International Journal of Scientific Research and Management (IJSRM)
||Volume||11||Issue||11||Pages||897-903||2023||
Website: www.ijsrm.net ISSN (e): 2321-3418
DOI: 10.18535/ijsrm/v11i11.mp03

Group A Streptococcus Infection in Children: Literature Review

(Infeksi Streptococcus Grup A pada Anak : Studi Pustaka)

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Abstract

Streptococci are a large and diverse group of gram-positive cocci that grow in pairs or chains. Invasive group A Streptococcus infection (GAS) is associated with significant morbidity and mortality. The mechanism for spreading Streptococcus from one person to another and one part of the body to another part of the body varies according to the clinical manifestations of the infection. Group A Streptococcus infection, consisting of non-invasive gas infection and invasive gas infection. Generally, for non-severe infections due to group A Streptococcus is good with very low morbidity and mortality rates. On the other hand, the more invasive and severe infections caused by group A Streptococcus carry with them significant mortality and morbidity rates. The purpose of writing this literature review is to improve understanding and treatment of group A streptococcal infections in children so that the mortality and morbidity associated with this infection can be reduced.

Keywords : Group A Streptococci; Infection; Children .

Abstrak

Streptococcus adalah kelompok besar dan beraneka ragam dari kokus gram positif yang tumbuh secara berpasangan atau berantai. Infeksi Streptococcus grup A invasif (GAS) berhubungan dengan angka morbiditas dan mortalitas yang signifikan. Mekanisme penyebaran Streptococcus dari satu orang ke orang lain dan satu bagian tubuh ke bagian tubuh lain bervariasi menurut manifestasi klinis dari infeksinya. Infeksi Streptococcus grup A, terdiri atas *non invasive gas infection* dan *invasive gas infection*. Umumnya, untuk infeksi yang tidak berat akibat Streptococcus grup A adalah baik dengan tingkat morbiditas dan mortalitas yang sangat rendah. Di sisi lain, infeksi yang lebih invasif dan berat yang disebabkan oleh Streptococcus grup A membawa serta tingkat kematian dan morbiditas yang signifikan. Tujuan penulisan studi pustaka ini adalah untuk meningkatkan pemahaman dan pengobatan infeksi streptococcus grup A pada anak sehingga mortalitas dan morbiditas yang terkait dengan infeksi ini dapat dikurangi.

Kata Kunci : Streptococcus Grup A; Infeksi; Anak

Background

Streptococci are a large and diverse group of gram-positive cocci that grow in pairs or chains. Some are normal flora, others are associated with important infections in humans. Group A streptococcus occurs in a limited number of hosts, more frequently in men than women. The epidemiology of group A Streptococcus infections shows differences between types of group A Streptococcus infections. [1] The mechanism of spread of Streptococcus from one person to another and one part of the body to another varies according to the clinical manifestations of the infection. [2]

Group A Streptococcus infection, consisting of *non-invasive gas infection* and *invasive gas infection* . *Non-invasive gas infections* consist of *streptococcal pharyngitis* , scarlet fever, perianal dermatitis, vaginitis, impetigo, *erysipelas* , *cellulitis* , vulvovaginitis and perianal cellulitis. *Invasive gas infection* consists of *Streptococcal Toxic Shock Syndrome* and *Acute Necrotizing Fasciitis* . [3] Generally, non-severe infections due to group A Streptococcus are favorable with very low morbidity and mortality rates, on the other hand, more invasive and severe infections caused by group A Streptococcus

carry with them significant rates of mortality and morbidity. [4]

Streptococcus Pyogenes bacteria (Group A Streptococcus)

Streptococcus pyogenes was first described by Billroth in 1874 in patients with infected wounds. [5] Streptococci are a large and diverse group of gram-positive cocci that grow in pairs or chains. Streptococcus pyogenes bacteria (S. pyogenes) are Gram positive, non-motile, non-spore-bearing, facultative anaerobes, in the form of chains with a diameter of 0.6 – 1.0 micrometers. [6]

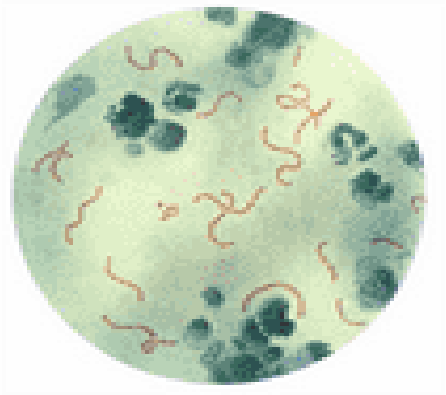

Figure 1 Microscopic view of Streptococcus pyogenes. [6]

Pathomechanism of Group A Streptococcus Bacteria as a Cause of Disease

Characteristics of Clinically Important Streptococci

S. pyogenes is widely distributed in humans, some being *asymptomatic carriers* . S.pyogenes colonizes the throat and skin of humans and forms a complex virulence mechanism to fight the body's defense system. [7]

S.pyogenes can cause superficial or systemic infections based on the toxins and immune response that mediate the mechanism of disease onset. [7]

Group A Streptococcus Toxins and Enzymes

Group A Streptococcus bacteria produce more than 20 antigenic extracellular products, including the following: [6]

- Hemolysin
- Streptokinase (Fibrinolysin)
- Streptodornase
- Hyaluronidase
- Pyrogenic Exotoxin
- Difosporidin Nucleotidase

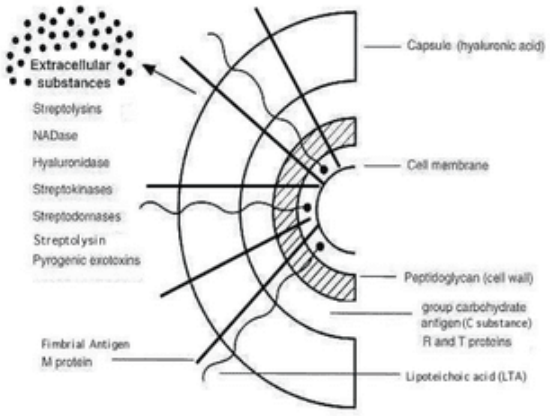

Figure 2 Streptococcus pyogenes toxins and enzymes. [6]

Mechanism of Group A Streptococcus Infection

S. pyogenes can infect when the host's defenses decrease when the organism is able to penetrate past the existing host defenses. Primary infection of the throat is damage to the epithelial cells of the pharynx. For this reason, these bacteria must compete with the flora in the pharynx, colonize in the throat and produce *bacteriocin like substance* , this substance is what causes respiratory tract infections. [8]

In the event of impetigo, S. pyogenes bacteria must compete with the local bacterial flora, there is an increase in S. pyogenes on the skin through skin fat and in vitro it will cause infection. [9]

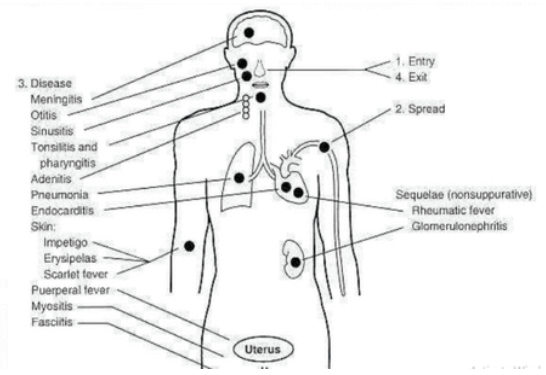

Figure 3 Pathomechanism of Streptococcus pyogenes infection. [8]

Pathogenesis and Immunity of Group A Streptococcus

The virulence of GAS is determined by the ability of bacteria to attach to cell surfaces, invade epithelial cells and avoid opsonization events, phagocytosis and produce various toxins and enzymes. [10] The organism binds to mucous membranes via lipotechoic acid (LTA) which is in the cell walls of

Streptococcus. Once bound, Streptococcus will survive phagocytosis, multiply and begin to invade surrounding tissue. [11]

The M protein region can bind factor H from serum β-globulin which is a regulatory protein for the alternative pathway of complement. The complement component C3b, a mediator for phagocytosis, is not stabilized by factor H. When C3b is bound to the cell surface in the M protein region, C3b will be degraded by factor H and phagocytosis will be prevented. [11]

Group A Streptococcus Infection in Children

Definition

Group A streptococcus can cause wide clinical variations, so that even though it is sensitive to penicillin, this organism can still cause medical and public health problems. Group A Streptococcus infection not only causes acute infections, but often causes carrier conditions. Usually the course of the disease is short and relatively mild, but can be severe and life-threatening. [3]

Epidemiology

The epidemiology of group A Streptococcus infections shows differences between types of group A Streptococcus infections in that skin infections, such as pyoderma and impetigo, are more common in preschool children and throat infections (pharyngitis), predominant in school-aged children. [12]

Based on geography and seasonal patterns, tonsillitis and pharyngitis often occur in cold temperatures/climates. Impetigo can occur all year round in tropical countries. [1] It is assumed that poverty, overcrowded living conditions and limited access to medical care are contributing factors. [13]

Transmission

The mechanism by which Streptococcus spreads from one person to another and one part of the body to another varies according to the clinical manifestations of the infection. [2] Transmission of GAS primarily occurs through respiratory droplets, or skin-to-skin contact with broken skin that has secretions from an infected wound. The environment is also a potential reservoir. Transmission of GAS infection through food is also possible. [14]

Epidemiologically, research on patients with Streptococcus throat infections shows that spread through the air (droplet nuclei, dust) and polluted environments (clothing, bedding) is a small part of the process of spreading Streptococcus. Anal transmission is known if there is an extraordinary incident of streptococcus infection due to lack of environmental hygiene. Some researchers say that rectal or anal transmission is more common than oral. [2]

Clinical Manifestations

Group A Streptococcus is the most common cause of bacterial pharyngitis in children. Streptococcal pharyngitis or tonsillitis infection period (12 hours-4 days). As many as 30-50% of infections are in the toxic form with high fever, nausea, vomiting and collapse generally occurring in 10% of sufferers. The tissue in the tonsil region appears inflamed or characterized by reddish swelling. Exudates in 50-90% of cases usually appear on day 2 and enlargement of the anterior cervical lymph nodes occurs in 30-60% of patients. [5]

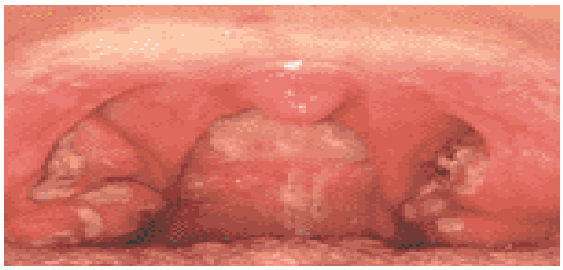

Figure 4 Yellowish white exudate in the tonsils and pharynx. [3]

Scarlet fever is characterized by a pale rash that spreads from the chest to the abdomen and extremities leaving a sandpaper-like texture on the skin. Desquamation of the fingers, toes, groin and axillae occurs a week or more later. The rash is visible within 24-48 hours after the onset of symptoms, starting around the neck and upper chest and spreading to the trunk and extremities. A diffuse, finely papular, erythematous rash that blanches when pressed. The tongue is often coated with a white coating (white strawberry tongue) which eventually turns fleshy red (red strawberry tongue). [15]

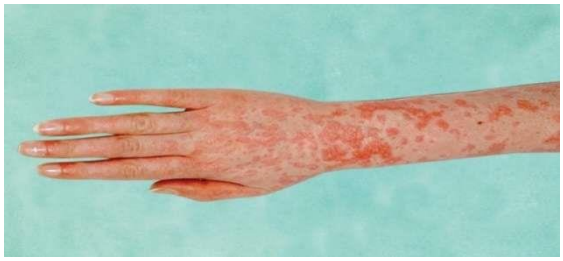

Figure 5 Scarlatiniform rash of scarlet fever. [16]

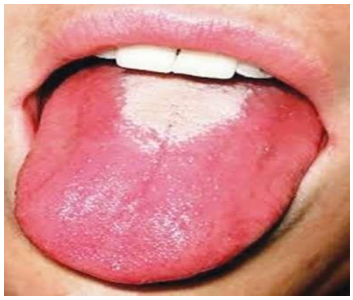

Figure 6 Strawberry tongue from dengue fever. [16]

In simple impetigo, the infection is limited to the epidermis with the formation of superficial crusted lesions on the face or other exposed parts of the body. Nonbullous impetigo usually manifests in open areas, such as the face and limbs. It is characterized by erythematous papules, which develop into vesicles that rupture rapidly to form a characteristic "honey-colored" exudate and thick crust. [16]

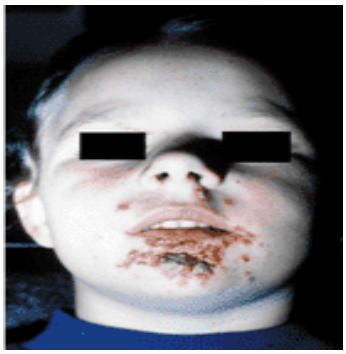

Figure 7 Impetigo with honey-colored exudate and thick crust. [16]

Erysipelas is a painful infection of the dermis and results in a well-defined area of inflammation and protrusion that often forms superficial bullae. Cellulitis involves deeper subcutaneous tissue causing areas of inflammation that are more diffuse and less clearly defined. [15]

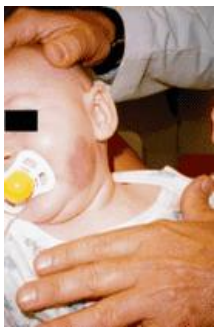

Figure 8 *Erysipelas* On the face of a small child. Note the raised, raised borders of the lesion. [16]

Perianal Streptococcus disease is characterized by well-defined perianal erythema. Physical examination revealed flat, pink to fleshy red perianal erythema with sharp borders 2 cm from the anus. [3]

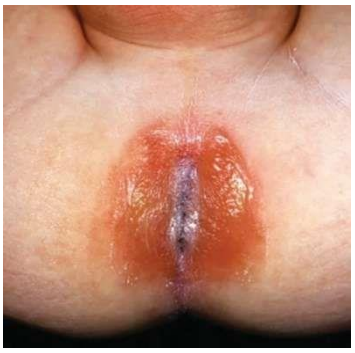

Figure 9 Perianal Dermatitis. [3]

Necrotizing fasciitis is a rapidly growing infection of the subcutaneous fat, superficial fascia, and deeper structures, including muscles. Initially, the overlying skin is spared and the pain is disproportionate to the clinical findings. The skin then becomes purplish and bullae may form and then peel. [15]

Streptococcal toxic shock syndrome is defined as GAS infection with hypotension and evidence of multiorgan failure. [3]

Supporting investigation

Specimen

The specimen taken depends on the Streptococcus infection that occurred. For culture, specimens from throat swabs, pus, or blood are used. Meanwhile, for antibody testing, serum specimens are used. [17]

Microscopic Examination

As a preliminary diagnosis of soft tissue infections or pyoderma, gram staining can be performed on samples originating from the affected tissue. The presence of gram-positive cocci in pairs and chains and the presence of leukocytosis is important because streptococcus is not normal flora on the skin. [17]

Biochemical Culture and Identification

Specimens suspected to contain streptococcus are incubated on blood agar media in an incubation atmosphere with 10% CO_2 to accelerate hemolysis. Blood cultures will grow group a streptococcus within a few hours to a few days. [17]

Antigen Detection

Streptococci are definitively identified based on group-specific carbohydrates by direct antigen detection assays. This test uses a chemical method to extract

antigen from a swab, then uses *enzyme immunoassay* (EIA) to see the presence of antigen. [17]

Antibody Detection

Patients who experience S. pyogenes infection produce antibodies against many specific enzymes. These include antistreptolysin O (ASO), especially for respiratory tract infections, anti-DNase, and antihyalurodinase in skin infections, antistreptokinase, specific anti-M antibodies. [17]

Governance

Group A streptococcus is generally sensitive to a number of antibiotics. Penicillin is the drug of choice for treatment, unless the sufferer is allergic. Penicillin is not potent against organisms that produce beta-lactamase in upper respiratory tract infections. [2]

Although it is difficult, eradication therapy for group A Streptococcus in the upper respiratory tract can be done with penicillin or other antibiotics. Erythromycin can be given to sufferers who are allergic to penicillin. Group A streptococcus is often resistant to tetracycline, whereas sulfonamides only suppress and do not eradicate the organism. In pharyngeal streptococcus therapy, eradication therapy against group A Streptococcus is needed to prevent development of acute rheumatic fever. [2]

Table 1 Recommended treatment for acute rheumatic fever. [3]

Antibiotic	*Mode of administration and dose*
Benzathine penicillin	Single intra muscular injection every 3–4 weeks*, 12 lack IU for children >30 kg and 6 lack IU for children <30 kg
Penicillin V	250 mg orally twice daily
Erythromycin (for penicillin allergy)	250 mg orally twice daily

*In high prevalence regions, 3-week injections are recommended for prophylaxis in patients >30 kg and every 2 weeks in patients <30 kg

Management of skin and soft tissue infections caused by GAS such as impetigo, erysipelas and cellulitis is described in table 2. [3]

Table 2 Management of GAS Skin and Soft Tissue Infections. [3]

Condition	*Antibiotic*	*Dosing*	*Duration (days)*
Impetigo	Mupirocin (topical)	Apply two times daily	5
	Retapumulin (topical)	Apply two times daily	5
	Cephalexin (oral)	25–50 mg/kg/day, 6–8 hourly	7
	Clindamycin (oral) (if MRSA is also suspected)	20–30 mg/kg/day, 8 hourly	7
Erysipelas (milder forms)	Amoxicillin (oral)	40–90 mg/day in 2–3 divided doses	5
Cellulitis (milder forms)	Cephalexin (oral)	50 mg/kg/day in 4 divided doses (maximum 500 mg/dose)	5
	Clindamycin (oral)	25–30 mg/kg/day, 8 hourly (maximum 1800 mg/dose)	5

In *streptococcal toxic shock syndrome* (STSS) antibiotics should cover GAS and staphylococcal infections because they are not easily differentiated clinically. Antibiotics should include penicillinase producers. Clindamycin, to mask superantigen-producing GAS. To cover staphylococcal infections, vancomycin may be added. [3]

In *acute necrotizing fasciitis* inflammation develops over the next few days involving the muscles, showing areas of necrosis. Inflammation progresses until aggressive surgical debridement is performed at the earliest. Antibiotic therapy is similar to STSS. [3]

Prevention

S. pyogenes infections are best prevented through effective hand hygiene. There is currently no vaccine available to protect against S. pyogenes infection, although research has been conducted to develop one. Difficulties in developing a vaccine include the wide variety of S. pyogenes strains present in the environment and the large amount of time and number of people required for proper trials for vaccine safety and efficacy. [18]

Group A Streptococcus vaccine development is divided into two groups which focus on the M protein antigen or non-M protein antigen. [12] The most advanced vaccine candidates are those based on the aminoterminus region. N-terminal vaccines based on type 26 emm have undergone phase I and II clinical trials, with evidence of good safety and immunogenicity. It is estimated that this 26 valent vaccine will provide protection against 80–90% of invasive GAS isolates. [19] GAS vaccine development is ongoing. However, a GAS vaccine is still at least several years away. [20]

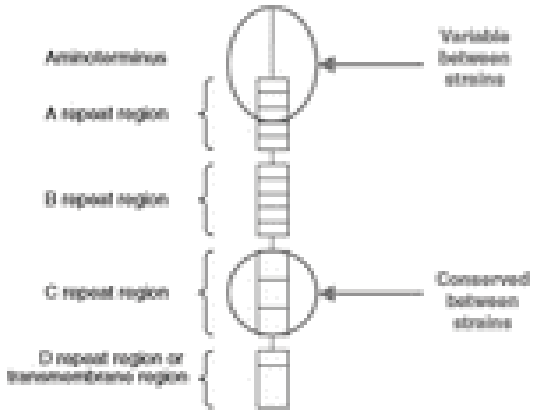

Figure 10 Schematic image of the Protein M. [20]

Complications

Apart from the morbidity and mortality associated with severe infections caused by GAS, one of the major complications that can occur due to mild infections is acute rheumatic fever. This is an autoimmune response to GAS pharyngitis. Another possible complication of GAS infection is post-Streptococcal glomerular nephritis. [21]

Prognosis

Patients with pharyngeal streptococcus or streptococcus impetigo can recover spontaneously, but in some cases suppurative complications occur and sometimes have non-suppurative sequelae. The risk of developing rheumatic fever after untreated streptococcal infection of the upper respiratory tract is 3%. Patients who have had one attack of rheumatic fever have a high risk of recurrence of group A Streptococcus infection (15-50%). The risk of acute glomerulonephritis depends on whether the infection is caused by a nephritogenic strain, the risk of attack is 10-15% and can occur in the course of a throat or skin infection. [2]

In general, the prognosis for mild infections due to GAS is good with very low morbidity and mortality rates. This applies to pharyngitis, cellulitis, and impetigo, which are effectively treated with standard oral antibiotic therapy and, in the majority of cases, even resolve spontaneously without medical intervention. [4] On the other hand, the more invasive and severe infections caused by GAS carry with them significant rates of mortality and morbidity. [4]

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