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STREPTOCOCCAL INFECTION

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INTRODUCTION

Streptococci has two main strains, hemolytic and non-hemolityc. Strains which infect man are chiefly hemolytic, while non-hemolytic strains are mostly saprophyt, which inhabit the upper respiratory tract and the intestine (Bradford, 1969).

A relationship between hemolytic streptococcal throat infection, rheumatic fever and glomerulonephritis has been adequately demonstrated (Phibbs *et al.*, 1958; Zuidema, 1959; WHO, 1966; Gordis, 1971). Not only the classical *strepthroat* with generalized septic symptoms but also the more benign and often unrecognizable streptococcal infection can lead to rheumatic complication (Jackson, 1963; WHO, 1966; Taranta, 1971).

The incidence of rheumatic and glomerulonephritis complications varies from 0,3% — 3% depending upon the virulence of the organism, epidemicity and climate (Jackson, 1966; WHO, 1966). In Jakarta, Hanifah *et al.* (1965) found that 10,25% of children and 71,2% of adults with heart disease were rheumatic. Such a high incidence of rheumatic heart disease strongly indicates that there must be a high incidence of rheumatic fever which in turn must have been caused by a high incidence of streptococcal infections. Oepomo *et al.* (1959) found 25% streptococci in the discharge of 66 cases with chronic otitis media.

CLINICAL SIGNS AND SYMPTOMS

Many streptococcal infections capable of precipitating an attack of rheumatic fever are not characteristic clinically or are so mild as to be practically unrecognizable, and some cannot easily by differentiated from viral infection of the upper respiratory tract.

The only clear clinical pattern of streptococcal infection is seen in scarlet fever. The incubation period is usually 2—4 days, with a maximum of 6 days. The primary infection, usually in the pharynx, is responsible for the toxic manifestations and septicemia.

The toxic manifestations include headache, fever, vomiting, rapid pulse, delirium, exanthem, enanthem, generalized lymphadenitis, myocarditis, nephritis and perhaps arthritis.

The septic manifestations, as a result of bacterial invasion of the tissue and blood stream, in addition to cellutitis of the pharynx and neck, and cervical adenitis, may include otitis media, sinusitis, mastoiditis, pyelonephritis, endocarditis, meningitis and other metastatic lesions (Bradford, 1969). For details, symptoms and signs of severe streptococcal infection see Table 1 (Committee

report of the prevention of theumatic fever of the American Heart Association 1965).

Table 1. Symptoms and signs of streptococcal sore throat

Symptoms

Sore throat — sudden onset, pain on swallowing
Headache — common
Fever — variable, but generally from 38,3°C to 40°C
Abdominal pain — more common in children than in adults
Nausea and vomiting — common especially in children.

Signs

Red throat
Exudate usually present, may not appear until the first day
Lymphadenopathy — swollen, tender lymphnodes at angle of jaw
Rash — scarlatiniform, when present usually diagnostic of streptococcal infection
Acute otitis media) may be due to streptococcus.
Acute sinusitis)

Note: In the absence of the above symptoms and signs occurence of any of the following symptoms is usually not associated with streptococcal infection: simple coryza, hoarseness, cough, conjunctivitis.

The moderate clinical patterns are:

Symptoms

Fever
Moderately sore throat.
Abdominal pain

Signs

Slightly tender, slightly enlarged peritonsillar lymphnodes
Moderately red pharynx
Medium exudate

And the mild clinical symptoms and signs are:

Symptoms

Minimal fever
Slightly sore or scratchy throat

Signs

Palpebral conjunctivitis
Slightly red or injected pharynx
Thin, wispy exudate in crypts
Hoarseness, cough.

Certain laboratory examinations are useful in assisting the physician in distinguishing streptococcal infection from other varieties of upper respiratory infection. Determination of white blood cell count is probably the simplest one. The white blood cell count is 10.000 — 20.000 of which 75 — 90% are polymorphonuclear cells. Eosinophilia may be observed after the fourth day of the rash (Bradford, 1969). Leucocytosis is helpful in differentiating between streptococcal and viral infection of the upper respiratory tract (WHO, 1966).

A properly performed and interpreted throat culture is the most reliable method of diagnosis.

Other forms of hemolytic streptococcal infection are in the skin manifesting as impetigo and erysipelas or St Antony's fire. The latter is clinically characterized by local erythematous induration, and it may be preceded by general constitutional symptoms such as: fever, malaise, irritability, vomiting and loss of appetite. The portal of entry is a wound of the skin which may be very slight, or may be surgical incision, or various lesions such as: eczema, impetigo, varicella and vaccinia (Bradford, 1969). According to Jawetz *et al.* (1971), 23% of children with skin infection developed nephritis.

MORPHOLOGY AND IDENTIFICATION

Streptococci are spherical or ovoid microorganisms characteristically arranged in chains. The length of the chains varies widely, depending upon environmental factors. Some streptococci produce a capsular polysaccharide which is comparable to that of pneumococci. Most of group A and group C elaborate capsules composed of hyaluronic acid. The capsule is most noticeable in very young cultures. It interferes with the ingestion of virulent streptococci by phagocytic cell. The streptococcal cell wall contains protein (M, T, R antigen), carbohydrates (group specific antigen) and mucopeptides (Jawetz *et al.*, 1971).

According to their action on red blood cell in culture, streptococci are grouped as:

I. Alpha-hemolytic strains causing green hemolysis in blood, possibly owing to the production of methemoglobin.
II. Beta-hemolytic streptococci producing a clear zone of hemolysis.
III. Non-hemolytic or gamma-hemolytic strains.

Most pathogenic strains belong to the beta-hemolytic strains (Bradford, 1969; Lynch *et al.*, 1969; Taranta *et al.*, 1971).

Subgrouping of the Beta-hemolytic streptococci is based on serologic reaction. As mentioned above, within the cell wall of the streptococci there are group specific carbohydrate antigens, which are easy to extract and identify with specific antisera. It is known as Lancefield grouping and designated by letters from A to Q (except I and J). Practically strains causing human infection belong to group A, a few to group B (Bradford, 1969; Lynch *et al.*, 1969). Within group A at least 49 types (subgroups) of streptococci have been identified upon the basis of the M substance. This substance is closely related to the virulence of group A streptococci and occurs chiefly in organism producing mucoid colonies (Bradford, 1969; Lynch *et al.*, 1969). Group A strains produce more than 20 extra-cellular antigens of clinical importance consisting of toxins and enzymes. Among these are the erythrogenic toxin, produced by over 90% of the strains, streptolysin O and S, streptokinase (fibrinolysin) and hyaluronidase (Jawetz *et al.*, 1971; Bradford, 1969).

The erythrogenic toxin is responsible for the rash that occurs in scarlet fever and only strains elaborating this toxin can cause the disease. The toxin is antigenic in nature, giving rise to the formation of specific antitoxin which neutralizes the toxin. Persons possessing such antitoxin are immune to the rash, though still susceptible to streptococcal infection (Jawetz *et al.*, 1971). Streptolysin O induces an antibody production. This antibody blocks hemolysis by

streptolysin O. This phenomenon forms the basis of a quantitative test for antibody.

The demonstration of antistreptolysin O indicates that the person has had a streptococcal infection, an important diagnostic test (Jawetz *et al.*, 1971; Bradford, 1969). A Committee of the American Heart Association has recommanded that the age of the patient should be taken into account and that a titre of 250 units or more be considered elevated in adults, and 333 units or more considered elevated in children older than 5 (Taranta *et al.*, 1971).

According to WHO 1966 a rising titre of antistreptolysin O in sera taken in the convalescent stage as compared with those taken in the acute stage confirms the diagnosis of streptococcal infection, and in single specimens the titre should be over 200.

The use of other antibody determination (such as: antihyaluronidase (AHO), antistreptokinase (ASK), anti-DPN-ase, anti-DNA-ase B) increases the precentage of positive results, but so far these antibodies have been used mainly in research studies (WHO, 1966; Taranta *et al.*, 1971).

LABORATORY TECHNIQUE

A throat swab, exudate, or blood is commonly obstained for culture. Serum is taken for antistreptolysin O titre, antihyaluronidase titre and others.

Procedure of culture:

The throat culture should be taken with a cotton-tipped or dacron-tipped applicator, swabbed vigorously against both tonsillar areas and posterior pharynx. The tongue should be depressed with a depresser or spoon, the pharynx should be clearly visualized and well lit, so that the tip of the applicator does not touch the tongue or the cheeks, to avoid contamination. Throat swab should be cultured on sheep blood agar immediately after collection.

Blood agar medium should have a layer about 6 mm thick, since it is difficult to differentiate the kinds of hemolysis on too thin or too thick plates. In streaking, the swab is rubbed and twisted onto the edge of a plate, covering only one-sixth of its surface. Growth in this area will be confluent and therefore not conducive to proper identification and isolation. A sterile platinum loop is streaked through the primary inoculum into approximately half of the plate in ten to twenty to and fro strokes. Without re-entering the side of primary inoculation, the resterilized loop is streaked through this of secondary inoculation into the remainder of the plate. Finally several stabs are made into the agar for observation of subsurface hemolysis. Than this plate is incubated for 18 to 24 hours in a standard incubator at 37°C in reduced oxygen tension.

Evalution:

We can distinguish three main types of hemolysis. Using the hemolytic characteristic as basis we can differentiate three groups of streptococci as mentioned above.

DIFFERENTIAL DIAGNOSIS

The confusing organism on sheep blood agar are hemolytic staphilococci, green streptococci, and gram negative cocci.

Gram negative cocci can be distinguished by gram stained preparations, and often by the colony morphology.

Staphilococci can be distinguished by the simple catalase test, performed by adding 0,5 ml of 3% hydrogen peroxide solution to bacterial growth on plain agar plate. Staphilococci cause the development of gas bubbles, but not streptococci.

Colonies of *S. hemolyticus* may resemble those of beta-hemolytic streptococci, but *S. hemolyticus* does not grow on sheep blood agar (Taranta *et al.*, 1971). Group A beta-hemolytic streptococci can be differentiated with 90% accuracy from the other group by bacitracin sensitivity test. Most of non-group A strains grow in the presence of a low concentration of bacitracin (0,02 units per paper disc), while Lancefield group A will be inhibited (Taranta *et al.*, 1971).

SEROLOGY TEST

There are many serologic tests which indicate that a streptococcal infection has been present and indicate the extent of the body's response to that infection, two of these are antistreptolysin O titre and anti-hyaluronidase titre.

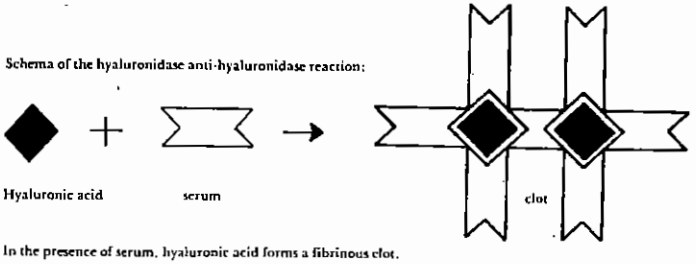
Anti-streptolysin-o titre:

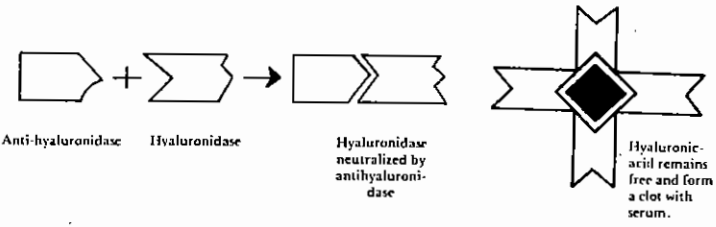
This test is used as an aid in the diagnostic of group A streptococcal infection and its complications (rheumatic fever and glomerulonephritis). In such condition the ASO titre is frequently raised.

A series of mixture is set up in which different quantities of serum are incubated with standard amounts of streptolysin. To the mixture is then added red blood cell suspension. The tube that has the least serum but no hemolysis has the amount of immune anti-streptolysin that exactly neutralized the standard amount of streptolysin. Results are expressed in Todd units (Lynch *et al.*, 1969).

Anti-hyaluronidase titre:

This test can give about 10% additional to the 80% revealed by ASO when both tests are performed in parallel.





(From BYK GULDEN Lomberg Gmbh, Konstnaz, Germany)

Hyaluronidase is an enzym which depolymerizes (splits) hyaluronic acid, which abounds in the connective tissues. The intercellular structure is loosened and diffusion increased as a result and this process in turn facilitates the penetration of toxic substances into the organism.

RELATION WITH RHEUMATIC FEVER AND GLOMERULONEPHRITIS

It is clear that following an acute group A streptococcal infection (especially a "strep throat"), rheumatic fever and glomerulonephritis may appear (WHO 1966, Jawetz *et al.*, 1971). And this relation has been known since 1930 and 1931 (Bradford, 1969). Acute glomerulonephritis develops in some persons 3 weeks following streptococcal infections, especially with types 12, 4, or 49.

Rheumatic fever is the most serious sequelae to hemolytic streptococcic infection because it results in damage to heart muscle and valves. This disease, like streptococcal infections, occurs most commonly in children between 5 and 15 years of age, with a peak incidence of first attacks at 6 — 8 years of age. The rarity of rheumatic fever is found in infants under three years of age and in older adults. When adults have frequent exposure to streptococcal infections, as in dormitory, in military service or through close contact with school age children, an increased risk of rheumatic fever may be expected. Usually rheumatic fever develops after 2 or 3 weeks streptococcal infection. Recurrent streptococcic infection cause more severe rheumatic heart damage, but not nephritis. It is therefore very important to protect rheumatic heart patients form recurrent group A hemolytic streptococcic infection by giving antibiotics or sulfonamides (Jawetz *et al.*, 1971; Bradford, 1969).

TREATMENT

Treatment is directed to streptococcal infection and the aim is the prevention of rheumatic fever or rheumatic heart diseases.

- Penicillin (WHO, 1966; Jackson, 1966; Bradford, 1969)
- Erythromycin (Jackson, 1965)
- Lyncomycin (Jackson, 1965).

Penicillin is given orally or intramuscularly. The following dosages are recommanded (WHO, 1966):

a) Penicillin G 200.000 IU or penicillin V 100 — 125 mg orally, 3 or 4 times a day for 7 to 10 days.

b) Dibenzyl penicillin, a single injection 1.2 million IU adult and 600.000 —900.000 IU in children.
c) A combination of crystalline penicilline G, procaine penicilline and dibenzyl penicillin are given as a single intra muscular injection of 1.2 million IU in adult, and 600.000 — 900.000 IU in children.

For maximal effectiveness antistreptococcal therapy has to be given for a full ten days to insure maximal result in erradicating the organism. Injectible benzathine peniciline, is the treatment of choice, especially for an uncooperative patient (Jackson, *et al.*, 1969; Gordis *et al.*, 1971). Patients allergic to penicilline are treated with erythromycine or lyncomycin in appropriate dosage also for ten days. Dosage of erythromycine 250 mg four times a day in adult, and 40 mg/kg/day in children (WHO, 1966). Dosage of lincomycine is 26 to 55 mg/kg body weight daily (Jackson *et al.*, 1965). Sulfonamide eventhough has been shown effective as an antistrep prophylaxis, it is definitely not indicated for treatment of strep infection. In fact, there is some evidence that it may do more harm than good (Jackson, 1972). Its dosage was based on 30 to 50 mg/kg body weight as an initial dose, and the daily dose is a half of the initial dose (Jackson *et al.*, 1963).

SUMMARY AND CONCLUSION

Streptococcal throat infections are closely related to glomerulonephritis and rheumatic fever. The incidence of which varies from 0,3—3%. In Indonesia the incidence of rheumatic heart disease is high, so we can suspect that the incidence of streptococcal infection is high too.

Clinical signs and symptoms of strepthroat are not characteristic, and difficult to differentiate from viral infections. Clinical manifestions may be severe, medium and mild. And all of them are capable of precipitating an attack of rheumatic fever. Recurrent streptococcal infections cause more severe rheumatic heart damage, but not glomerulonephritis, so patients with rheumatic heart disease need prophylaxis.

Streptococcal bacteria can be divided:

a). Based on hemolytic characteristic on sheep blood agar into alpha, beta and gamma hemolytic.
b). Based on serologic test into group A to Q (without I and J) while group A is further divided into at least 49 types (subgroup).

Group A strains release a number of extracellular antigen.

Treatment: Early and adequate treatment of streptococcal infections means preventing rheumatic fever and rheumatic heart disease. The drug of choice are: penicillin, erythromicyn, lyncomycin. Sulfonamide definitely not indicated for treatment since it may do more harm than good, its values is only for prophylaxis.

RINGKASAN DAN KESIMPULAN

Pharingitis karena Streptococcus punya hubungan erat dengan terjadinya glomerulonephritis dan demam rheumatik. Incidensnya bervariasi antara 0,3—3%. Di Indonesia incidens demam rheumatik masih tinggi, sehingga

dengan demikian kita dapat mengambil kesimpulan bahwa incidens infeksi streptococcus juga tinggi.

Gejala klinis dari pharingitis karena steptococcus tidak khas, sehingga sukar untuk didifferensiasi dengan pharingitis karena virus. Ada tiga tingkatan gejala klinis, yalah berat, medium dan ringan, dan semuanya ini dapat merupakan pendahuluan dari demam rheumatik.

Infeksi streptococcus yang berulang-ulang akan memberatkan kerusakan valvula pada kelainan jantung rheumatik, sehingga pada kelainan ini perlu dilakukan profilaksi. Tapi profilaksi ini tak perlu dikerjakan pada penderita glomerulonephritis, karena padanya infeksi ulang tak memberatkan.

Bakteri streptococcus dapat diklasifikasikan sebagai berikut:

a). Didasarkan pada sifat-sifat haemolisisnya pada agar darah kambing, maka bakteri ini diberi nama: alpha-, beta-, dan gamma-haemolisis.

b). Didasarkan pada test serologis maka diberi nama grup A – Q (tanpa I dan J), sedang grup A sendiri dibagi jadi paling sedikit 45 tipe (subgrup).

Strain group A dapat melepaskan sejumlah antigen extracellular.

Pengobatan: Bila kita melakukan pengobatan awal dan cukup berarti kita mencegah terjadinya demam rheumatik dan kelainan jantung rheumatik. Obat-obat yang paling baik untuk infeksi ini yalah: penicilin, erythromycin dan Lincomycin. Sulfa tidak dapat digunakan sebagai pengobatan, karena resikonya lebih besar daripada kegunaanya. Tapi sulfa dapat digunakan sebagai profilaksi.

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