

Lecture 44: Streptococci

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Suggested reading : Murray, Fifth Edition Chapter 23 and 24

KEY WORDS

Lancefield groups	Group B streptococcus (<i>S. agalactiae</i>)
Hemolysis (alpha, beta, gamma)	Neonatal septicemia/meningitis
Group A streptococcus (<i>S. pyogenes</i>)	CAMP test
Bacitracin susceptibility test	Hippurate hydrolysis test
M, T, R proteins	Group D streptococcus
Streptolysins O and S	Urinary tract infection/ endocarditis
Lipoteichoic acid/F protein	Bile-esculin test
Rheumatic fever/carditis/arthritis	Enterococci
Glomerulonephritis	Non-enterococci
Scarlet fever	Large colony
Erythrogenic toxin	Minute colony
Toxic shock-like syndrome/bacteremia	Viridans streptococci
“Flesh-eating bacteria”	Dental caries/endocarditis
Pyrogenic toxin	

Streptococci are facultative anaerobic, Gram positive organisms that usually observed as chains (but sometimes pairs) and are catalase negative (staphylococci are catalase positive). Streptococci are sub-divided into groups with antibodies that recognize carbohydrate antigens. These groups may include one or more species. The most important groupable streptococci are A, B and D. Among the groupable streptococci, most commonly infectious disease (particularly pharyngitis) is caused by group A which is thus emphasized here. *Streptococcus pneumoniae* (a major cause of human pneumonia) and *Streptococcus mutans* and other so-called viridans streptococci (among the causes of dental caries) do not possess group antigens.

Three types of hemolysis reaction are seen after growth of streptococci on sheep blood agar (alpha, beta and gamma). α refers to partial hemolysis with a green coloration (from production of an unidentified product of hemoglobin) seen around the colonies; β refers to complete clearing and γ means there is no lysis. Group A and group B streptococci are β hemolytic, whilst D are usually α or γ . *Streptococcus pneumoniae* and viridans ("green") streptococci are α hemolytic. The hemolysis reaction along with one physiologic characteristic is considered adequate for clinical identification.

Group A streptococcus (*S. pyogenes*)

This organism most commonly causes a suppurative, but non-invasive pharyngitis and less frequently the skin infection, impetigo. Rheumatic fever is a non-suppurative disease of the heart that can occur after the initial pharyngitis subsides. A severe form of "invasive" bacteremia, a toxic shock-like syndrome (as seen with *S. aureus*) is occasionally seen and these strains are sometimes referred to as "flesh eating" bacteria.

Group A streptococcal infections affects all ages with peak incidence at 5-15 years of age. The serious complications (including rheumatic fever and invasive bacteremia) primarily affect those with some underlying defect in their immune system (including infants, elderly people and those immunocompromised). However, previously healthy children and adults are definitely at risk of serious complications.

Rheumatic fever: Rheumatic fever is an inflammatory disease affecting primarily the heart and joints. Although severe it can take an extended period of time to develop. The mechanism of chronic immunopathology of rheumatic fever is not resolved. Immunity to M protein leads to the development of autoimmunity against heart myosin. Also the group A streptococcal cell wall is highly resistant to degradation in the host. These antigens persist for months *in vivo* and experimentally elicit diseases that resemble rheumatic arthritis and carditis. Rheumatic arthritis should not be confused with the most common rheumatic disease - rheumatoid arthritis. Early termination of throat infections with penicillin therapy decreases the incidence of the subsequent development of rheumatic carditis.

Acute glomerulonephritis: is an immune complex disease of the kidney.

Scarlet fever: The characteristic rash is caused by erythrogenic toxin which is phage encoded.

Bacteremia and toxic-shock: Invasive (and sometimes fatal) forms of streptococcal infections occur associated with a toxic shock-like disease (including rash, fever and shifting of fluid from the bloodstream to peripheral tissues with resulting edema) and/or necrotizing myositis and fasciitis. These strains often produce pyrogenic toxins (A, B and C). Pyrogenic toxin is a superantigen (a mitogen) for T cells causing non-specific activation of the immune system. This may be involved in pathogenesis. This disease is still uncommon but can progress very quickly (a few days) and is life-threatening. Pyrogenic toxin and erythrogenic toxin are now known to be the same protein!

General features in pathogenesis

Adhesion: Lipoteichoic acid is localized in the cell membrane of many bacteria. For group A streptococci, much is also present in the fimbriae on the cell exterior. Lipoteichoic acid and "F (fibronectin-binding) protein" bind streptococci to epithelial cells via fibronectin.

(1) In the test tube: Group A streptococci, in the absence of fibrinogen, fix complement to the peptidoglycan layer and (in the absence of antibodies) are phagocytosed by leukocytes. (2) In

vivo (non-immune individual): The M protein (also found in fimbriae) binds fibrinogen from plasma and blocks the binding of complement to the underlying peptidoglycan. This allows survival of the organism by inhibiting phagocytosis. (3) *In vivo* (immune individual): neutralizing antibodies reactive with M protein elicit phagocytosis which results in killing of the organism. This is the major mechanism by which immunity is able to terminate group A streptococcal infections.

Unfortunately certain M protein types cross-react antigenically with the heart and may be responsible for rheumatic carditis. The fear of autoimmunity has rightly caused caution concerning the use of group A streptococcal vaccines. However, distinct protective versus cross-reactive epitopes have been defined and a vaccine has been developed. M proteins vary antigenically between strains; thus immunity to one M protein does not imply general immunity to all *S. pyogenes* strains. M typing along with other antigens (T and R) were primarily used for serotyping; but now largely replaced by sequencing of the gene coding for M protein.

Strains can be mucoid or non-mucoid; mucoid strains having prominent capsules are also important in inhibiting phagocytosis.

Laboratory diagnosis

1. Direct detection without culture- the antigen is extracted from a throat swab. The antigen extract will then bind with antibody specific to the group A streptococcal carbohydrate. This has classically involved agglutination of antibody-coated beads. However, tests that are easier to read have been introduced. Results are available within minutes.

2. Testing colonies:

- (i) Lancefield grouping of isolated beta hemolytic colonies (see above).
- (ii) Colonies are beta hemolytic and their growth is inhibited by bacitracin.
- (iii) Colonies are beta hemolytic and they hydrolyze pyrrolidonyl amidase - red product.

3. Testing patient serum for antibodies to streptolysin O or other streptococcal antigens (serology). This is important if delayed clinical sequelae occur.

β hemolysis is caused by two hemolysins O and S; the former is inactive in the presence of oxygen. Thus stabbing of the plate increases the intensity of the hemolysis reaction.

Group B streptococcus (*S. agalactiae*)

These organisms cause neonatal meningitis and septicemia after transmission from the normal vaginal flora of the mother.

The organism can be identified on the basis of β hemolysis, hydrolysis of hippurate and

the CAMP reaction. CAMP is an abbreviation for the names of the 4 individuals who originally described the test. Group B streptococci produce a factor that increases β hemolysis of an *S. aureus* indicator strain.

Group D streptococcus

Growth on bile-esculin produces a black precipitate derived from esculin; many other bacteria will not grow in the presence of bile. Group D streptococci are divided into those that will grow in 6.5% saline (enterococci) and those that will not (non-enterococci). Enterococci much more commonly cause human disease than non-enterococci. Enterococci are often resistant to many common antibiotics. Enterococci are distantly related to other streptococci and have been moved into the genus *Enterococcus*; the most commonly isolated is *E. (S.) faecalis*. As the name implies enterococci are found in the gut flora and infection often follows from fecal contamination. Enterococcal infections are a significant cause of urinary tract infections (much less common than *E. coli*) and also opportunistic infections (including intra-abdominal, septicemia and endocarditis). Colonies are usually α or γ hemolytic.

Other β hemolytic groups

Groups C and G occasionally (and rarely group F) can cause human disease (particularly pharyngitis).

Minute colony streptococci

The normal human flora contains organisms that may be group A or C, other groups, or non-groupable. Group A (minute colony) do not cause rheumatic fever.

Viridans streptococci

A diverse group of species commonly found orally (including *S. mutans*). Cause endocarditis after release into the bloodstream from tooth extraction. They are also involved in dental caries. Are α hemolytic and negative for other tests described above. They are non-groupable

