is easier to interpret than is the case for latex agglutination. If the antigen is present, a colored line will be present within the positive testing window [16].

Optical immunoassay (OIAs.)

The optical immunoassay (OIA) was first developed for use in the diagnosis of GAS pharyngitis. Similar to other GAS RADTs, the test procedure has an extraction and testing phase that requires the release and capture of GAS carbohydrate antigen. The test is referred to as an optical test due to the color change of a silicon wafer from a gold/yellow color to purple when GAS carbohydrate antigen is captured [16].

Antibody detection of S. pyogenes

The diagnosis of post streptococcal diseases, such as rheumat-

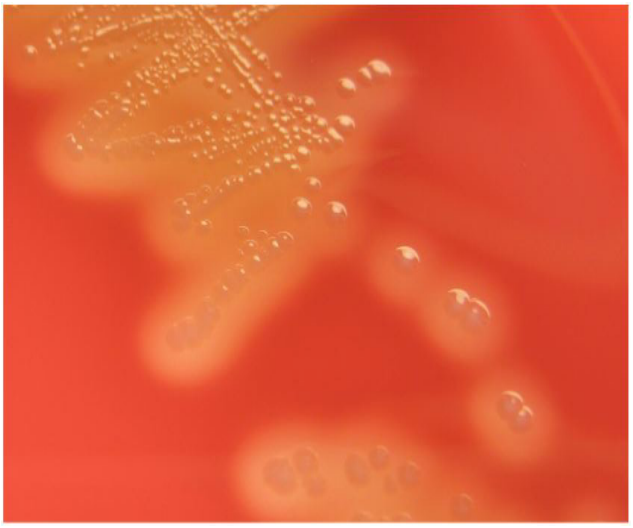

Figure 7: *Typical appearance of S. pyogenes on sheep-blood agar plates, following 24 hour incubation under aerobic conditions(Adopte as is) [49].*

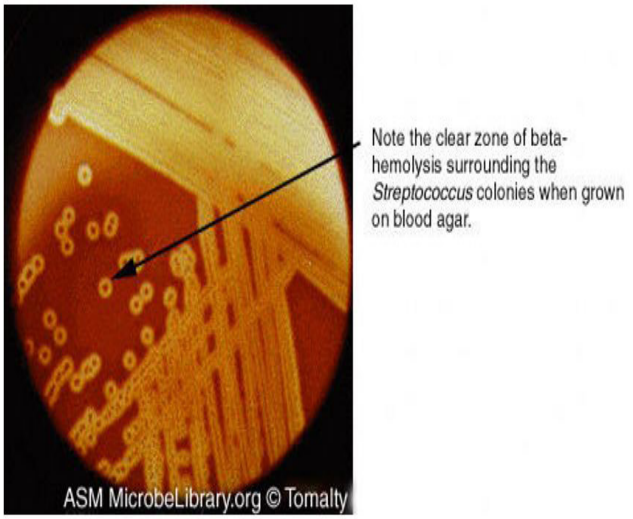

Figure 8: *Beta (complete) -Hemolysis of S. Pyogenes (Adopte as is) [49].*

ic fever or glomerulonephritis, can be aided by the detection of certain streptococcal antibodies the host responds immunologically to streptococcal infections with a plethora of antibodies against many cellular and extracellular components. Serological diagnosis of GAS infection is based on immune responses against the extracellular products streptolysin O, DNase B, hyaluronidase, NADase, and streptokinase, which induce strong immune responses in the infected hosts. Antistreptolysin O (ASO) is the antibody response most often examined in serological tests to confirm antecedent streptococcal infection, and helps in the diagnosis of rheumatic fever [4].

ASO

Is useful for confirming rheumatic fever or acute glomerulonephritis resulting from a recent streptococcal pharyngeal infection

Anti-DNase B test

Should be performed if streptococcal glomerulonephritis is suspected

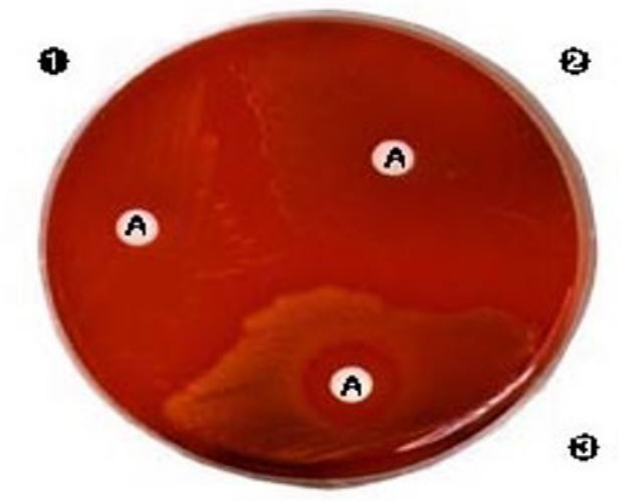

Figure 9: *Shows S. Pyogenes sensitivity to bacitracin (Adopte as is) [49].*

Molecular Test

Due to the lower sensitivities of RADTs and the need to treat patients based on diagnostic results, nucleic acid amplification tests (NAATs) have been developed for the detection of GAS. While multiple assays and instruments have been [14].

Roche cobas strep A assay

The cobas strep assay can detect Streptococcus pyogenes in throat swabs with a limit of detection (LOD) of 5 to 20 CFU/ml [14].

Abbott strep A and strep A2 assays

The ID Now platform uses isothermal DNA amplification for the qualitative detection of different pathogens, including GAS. Results are available in as little as 2 min for a positive result and 6 min for a negative result [14].

Treatment

Penicillin or amoxicillin used to treat pharyngitis; oral cephalosporin or macrolide for penicillin-allergic patients; intravenous penicillin plus clindamycin used for systemic infections Or pharyngeal carriage occurring after treatment can be re-treated; treatment is not indicated for prolonged asymptomatic carriage because antibiotics disrupt normal protective flora Starting antibiotic therapy within 10 days in patients with pharyngitis prevents rheumatic fever For patients with a history of rheumatic fever, antibiotic prophylaxis is required before procedures that can induce bacteremia's leading to endocarditis For glomerulonephritis, no specific antibiotic treatment or prophylaxis is indicated S. pyogenes is very sensitive to penicillin, so oral penicillin or amoxicillin can be used to treat streptococcal pharyngitis. For penicillin-allergic patients, an oral cephalosporin or macrolide may be used. The combined use of intravenous penicillin with a protein-synthesis–inhibiting antibiotic (e.g., clindamycin) is recommended for severe, systemic infections. Resistance or poor clinical response has limited the usefulness of the tetracycline's and sulfonamides, and resistance to erythromycin and the newer macrolides (e.g., azithromycin, clarithromycin) is increasing in frequency [50].

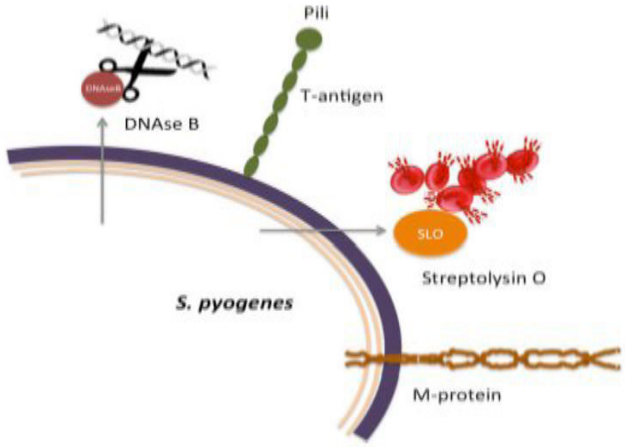

Figure 10: *Common antigenic proteins of S. pyogenes used for diagnostic and typing purposes. (Adopte as is) [49].*

Prevention and control

Good hand washing, particularly after coughing and sneezing, is important to prevent the spread of GAS infection. It is important to cover the nose and mouth when coughing and sneezing. In addition, washing, treating and covering infected wounds and sores prevents the spread of bacteria. Drainage and aggressive surgical debridement must be promptly initiated in patients with serious soft-tissue infections. Delivery primary and secondary prophylaxis to control transmission of GAS and incidence of GAS pharyngitis and ARF/RHD. The development of a safe and efficacious vaccine against GAS has received a major impetus to move forward with the re-emergence of invasive disease in the developed countries and increased recognition of the devastating public health impact on developing countries. One of the major vaccine candidates that are under Clinical Trials M protein, non-M protein, and carbohydrate-derived antigens [43].

Conclusion

The ability of GAS to produce serious invasive infections in previously healthy individuals defines a robust capacity of this pathogen to counteract these multifaceted host defenses. The functional redundancy of GAS virulence determinants, with individual GAS factors cooperating to resist a key innate immune clearance mechanism or with a single GAS virulence determinant harboring distinct functional domains that interfere simultaneously with multiple host defense components. Despite intensive efforts and considerable new information, the molecular mechanisms of GAS immune sequelae such as ARF and post-streptococcal glomerulonephritis remain to be conclusively defined. The resistance of GAS to antibiotics other than penicillin and cephalosporin is an increasing concern. A number of factors need careful consideration when developing GAS vaccines, including serotype coverage of antigens, the geographical distribution of serotypes, Future global eradication of GAS disease may be achieved by preparations that optimally address each of these factors.

References

1. K Gr€Ondahl-Yli-Hannuksela, HL Hyyryl€Ainen, T Kallonen, JM Musser, J Vuopio, et al. Genetic Evolution of Invasive Emm28 Streptococcus Pyogenes Strains and Significant Association with Puerperal Infections In Young Women in Finland. Clinical Microbiology And Infection. 2020; 1-7.
2. Julie Bennett1, Jane Oliver, Julian Crane, Deborah A Williamson, Dianne Sika-Paotonu, et al. Understanding Group A Streptococcal Pharyngitis and Skin Infections As Causes Of Rheumatic Fever: Protocol For a Prospective Disease Incidence Study. Bmc Infectious Diseases. 2019; 19: 1-10.
3. Sistla, TAAS. Decoding the Molecular Epidemiology of Group A Streptococcus - An Indian Perspective. Journal of Medical Microbiology. 2019; 68: 1059-1071.
4. CA Azike, VNAABBA. The Prevalence of Group A Streptococcus as a Re-Emerging Microorganism in Port Harcourt Metropolis. International Journal of Pathogen Research. 2019; 2: 1-6.
5. Al-Gazally, FAATJKAKME. Characterization of Streptococcus Pyogenes Isolated From Throat Swabs In Baghdad Children Patients. Journal of Babylon University/Pure And Applied Sciences/. 2016; 24: 1227-1233.
6. Céline Plainvert, Elise Seringe, Benjamin Saintpierre, Elisabeth Sauvage, Laurence Ma, et al. A Clone of the Emergent Streptococcus Pyogenes Emm89 Clade Responsible For A Large Outbreak in a Post-Surgery Oncology Unit in France. Medical Microbiology And Immunology, Springer. 2018; 207: 287-296.
7. Patricia Therese Campbell1, Nicholas Geard, Mark R Davies, Kate A Worthing, Jake A Lacey, et al. Longitudinal Analysis of Group A Streptococcus Emm Types and Emm Clusters in a High Prevalence Setting Reveals Past Infection Does Not Prevent Future Infection. Victorian Infectious Diseases Reference Laboratory Epidemiology Unit. 2019; 10: 1-20.
8. Tazin Fahmi, SF, Gary C Port, Kyu Hong Choa. The Second Messenger C-Di-Amp Regulates Diverse Cellular Pathways Involved in Stress Response, Biofilm Formation, Cell Wall Homeostasis, Speb Expression, and Virulence in Streptococcus Pyogenes. Infection And Immunity. 2019; 87: 1-19.
9. Sunil D Saroj, LM, Raquel Tavares, Ann-Beth Jonsson. Lactobacilli Interfere With Streptococcus Pyogenes Hemolytic Activity and Adherence to Host Epithelial Cells. Frontiersinmicrobiology. 2016; 7: 1-8.
10. Vincent A Fischetti, JBD. One More Disguise in the Stealth Behavior of Streptococcus Pyogenes. Commentary. 2016; 7: 1-2.
11. Michelle P Aranha, Jay A Spencer, Rupesh Agarwal, Jerome Baudry, James B Dale, et al. Structure-Based Group A Streptococcal Vaccine Design: Helical Wheel Homology Predicts Antibody Crossreactivity Among Streptococcal M Protein-Derived Peptides. Department of Biochemistry And Cellular And Molecular Biology. 2020; 1-24.
12. Zeinab M Helal, DER, Mohamed M Adel El-Sokkary, Ramadan Hassan. Prevalence And Characterization of Streptococcus Pyogenes Clinical Isolates From Different Hospitals and Clinics in Mansoura. International Journal Of Microbiology. 2020; 1-11.
13. Getnet Tesfaw, GK, Demeke Mekonnen, Alemseged Abdissa. Prevalence of Group A B-Haemolytic Streptococcus Among Children With Pharyngitis In Jimma Town, Southwest Ethiopia. Egyptian Journal of Ear, Nose, Throat and Allied Sciences. 2015; 16: 35-40.
14. Luchang Zhu, Stephen B Beres, Matthew Ojeda Saavedra, Samantha L Kubiak, Concepcion C Cantu, et al. Genome-Wide Screens Identify Group A Streptococcus Surface Proteins Promoting Female Genital Tract Colonization and Virulence. The American Journal of Pathology. 2020; 190: 863-873.
15. Hannah R Frost, MSS, Mark Walker, Anne Botteaux, Pierre R Smeesters. Group A Streptococcal M-Like Proteins: From Pathogenesis to Vaccine Potential. Fems Microbiology Reviews. 2018;

42: 193-204.

16. Pacôme Monemo, Fidèle S Touré, Adjartou Traoré, Christelle Avi, Micheline A N'guessan, et al. Pharyngeal Carriage of Beta-Haemolytic Streptococcus Species and Seroprevalence of Anti-Streptococcal Antibodies In Children In Bouaké, Côte D'ivoire. Trop. Med. Infect. Dis. 2020; 5: 1-8.

17. Raina Gergovaa, Ivan Mitova, Lena Setchanovaa, Kalina Mihovab, Radka Kanevab, et al. Relation Between Emm Types and Virulence Gene Profiles among Bulgarian Streptococcus Pyogenes Clinical Isolates. Infectious Diseases. 2019; 1-8.

18. Report HP. Group A Streptococcal Infections: First Report on Seasonal Activity in England, 2019/20. Protecting and Improving Nations Health. 2020; 14: 1-8.

19. Taariq Salie, Kelin Engel, Annesinah Moloi, Babu Muhamed, James B Dale, et al. Systematic Review And Meta-Analysis of the Prevalence of Strep a Emm Clusters in Africa to Inform Vaccine Development. Afrostrep Research Group. 2020; 5: 1-33.

20. C Mwaba, Cert Paed Neph, R Nakazwe, E Mpabalwani, C Lukwesa-Musyani, et al. Prevalence And Antibiotic Susceptibility of Group a Beta-Haemolytic Streptococcal Isolates in Children Presenting With Acute Pharyngitis In Lusaka, Zambia. S Afr J Child Health. 2020; 14: 99-103.

21. Javier Gutiérrez-Jiménez, Alejandra Vicente-Serrano, Lorena Mercedes Luna-Cazáres, José Manuel Feliciano-Guzmán, José Antonio Girón-Hernández, et al. Virulence Genes and Resistance to Antibiotics of Beta-Hemolytic Streptococci Isolated From Children in Chiapas, Mexico. J Infect Dev Ctries. 2018; 12: 80-88.

22. Jane Oliver, Alissa Mcminn, Ciara Baker, Philip N Britton, Julia E Clark, et al. Invasive Group A Streptococcus Disease in Australian Children: 2016 To 2018- A Descriptive Cohort Study. Bmc Public Health. 2019; 19: 1-10.

23. Arwa Mohammed Othman, RMA, Huda Zaid Alshami, Riyadh Saifali. Asymptomatic Carriage of Streptococcus Pyogenes Among School Children In Sana'a City, Yemen. Bmc Res Notes. 2019; 12: 1-5.

24. Armira Azuar, Saori Mukaida, Waleed M Hussein, Istvan Toth, Mariusz Skwarczynski, et al. Recent Advances In The Development of Peptide Vaccines and Their Delivery Systems Against Group A Streptococcus. Vaccines. 2019; 7: 1-26.

25. By Shigeyuki Hamada, SKAIN. Molecular And Genomic Characterization Of Pathogenic Traits of Group A Streptococcus Pyogenes. Proc. Jpn. Acad. Ser. 2015; 91 539-559.

26. Monika L Dietrich, M, Russell W Steele Md. Group A Streptococcus. Pediatrics In Review. 2018; 39: 379-391.

27. Hannah R Frost, Valérie Delforge, Dalila Lakhloufi, Martina Sanderson-Smith, Velusamy Srinivasan, et al. Analysis of Global Collection of Group A Streptococcus Genomes Reveals that the Majority Encode a Trio of M and M-Like Proteins. Clinical Science and Epidemiology. 2020; 5: 1-10.

28. James M Musser, Luchang Zhu, Randall J Olsen, Jaana Vuopio, Hanne-Leena Hyyryläinen, et al. Reduced In Vitro Susceptibility of Streptococcus Pyogenes to -Lactam Antibiotics Associated with Mutations In The Pbp2x Gene Is Geographically Widespread. Journal Of Clinical Microbiology. 2020; 58: 1-17.

29. Rao Muhammad Abid Khana, SA, Zaid Ahmed Pirzadaa. The Emergence of Lincosamide and Macrolide Resistance in Streptococcus Pyogenes from Pakistan. Asian Biomedicine. 2015; 9: 321-324.

30. Rachel Greer, Clare Ling, Daranee Intralawan, Supalert Nedsuwan, Janjira Thaipadungpanit, et al. Prevalence of Group A Streptococcus In Primary Care Patients And The Utility of C-Reactive Protein And Clinical Scores For Its Identification In Thailand. Am. J. Trop. Med. Hyg. 2020; 102: 377-383.

31. Paul A Wilson, HV. Severe Community-Acquired Pneumonia Due to Streptococcus Pyogenes in The Newcastle Area. Communicable Diseases Intelligence. 2020; 44: 1-10.

32. Nada Zaidan Khalaf, LMN, Asraa Adnan Abdul-Jalil. Molecular Study of Spy1258 Gene in Streptococcus Pyogenes Isolated From Pharyngitis Patients in Fallujah City. Medico-Legal Update. 220; 20: 586-590.

33. Marylin Schmitz, Benedikt Huttner, Jérôme Pugin. Streptococcal Toxic Shock Syndrome in the Intensive Care Unit. Ann. Intensive Care. 2018; 8: 1-10.

34. Luis Alberto Vega, Brittany J Shah, Anthony R Floresa. Strain-Dependent Effect of Capsule on Transmission and Persistence in An Infant Mouse Model of Group A Streptococcus Infection. Infection And Immunity. 2020; 88: 1-17.

35. Mörgelin JS, Peter A Rice, Lars Björck, David Ermert, Antonin Weckel, et al. Streptococcus Pyogenes Through Complement Human Igg Increases Virulence of Evasion. J Immunol. 2018; 200: 3495-3505.

36. Heema KN Vyas, Arun Everest-Dass, Nicolle H Packer, David M P De Oliveira, Marie Ranson Jason D Mcarthur, et al. Sanderson-Smith 2020. Assessing the Role of Pharyngeal Cell Surface Glycans in Group A Streptococcus Biofilm Formation. Antibiotics. 2020; 9: 1-22.

37. Gregory Calfee AJLD, Ira Jain, Eric W Miller, Poulomee Sarkar, Brian Tjaden, et al. Identification And Characterization of Serotype-Specific Variation In Group A Streptococcus Pilus Expression. Infection And Immunity. 2018; 86: 1-16.

38. Gabrielle De Crombrugghe, Anne Botteaux, Nicole J Moreland, Deborah A Williamson, Andrew C Steer, et al. The Limitations of the Rheumatogenic Concept For Group A Streptococcus: Systematic Review And Genetic Analysis. Clinical Infectious Diseases. 2020b; 70: 1453-1459.

39. Chuan Chiang-Ni, Yong-An Shi, Cheng-Hsun Chiub. Effect Of Phosphatase Activity of The Control Of Virulence Sensor (Covs) on Clindamycin-Mediated Streptolysin o Production In Group a Streptococcus. Infection And Immunity. 2019; 87: 1-11.

40. Christian Kosisochukwu Anumudu, MNAAICA. Antimicrobial Activity of Cannabis Sativa Extracts on Lancefield Group a Streptococcus Species Associated With Streptococcal Pharyngitis (Strep Throat. African Journal of Biological Sciences. 2020; 2: 9-15.

41. Anthony R Flores, Concepcion Cantu, Kyler B Pallister, Fermin Guerra, Jovanka M Voyich, et al. Increased Pilus Production Conferred By a Naturally Occurring Mutation Alters Host-Pathogen Interaction In Favor of Carriage In Streptococcus Pyogenes. Infection And Immunity. 2017; 85: 1-14.

42. Anshu Babbar, Dietmar H Pieper, Andreas Itzek. Superantigen Spea Attenuates. The Biofilm Forming Capacity Of Streptococcus Pyogenes. Journal Of Microbiology. 2019; 57: 1-11.

43. Mohammad Omer Faruck, Waleed M Hussein, Zeinab G Khalil, Robert J Capon, Mariusz Skwarczynski, et al. Polyacrylate-Peptide Antigen Conjugate As a Single-Dose Oral Vaccine Against Group A Streptococcus. Vaccines. 2020; 8: 1-10.

44. Thomas Z Thompson, Allison R McMullen. Group A Streptococcus Testing In Pediatrics: The Move To Point-Of-Care Molecular Testing. Journal Of Clinical Microbiology. 2020; 58: 1-8.

45. Adile Muhtarova, Rumyana Markovska, Ivan Mitov, Radka Kaneva, Raina Gergova, et al. Molecular Emm Typing of Bulgarian Macrolide-Resistant Streptococcus Pyogenes Isolates. Acta Microbiologica Et Immunologica Hungarica. 2019; 1-4.

46. RV Wilkening, MJ Federle. Evolutionary Constraints Shaping Streptococcus Pyogenes Host Interactions. Trends Microbiol. 2017; 25: 562-572.

47. Gabrielle De Crombrugghe, NB Anne Botteaux, Nicole J Moreland, Deborah A Williamson, Andrew C Steer, et al. The Limitations of the Rheumatogenic Concept For Group A Streptococcus: Systematic Review And Genetic Analysis. Clinical Infectious Diseases. 2020a; 70: 1453-1460.

48. HR Frost, A Erhart, S Darboe, A Steer, MJ Walker, et al. Updated Emm-Typing Protocol For Streptococcus Pyogenes. Clinical Mi-

crobiology And Infection. 2020; 26: 1-3.

49. Theresa Nh Leung, KH Alexander Kc Leung. Group A Streptococcus Disease in Hong Kong Children: An Overview. Hong Kong Med J. 2018; 24: 593-601.

50. TC Barnett, JR Carapetis. The Fall and Rise of Group A Streptococcus Diseases. Epidemiology and Infection. 2020; 1-6.