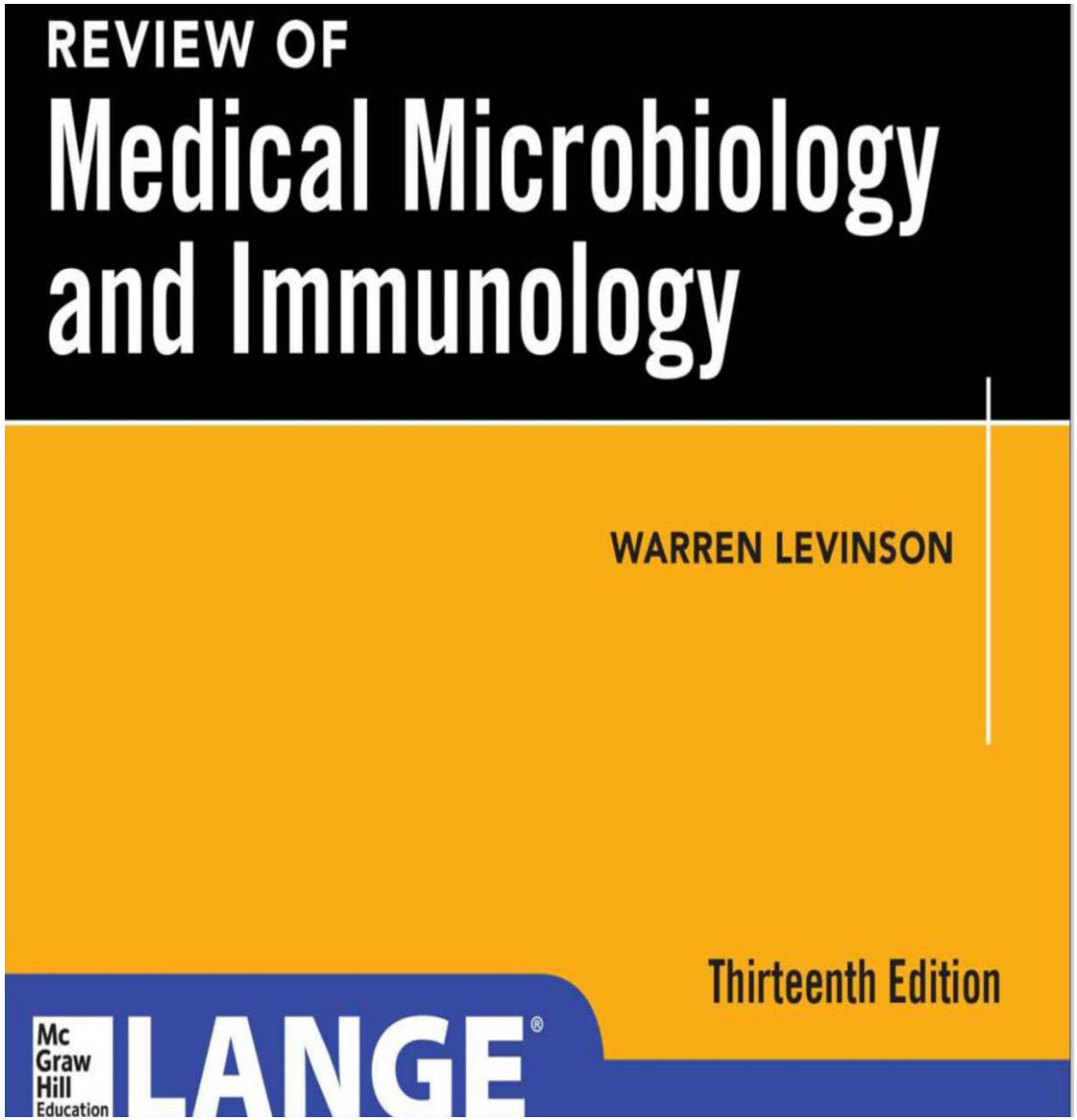
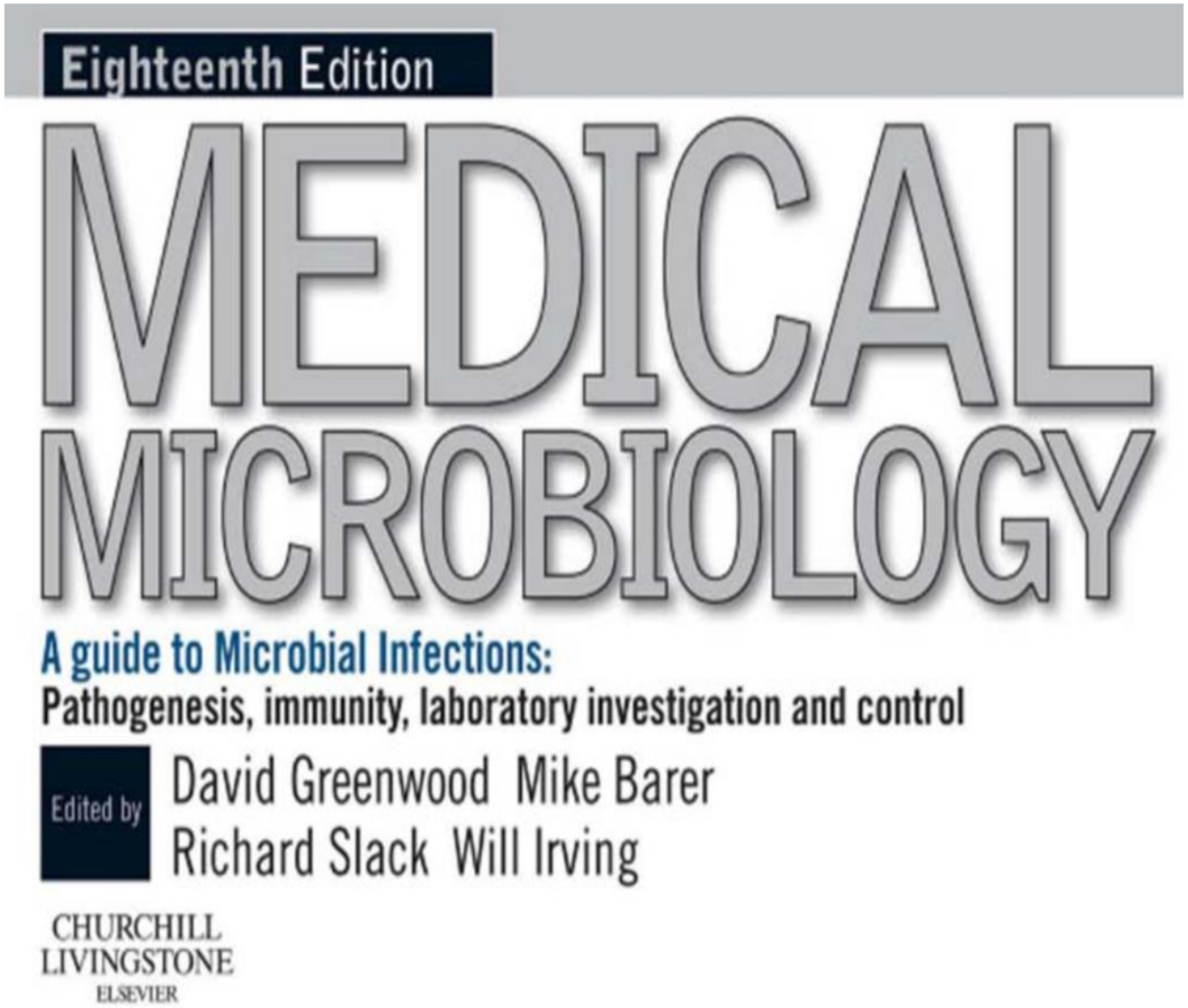
Levinson, W., Review of medical microbiology and immunology. Fourteenth edition. ed. 2016, New York: McGraw-Hill Education. ix, 821 pages.





Chapter 14-15, all tables and figures taken from this chapter

STREPTOCOCCUS

- The “other” Gram positive Coccus
- Streptococci of medical importance are shown in the following table table.
- streptococci (especially those of medical importance) are many, and thus we use a classification system to group and classify them
- This grouping according to the genetic features of these organisms is what we use to diagnose diseases caused by these bugs rather by species.

Important Properties

- Streptococci are Gram-positive cocci arranged in chains or pairs
- All streptococci are catalase-negative, whereas staphylococci are catalase-positive
- However to be able to tolerate oxygen reactive species, they contain superoxide dismutase

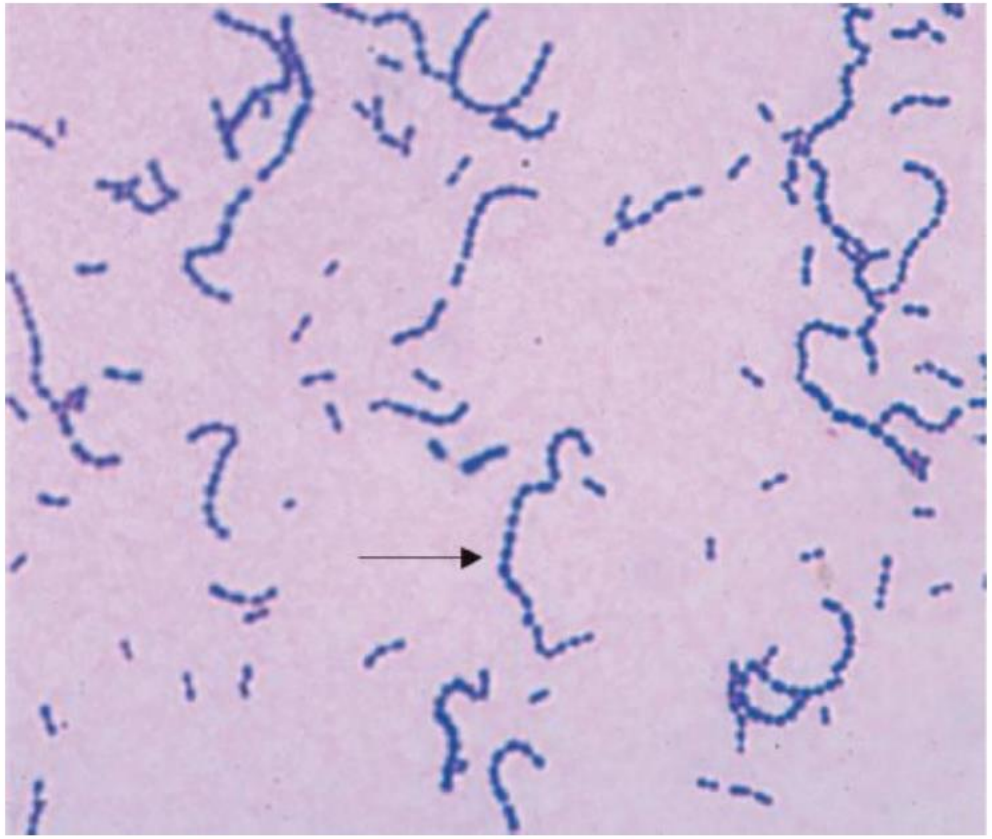


FIGURE 15–11 *Streptococcus pyogenes*—Gram stain. Arrow points to a long chain of gram-positive cocci. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

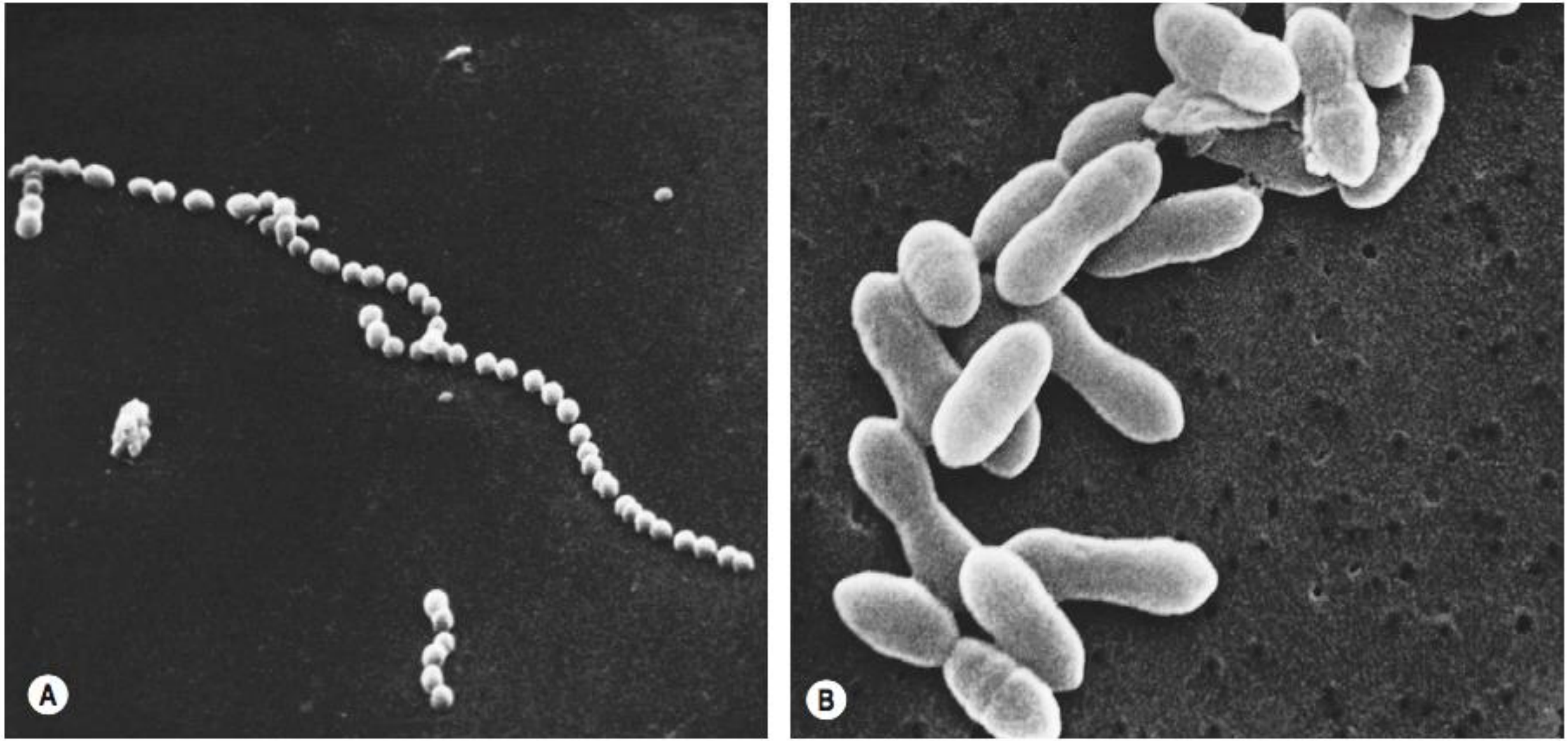


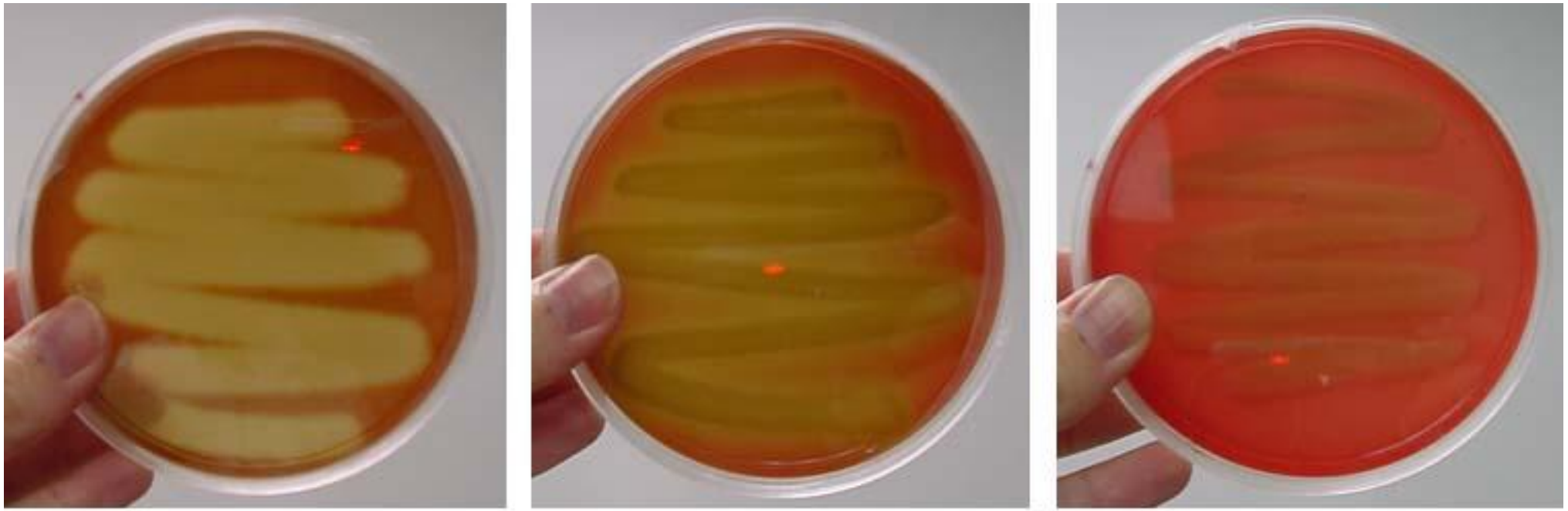
Fig. 16.1 Scanning electron micrograph of (A) *Str. pyogenes* showing typical chain formation (original magnification ×2000) and (B) *Str. pneumonia* showing typical diplococcus formation (original magnification ×7000). Courtesy of AP Shelton, University Hospital, Nottingham.

Sorting through the streps

- Due to the large number of streptococci , to hone in on the ones that are causative of disease (in this case URTI), a combination of two systems were devised

- Hemolysis: pathogenic strains (disease causing strains) are usually able to completely break down blood when these bacteria are grown on a sheep blood agar (beta hemolysis), commensals are either alpha hemolytic (partial destruction of RBCs) or gamma hemolytic (no hemolysis)

One of the most important characteristics for identification of streptococci is the type of hemolysis



Beta Hemolysis

Alpha Hemolysis

Gamma Hemolysis

http://iws2.collin.edu/dcain/CCCCD%20Micro/Hemolysis3.jpg

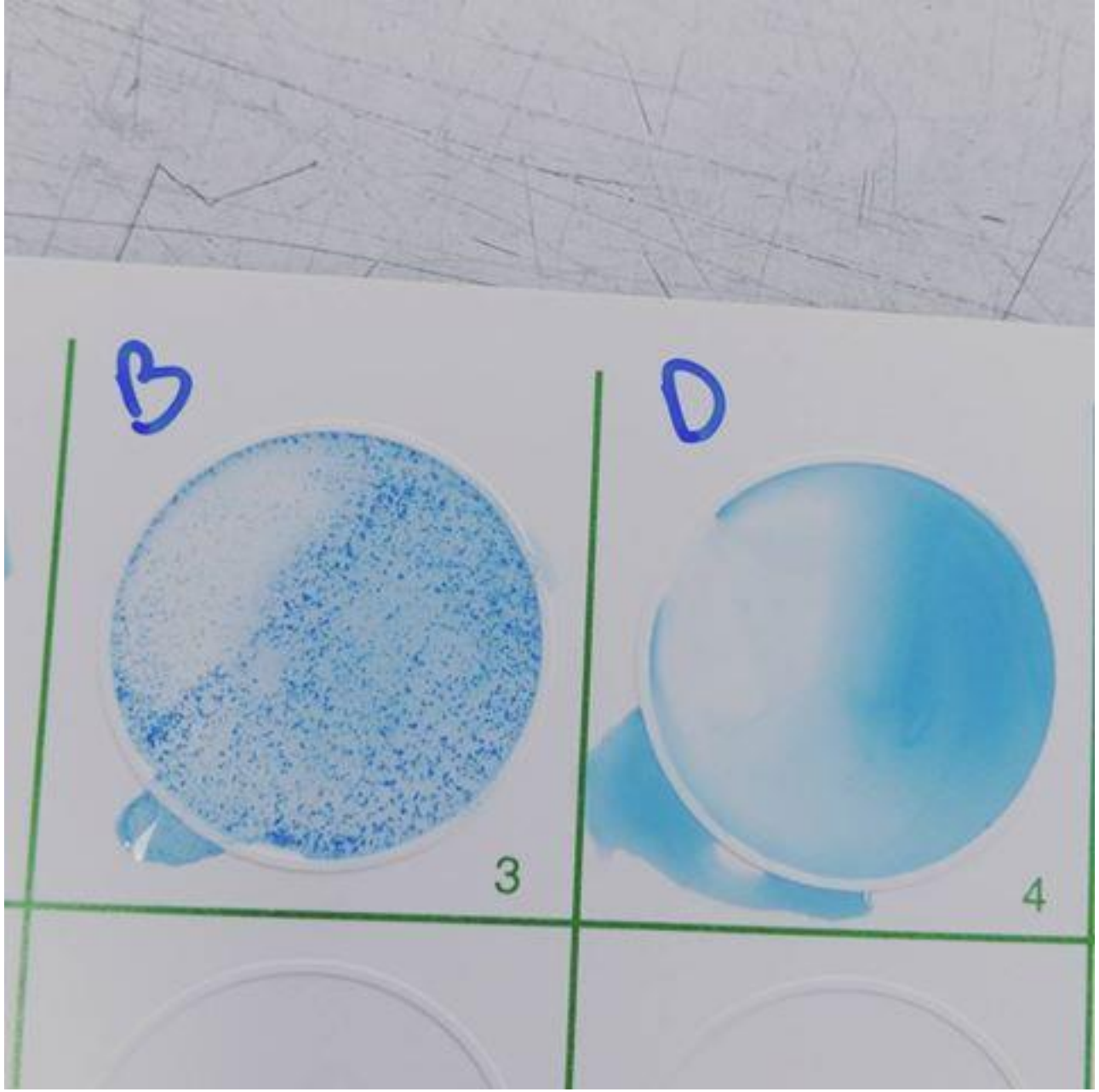
- (1) α-Hemolytic streptococci form a **green** zone around their colonies as a result of incomplete lysis of red blood cells in the agar. The green color is formed when hydrogen peroxide produced by the bacteria oxidizes hemoglobin (red color) to biliverdin (green color).

- (2) β-Hemolytic streptococci form a clear zone around their colonies because complete lysis of the red cells occurs. β-Hemolysis is due to the production of enzymes (hemolysins) called streptolysin O and streptolysin S (see “Pathogenesis” later).
-
- (3) Some streptococci are nonhemolytic (γ-hemolysis).

Lancefield Grouping

- Lancefield is a bacteriologist
- Serological identification (based on the presence of polysaccharide and teichoic acid antigens of streptococci), grouped them into groups
- Nowadays latex agglutination is used
- Only those that are Catalase negative and coagulase negative are grouped
- Groups A B and D are human pathogens

- the antibodies are bound on latex, once you pass the serum on the latex (well) beads will form (seen in B) if the antigen is not present to that specific antibody on the latex, no beads form (D)



http://www.imgrum.org/user/pleasebcereus/2671522170/1213225676180680696_2671522170

Species	Lancefield Group	Typical Hemolysis	Diagnostic Features[1]
S. pyogenes	A	β	Bacitracin-sensitive
S. agalactiae	B	β	Bacitracin-resistant; hippurate hydrolyzed
E. faecalis	D	α or β or none	Growth in 6.5% NaCl[2]
S. bovis[3]	D	α or none	No growth in 6.5% NaCl
S. pneumoniae	NA[4]	α	Bile-soluble; inhibited by optochin
Viridans group[5]	NA	α	Not bile-soluble; not inhibited by optochin

Resistant to penicillins

sensitive to penicillins

[1] All streptococci are catalase-negative.

[2] Both *E. faecalis* and *S. bovis* grow on bile-esculin agar, whereas other streptococci do not. They hydrolyze the esculin, and this results in a characteristic black discoloration of the agar.

[3] *S. bovis* is a nonenterococcal group D organism.

[4] NA, not applicable.

[5] Viridans group streptococci include several species, such as *S. sanguinis, S. mutans, S. mitis, S. gordonii, S. salivarius, S. anginosus, S. milleri,* and *S. intermedius.*

https://i.imgur.com/w4tWgwx.png

Group A Beta hemolytic streptococci (GAS)

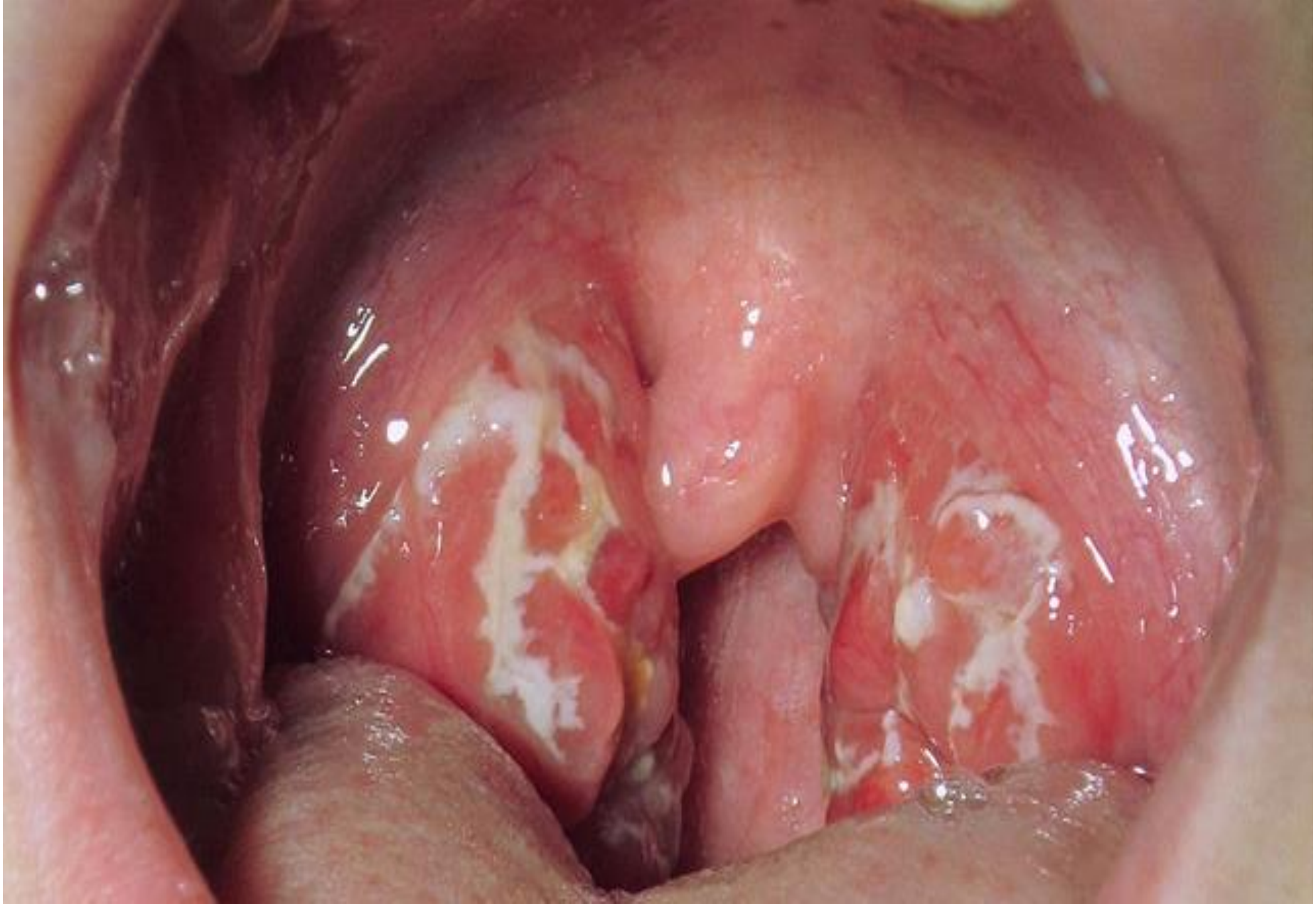
- ***STREPTOCOCCUS PYOGENES (GAS)***
- This species consists of Lance field group A streptococci, is **among the most prevalent of human bacterial pathogens**.
- **GAS are exclusively human pathogens.**
- It causes a wide range of suppurative (pus forming) infections in:
- 1) the respiratory tract (Pharyngitis)
- 2)skin
- 3) life-threatening soft tissue infections, and certain types of **toxin-associated reactions**.
- Streptococci have serious hallmark POST infective IMMUNOLOGICAL reactions
- A similar spectrum of infections may be caused by the closely related group C and group G streptococcis (*Str. equisimilis,* also known as *Str. dysgalactiae subspecies equisimilis*).

Pathogenesis

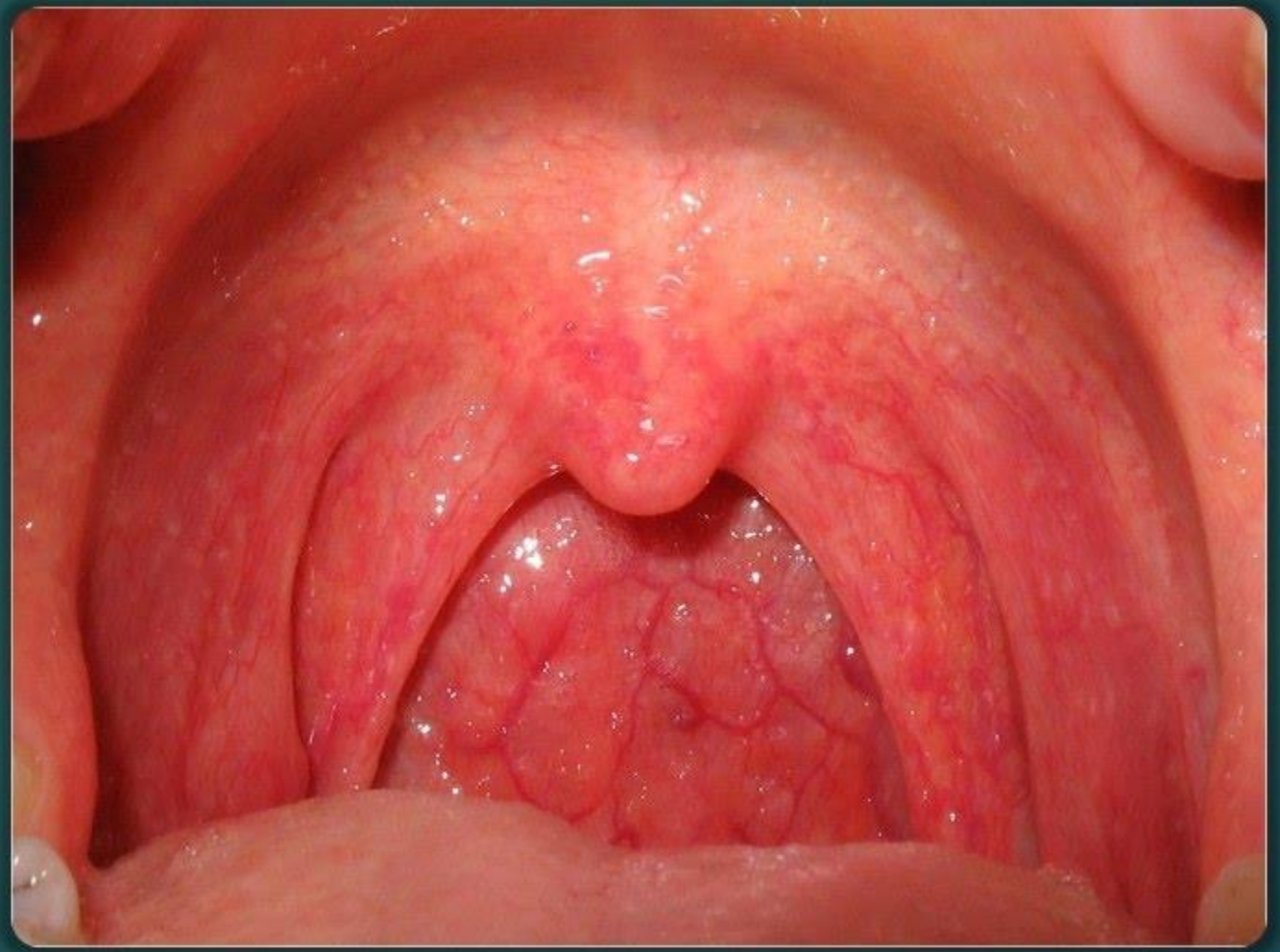
- Group A streptococci (*S. pyogenes*) cause disease by three mechanisms all similar to staph (both are skin flora):
- (1) pyogenic inflammation, which is induced locally at the site of the organisms in tissue (whether in the pharynx or skin);
- (2) exotoxin production, which can cause widespread systemic symptoms in areas of the body where there are no organisms;
- (3) immunologic, which occurs when antibody against a component of the organism cross-reacts with normal tissue or forms immune complexes that damage normal tissue (post strep diseases).
- The immunologic reactions cause inflammation (e.g., the inflamed joints of rheumatic fever), but there are no organisms in the lesions.

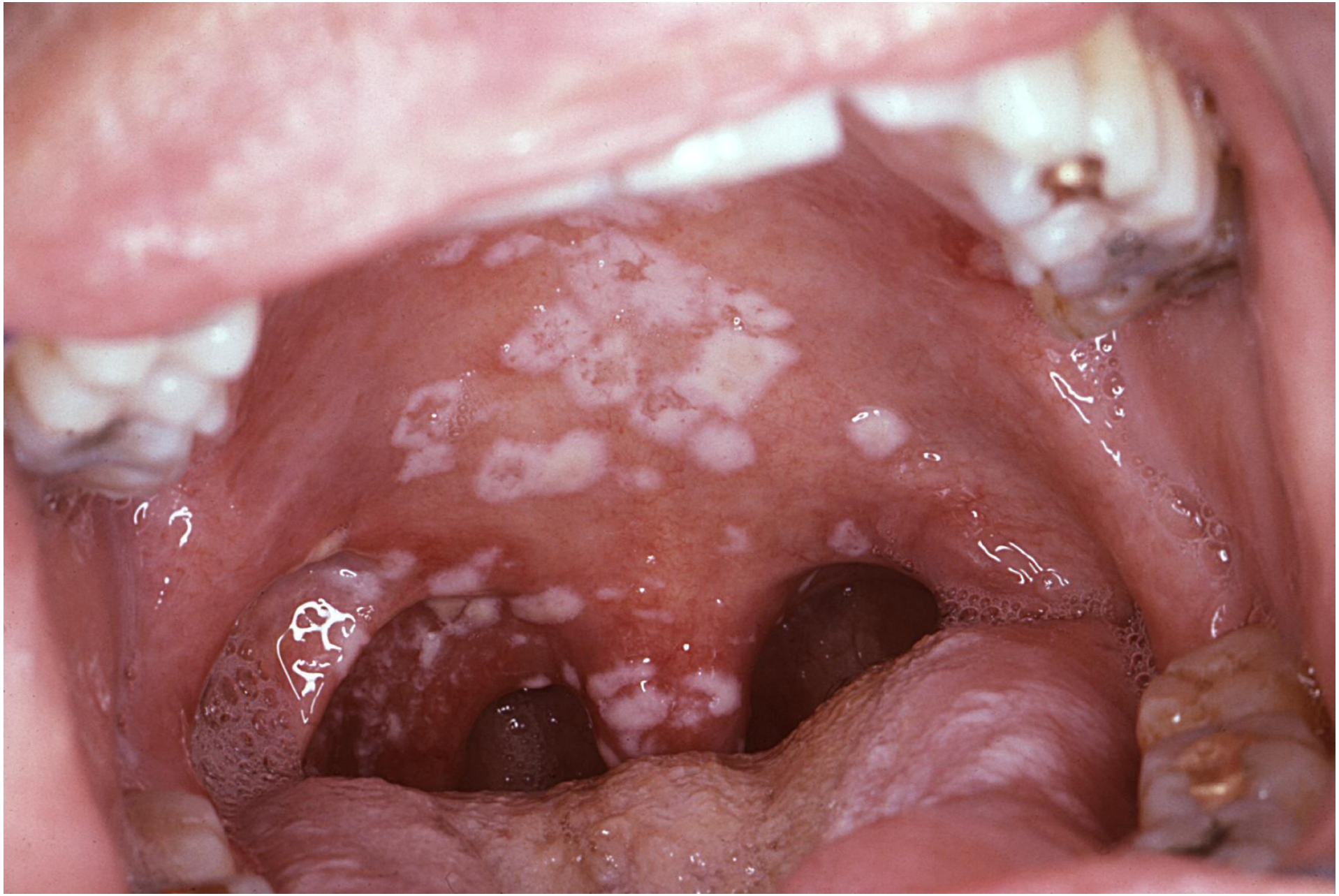
Transmission

- *S. pyogenes* is **found** on the skin and in the oropharynx in small numbers;
- Unlike other streptococci that cause illness opportunistically (they are commensals, commonly found in the body)
- When someone who is infected coughs or sneezes, the bacteria travels in small droplets of water called respiratory droplets and infect others

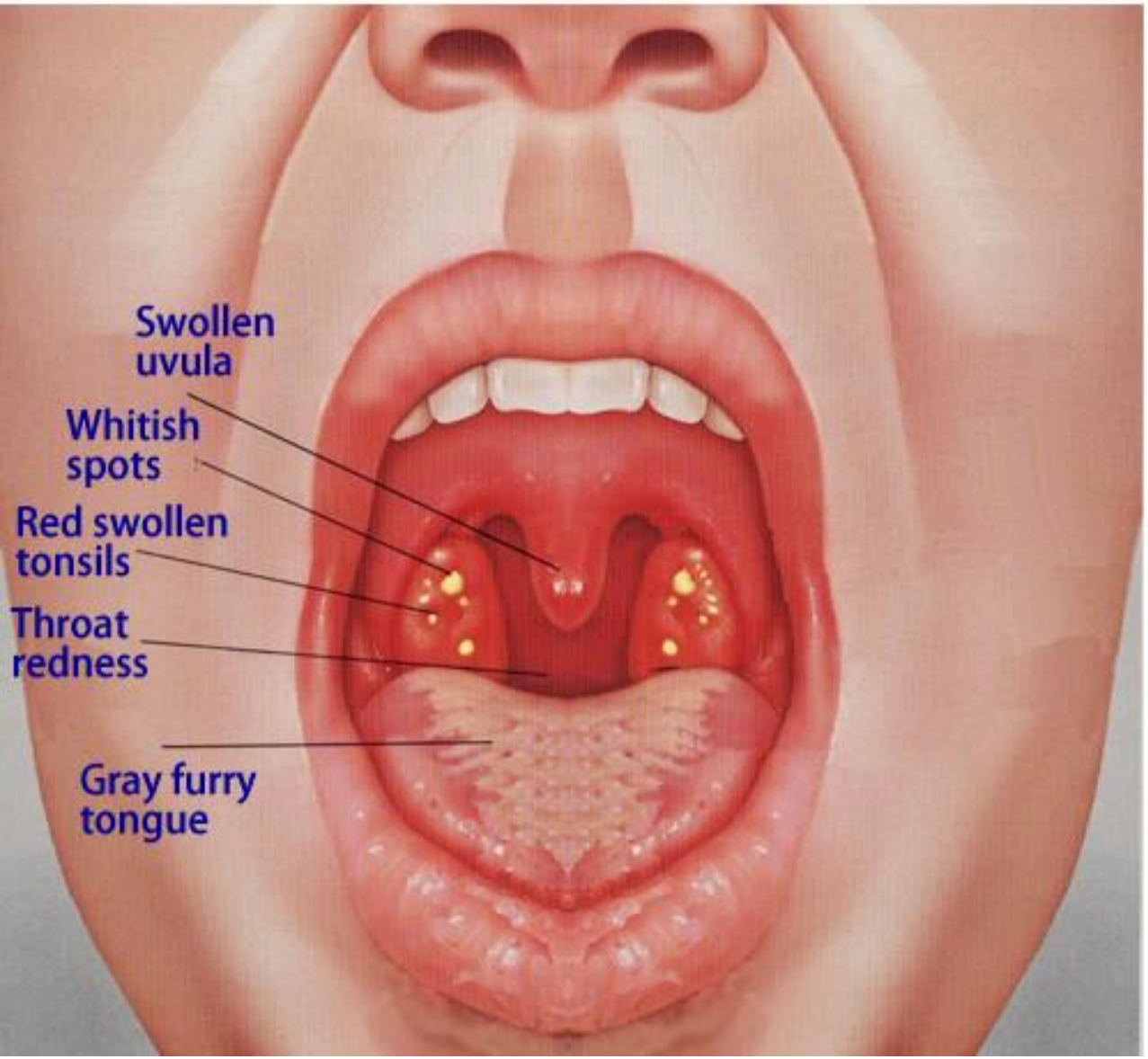


Viral Pharyngitis

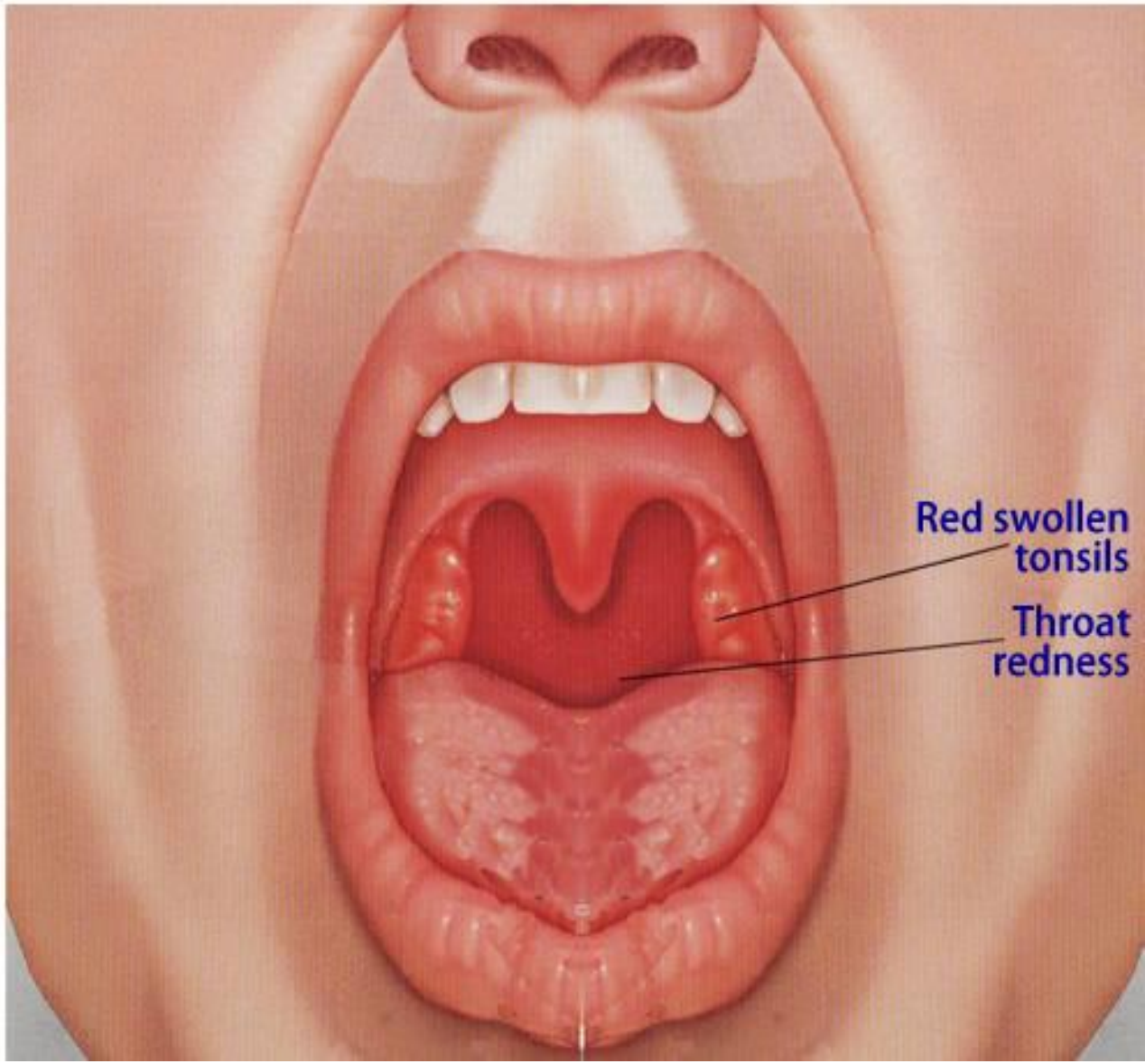




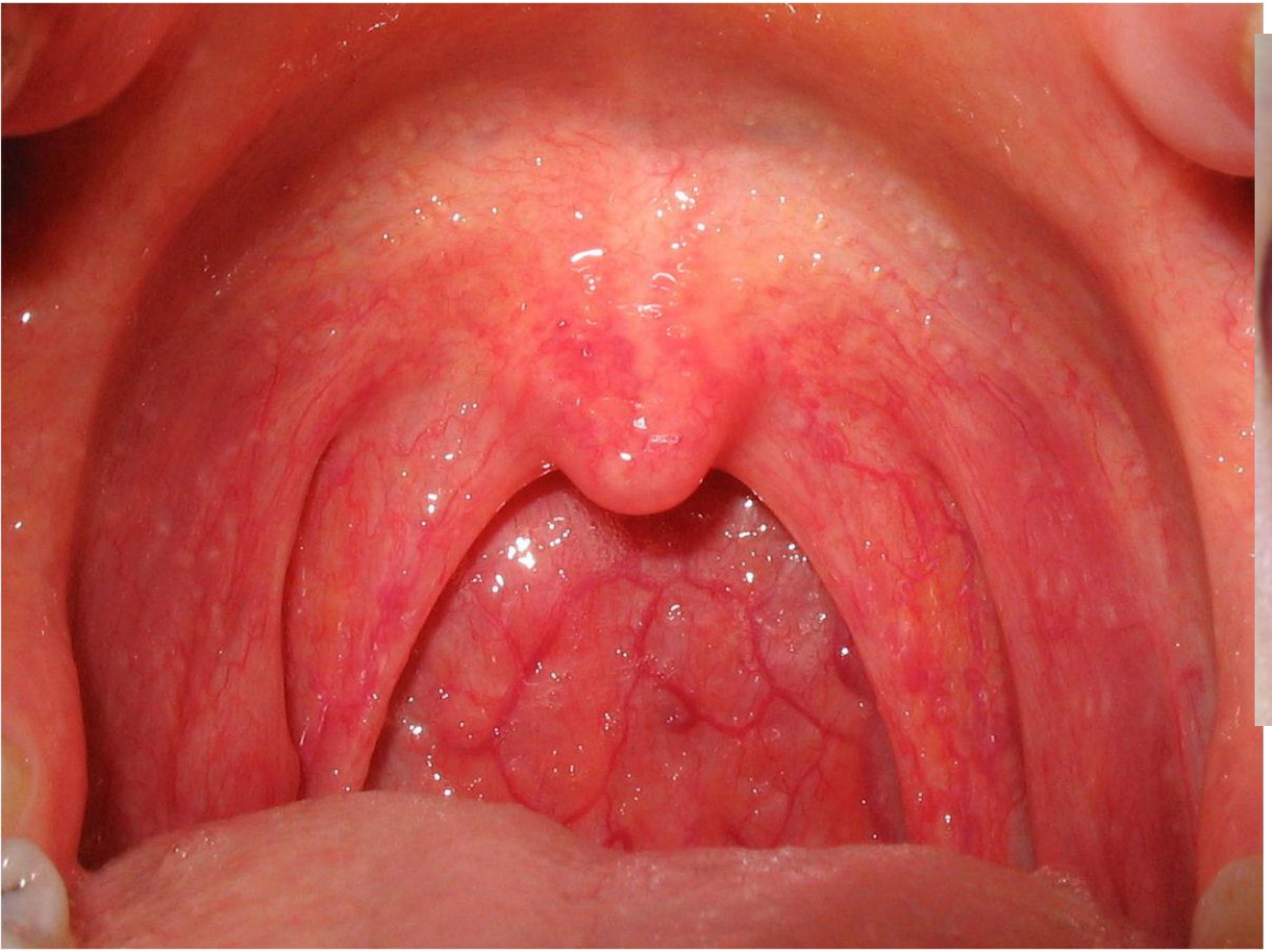
Bacterial

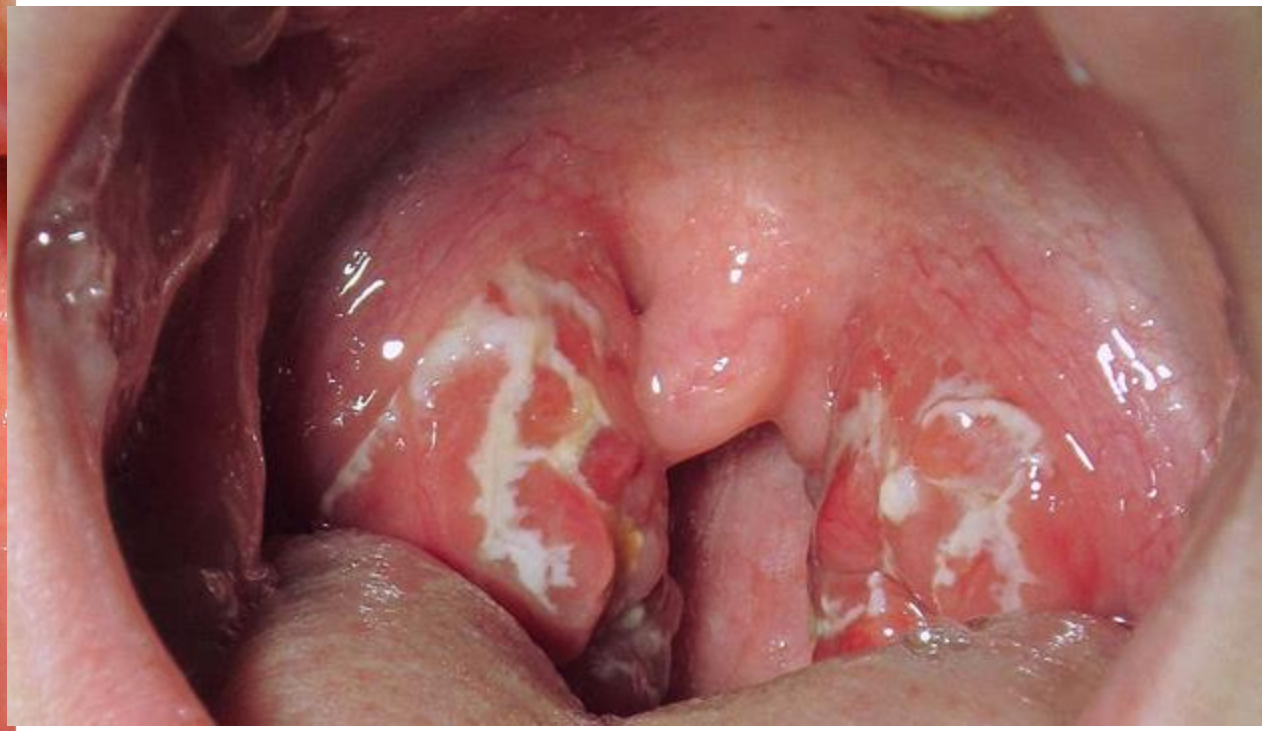


Viral



http://www.tabletsmanual.com/wiki/read/angina



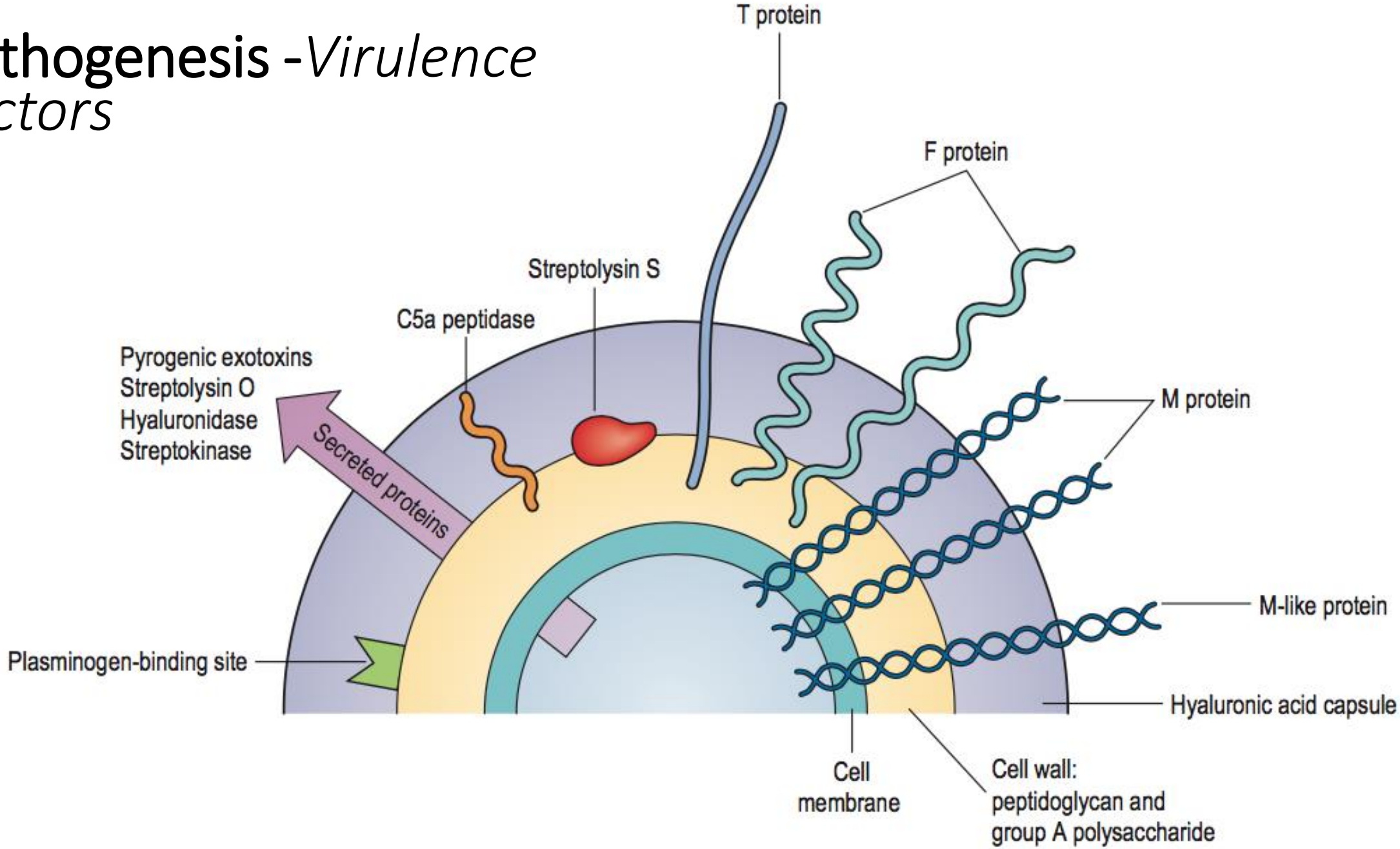


https://en.wikipedia.org/wiki/Pharyngitis

http://rebelem.com/patients-strep-throat-need-treated-antibiotics/

Organism	Type of Pathogenesis	Typical Disease	Main Site of Disease (D), Colonization (C), or Normal Flora (NF)
S. pyogenes (group A)	1. Pyogenic		
	a. Local	Impetigo, cellulitis	Skin (D)
		Pharyngitis	Throat (D)
	b. Disseminated	Sepsis	Bloodstream (D)
	2. Toxigenic	Scarlet fever	Skin (D)
		Toxic shock	Many organs (D)
	3. Immune-mediated (poststreptococcal, nonsuppurative)	Rheumatic fever	Heart, joints (D)
		Acute glomerulonephritis	Kidney (D)
S. agalactiae (group B)	Pyogenic	Neonatal sepsis and meningitis	Vagina (C)
E. faecalis (group D)	Pyogenic	Urinary tract infection, endocarditis	Colon (NF)
S. bovis (group D)	Pyogenic	Endocarditis	Colon (NF)
S. pneumoniae	Pyogenic	Pneumonia, otitis media, meningitis	Oropharynx (C)
Viridans streptococci	Pyogenic	Endocarditis	Oropharynx (NF)

Pathogenesis -*Virulence factors*



Adhesion.

- Bronectin, a matrix protein present on eukaryotic cells (pharynx and skin) is recognized by surface F protein on *S. pyogenes*.
- This binding interaction between GAS F protein and bronectin, also facilitates internalization of bacteria into host cells.
- Adhesion is also aided by other factors that are common on the surface of Gram positive bacteria F protein, surface-exposed lipoteichoic acid and M proteins (see later) to be involved in adherence to mucosal and skin epithelial cells.

M proteins.

- M proteins provide GAS with the ability to resist phagocytosis by host polymorphonuclear leucocytes
- Some strains produce two different M proteins with antiphagocytic activity, and some an additional structurally related M-like protein.
- What these proteins do is they bind host (self) proteins and coat the bacterial surface with them (host proteins such as brinogen, plasminogen, albumin, immunoglobulin (Ig) G, IgA, the proteinase inhibitor α2-macroglobulin.
- They also prevent opsonisation of C3b and even some regulatory factors from the complement system.
- Resistance to GAS is formed when antibodies are formed against the M protein, however, the distal part of the protein shows hyper variability and thus recurrent infections

Capsule.

- Although rarely seen in UNCOMPLICTAED cases, severe and difficult cases are often found to be capsulated.
- Capsule are anti-phagocytic factors of their own right and have a different mechanism from M proteins, this combined anti-phagocytic effect of M protein and capsule make these strains much harder to clear and thus a lot more
- The capsule is identical to the hyaluronic acid of the connective tissue of the host and is not immunogenic. In this way the bacteria can disguise themselves with an immunological ‘self’ substance.

C5a peptidase.

- The C5a peptidase is present on the surface of all strains
- *Str. pyogenes*. It specifically cleaves, and thereby inactivates, human C5a, one of the principal chemo- attractants of phagocytic cells.

Streptolysins.

- *Str. pyogenes* produces two distinct haemolysins (haeme lysing enzymes, they lyse RBCs and some PMNs), Streptolysin O (oxygen labile) and S (serum soluble).
- Streptolysin O belongs to a family of haemolysins found in many pathogenic bacteria. (when injected into experimental animals it causes death within seconds)
- Significant use for this, is to detect PREVIOUS GAS infections as Streptolysin O is immunogenic

Other virulence factors

- SPE-A, SPE-B and SPE-C are Pyrogenic (fever inducing) and erythrogenic (rash inducing) exotoxins.
- These function as super antigens and cause an exaggerated immune response (rash), the cytokines induced by these erythrogenic toxins are thought to be responsible for the hypotensive shock and organ failure in severe GAS infections.

- These exotoxins are implicated in scarlet fever (see later) and Toxic shock

Invasion/escape factor

- *GAS* secrete hyaluronidase to degrade hyaluronic acid, the ground substance of host connective tissue. Usually pathogenic bacteria harbor this enzyme which facilitates tissue invasion.
- Streptokinase, in contrast so S.A. (which use staphylokinase to wall themselves with coagulated plasma) Streptococci use their streptokinase to stop host build up of serum barriers, thus facilitating spread (over abscess formation in Staphylococci)
- DNAase, eznymes to break DNA net that is released from phagocytes (‘neutrophil extracellular traps’).

Clinical features

Transmission

- The most common route of entry of *GAS* is the upper respiratory tract, and is usually the primary site of infection and also serves as a focus for other types of infection.
- Spread from person to person is by respiratory droplets or by direct contact with infected wounds or sores on the skin.
- Not all individuals colonized by *Str*. *pyogenes* in the upper respiratory tract develop clinical signs of infection.
- After an acute upper respiratory tract infection, the convalescent patient may carry the infecting streptococci for some weeks.
- Only a few healthy adults carry *Str*. *pyogenes* in the respiratory tract, but the carriage rate in young school children is just over 10%. It may be considerably higher before or during an epidemic.

summary of Clinical Findings

- S. pyogenes causes three types of diseases:
- (1) pyogenic diseases such as pharyngitis and cellulitis,
- (2) toxigenic diseases such as scarlet fever and toxic shock syndrome
- (3) immunologic diseases such as rheumatic fever and acute glomerulonephritis (AGN).
- *S. pyogenes* (group A streptococcus) is the most common bacterial cause of pharyngitis (sore throat).
- Streptococcal pharyngitis (strep throat) is characterized by throat pain and fever.
- On examination, an inflamed throat and tonsils, often with a yellowish exudate, are found, accompanied by tender cervical lymph nodes. 💬
- If untreated, spontaneous recovery often occurs in 10 days, but rheumatic fever may occur.
- Untreated pharyngitis may extend to the middle ear (otitis media), the sinuses (sinusitis), the mastoids (mastoiditis), or the meninges (meningitis), Continuing inability to swallow may indicate a peritonsillar or retropharyngeal abscess.

Non invasive disease (Pharyngitis and Skin infection)

- The most common infections caused by *Str*. *pyogenes* are relatively mild and non-invasive infections of the upper respiratory tract (*pharyngitis*) and skin (*impetigo*).
- In the USA more than 10 million cases of non-invasive *Str*. *pyogenes* infection are estimated to occur annually.
- This is something you will see many many times as a GP, get familiar with it.

Pharyngitis.

- This is the most common infection caused by *Str. pyogenes*.
- Clinical signs and symptoms:
- abrupt onset of sore throat
- fever, malaise and headache generally develop 2–4 days after exposure to the pathogen.
- Redness of he posterior
- **enlarged tonsils** that may show **patches of grey–white exudate** on their surface
- Inflammation causes swelling of cervical lymph nodes.
- tonsillar abscesses may develop, these are very painful and potentially dangerous as the pathogen may spread to neighbouring regions and to the bloodstream.

This slide is important

- **Despite the significant symptoms and clinical signs → differentiating streptococcal pharyngitis (‘*strep throat*’) from viral pharyngitis is impossible without microbiological or serological examination.**
- **Culture studies show that 20–30% of cases of pharyngitis are associated with *Str. pyogenes* and *Str. equisimilis*.**
- **What does that mean?**
- **It means we are treating viruses with antibacterial agents! And we are causing positive selection and aiding in the increase of antimicrobial resistance.**

Scarlet fever.

- If the GAS causing pharyngitis produces exotoxins mentioned, the URTI will be associated with a diffuse erythematous rash of the skin and mucous membranes (next slide).
- This condition is called *scarlet fever*.
- The rash develops within 1–2 days after the first symptoms of pharyngitis they are first seen on the upper chest, then extremities. After an initial phase with a yellowish-white coating, the tongue becomes red and denuded (’s*trawberry tongue*’).
- This used to be a major killer disease (esp in the current UK)

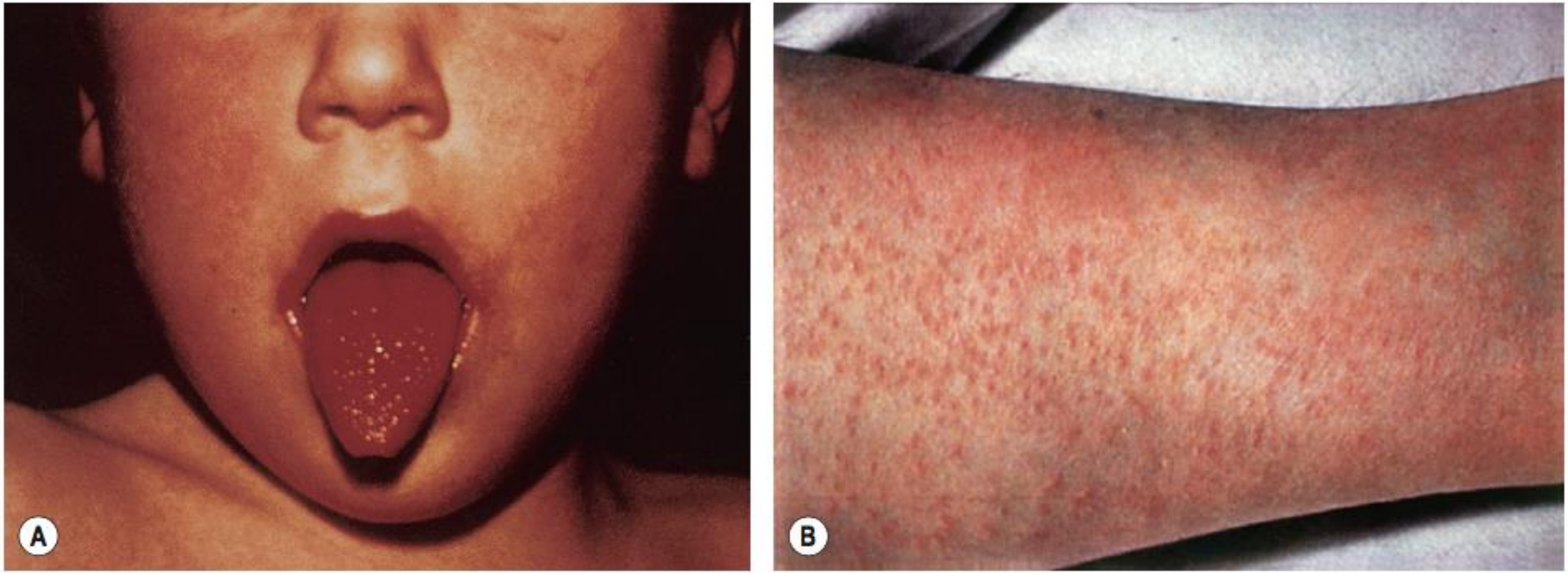
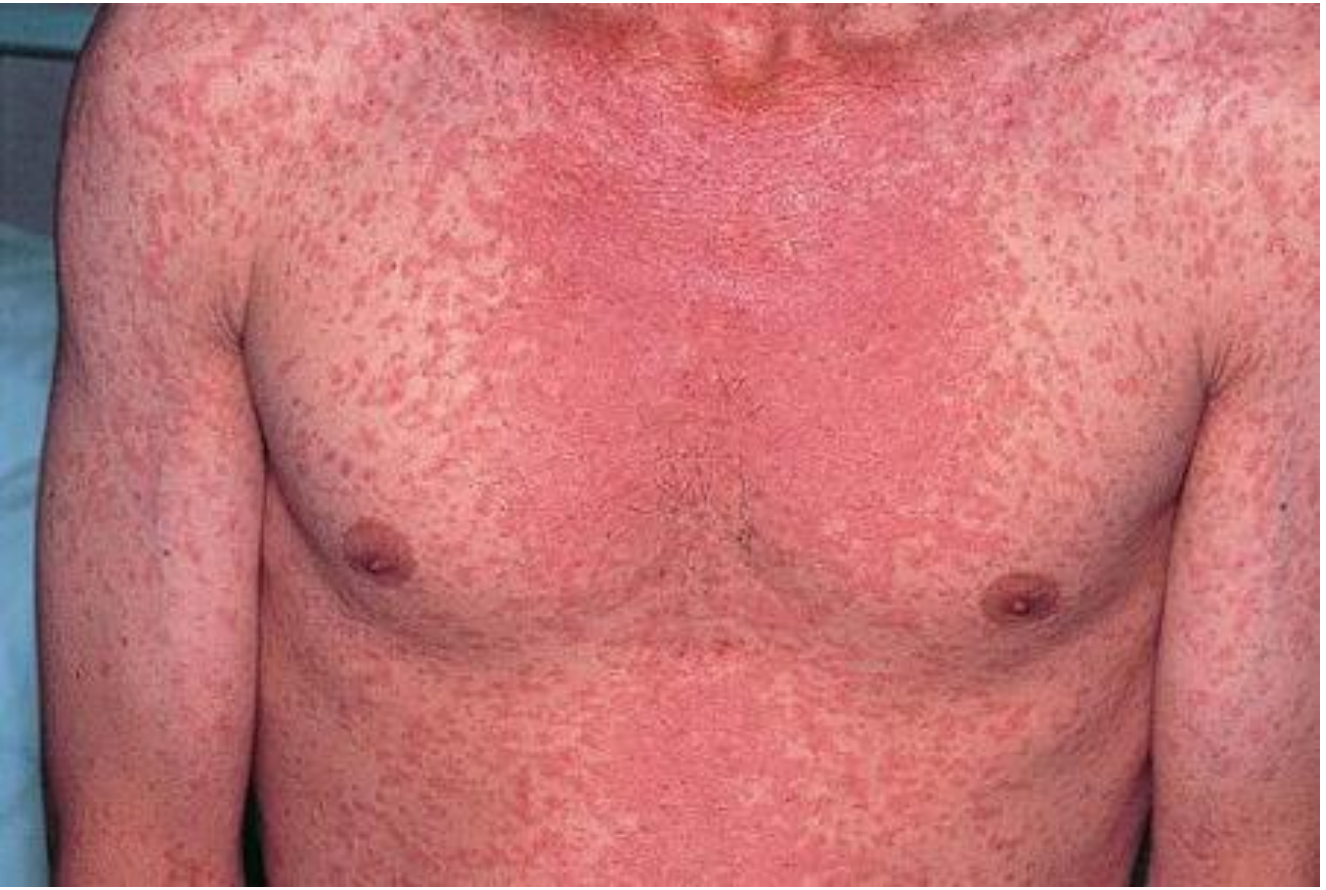


Fig. 16.3 The characteristic erythematous rash on (A) tongue and (B) skin associated with scarlet fever.

Scarlet fever



https://www.google.jo/search?q=scarlet+fever&source=lnms&tbm=isch&sa=X&ved=0ahUKEwifyJX-tLjXAhWHFuwKHTyoAGAQ_AUICigB&biw=1440&bih=754#imgrc=ji3qI8MCGty8ZM:

- Scarlet fever develops in patients that are infected with erythrogenic toxin producing GAS, in the event that the patient doesn't have the protective antibodies (antitoxin).
- The “strawberry” tongue is the characteristic lesion seen in scarlet fever.
- *S. pyogenes* also causes another toxin-mediated disease, streptococcal toxic shock syndrome, which has clinical findings similar to those of staphylococcal toxic shock syndrome.
- Different from Staph Toxic shock, streptococcal toxic shock syndrome usually has a recognizable site of pyogenic inflammation and blood cultures are often positive, whereas staphylococcal toxic shock syndrome typically has neither a site of pyogenic inflammation nor positive blood cultures. 💬
- Group A streptococci cause skin and soft tissue infections, such as cellulitis, erysipelas necrotizing fasciitis (streptococcal gangrene), and impetigo
- Impetigo: superficial skin infection characterized by “honey-colored” crusted lesions, similar to those seen in Staph infections. 💬
- Lymphangitis can occur, especially on the forearm associated with an infection on the hand.

Poststreptococcal (Nonsuppurative) Diseases

- These are disorders in which a local infection (in the tissue, not systemic infections) with **GAS** is followed **weeks (it takes that much time for enough cross reacting antibodies to be produced, remember adaptive immunity takes time to develop)** later by inflammation in an organ that was **not** infected by the streptococci.
- This is due to the inflammation caused by an immunologic (antibody mediated) response to streptococcal M proteins that cross-react with human tissues.
- Some strains of *S. pyogenes* bearing certain M proteins (remember there are 80+ types of this protein) are nephrogenic and cause AGN while other strains bearing different M proteins are rheumatogenic and cause acute rheumatic fever.

Acute Glomerulonephritis

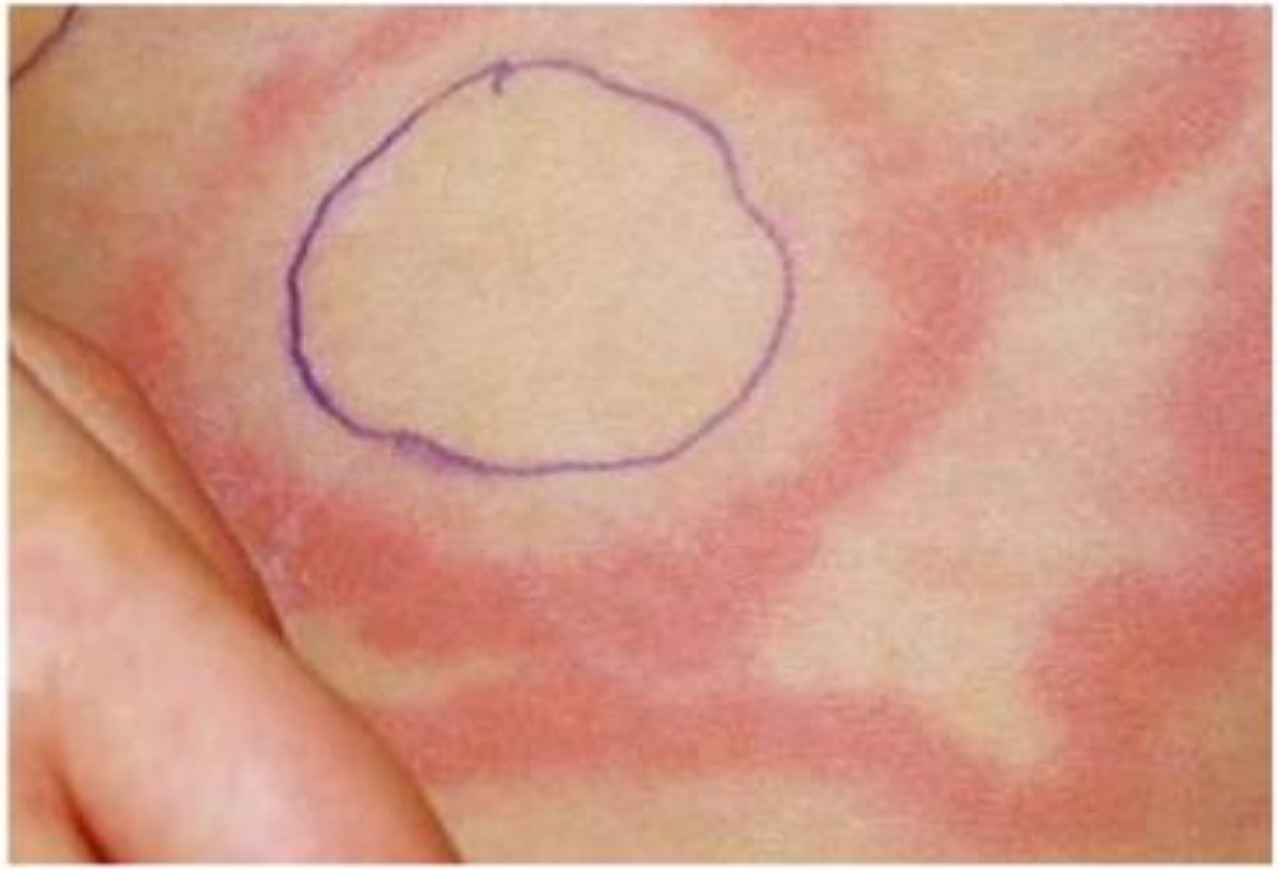
- Typically occurs 2 to 3 weeks after **skin** infection by certain group A streptococcal types in **children** (e.g., M protein type 49 causes AGN most frequently).
- AGN occurs more often following skin infections rather than after pharyngitis.
- The most striking clinical features are
  - hypertension (almost always a very odd finding in children)
  - edema of the face (especially periorbital edema) and ankles (loss of protein)
  - “smoky” urine (due to red cells in the urine).
- Most patients recover completely, however they are still not prone to develop this again if reinfection with streptococci happens.
- The antibodies cross react to a self antigen the glomerular basement membrane, and soluble antigens from streptococcal membranes may be the inciting cross reacting antigen (the antigen-antibody complexes deposit in the glomerular Basement membrane.
- **It can be prevented by early eradication of nephritogenic streptococci from skin colonization sites but not by administration of penicillin after the onset of symptoms (why?).**
- → Antibodies would have already developed at this point, destroying the bacteria will not stop antibodies

Acute Rheumatic Fever

- Approximately 2 **weeks after a group A streptococcal infection—usually pharyngitis (opposite to AGN) —rheumatic fever can occur.**
- RF is characterized by
- 1- fever,
- 2-migratory polyarthritis
- 3- carditis, may develop (heart damage).
- The carditis (inflammation of heart muscle tissue) is the most serious, as damage to the myocardial and endocardial tissue, especially the mitral and aortic valves, can result in vegetation on the valves.
- 4- Uncontrollable, spasmodic movements of the limbs or face (chorea) may also occur (brain damage).
- **ASO titers and the erythrocyte sedimentation rate (ESR) are elevated.**
- Note that group A streptococcal **skin** infections do not cause rheumatic fever, most cases of pharyngitis caused by group A streptococci occur in children age 5 to 15 years, and hence rheumatic fever occurs in that age group.

- Similar to post strep AGN, rheumatic fever is due to an immunologic reaction between cross-reacting antibodies to certain streptococcal **M proteins** and antigens of joint (migratory polyarthritis), heart (carditis), and brain tissue (chorea).
- It is also an autoimmune disease, however, unlike post strep AGN, it is GREATLY exacerbated(made worse) by recurrence of streptococcal infections.
- If streptococcal infections are treated **within 8 days** of onset (onset of pharyngitis in this case), rheumatic fever is usually prevented.
- After a heart-damaging attack of rheumatic fever, reinfection must be prevented **by long-term prophylaxis**.
- In the United States, fewer than 0.5% of group A streptococcal infections lead to rheumatic fever, but in developing tropical countries, the rate is higher than 5%.

Rheumatic fever-diagnosis



Erythematous patches with central clearing

Erythema marginatum

https://www.slideshare.net/azadhaleem/rheumatic-fever-46427613

Laboratory Diagnosis Microbiologic

- Gram-stained smears are useless in streptococcal **pharyngitis** because viridans streptococci are members of the normal flora and cannot be visually distinguished from the pathogenic *S. pyogenes*.
- However, stained smears from **skin** lesions or wounds that reveal streptococci are diagnostic.
- Cultures of swabs from the pharynx or lesion on blood agar plates show small, translucent β-hemolytic colonies in 18 to 48 hours. If inhibited by bacitracin disk (sensitives to bacitracin), they are likely to be group A streptococci.
- Group B streptococci are characterized by their ability to hydrolyze hippurate and by the production of a protein that causes enhanced hemolysis on sheep blood agar when combined with β-hemolysin of *S. aureus* (CAMP test).
- Group D streptococci hydrolyze esculin in the presence of bile (i.e., they produce a black pigment on bile-esculin agar).
- The group D organisms are further subdivided: the enterococci grow in hypertonic (6.5%) NaCl, whereas the nonenterococci do not.


Bacitracin test for *Streptococcus pyogenes*


HARDY
DIAGNOSTICS
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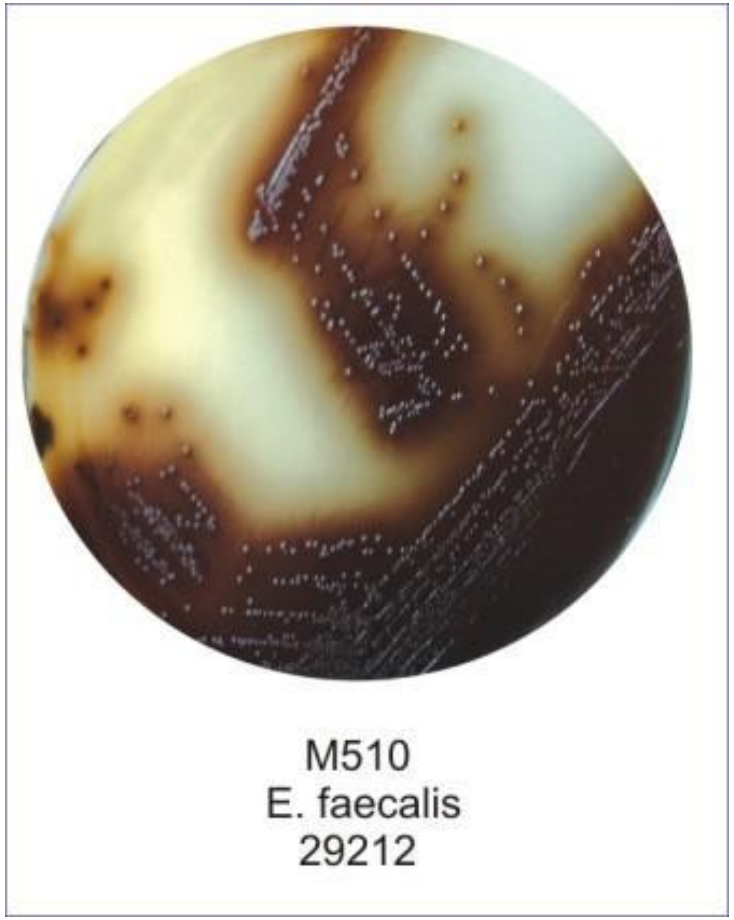
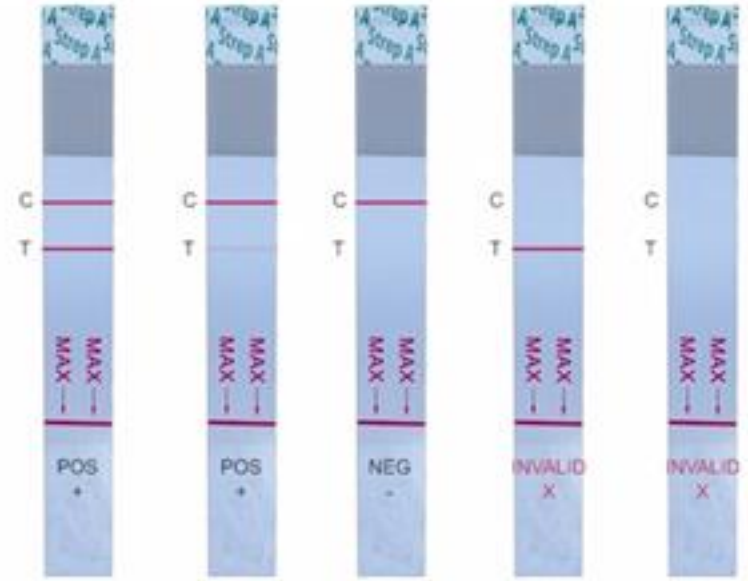
Bile esculin : *e. faecalis*



- Although cultures remain the gold standard for the diagnosis of streptococcal pharyngitis, a problem exists because the results of culturing are not available for at least 18 hours, and it is beneficial to know while the patient is in the office whether antibiotics should be prescribed. For this reason, rapid tests that provide a diagnosis in approximately 10 minutes were developed.
- The rapid test detects bacterial antigens in a throat swab specimen. In the test, specific antigens from the group A streptococci are extracted from the throat swab with certain enzymes and are reacted with antibody to these antigens bound to latex particles.
- Agglutination of the colored latex particles occurs if group A streptococci are present in the throat swab. The specificity of these tests is high, but the sensitivity is low (i.e., false-negative results can occur).
- If the test result is negative but the clinical suspicion of streptococcal pharyngitis is high, a culture should be done.

RST, rapid step test (GAS)



Serologic

- ASO titers are high soon after group A streptococcal infections.
- Since the bacteria is usually cleared by the time antibodies develop for RF, patients suspected of having rheumatic fever, an elevated ASO titer is typically used as evidence of previous strep THROAT infection.
- Titers of anti-DNase B are high in group A streptococcal **skin** infections and serve as an indicator of previous streptococcal infection in patients suspected of having AGN.

Treatment

- Group A streptococcal infections can be treated with either penicillin G or amoxicillin (as mentioned this is not protective for antibody mediates illnesses such as rheumatic fever or AGN, these patients do not benefit from penicillin treatment after the onset of the two diseases).
- In mild group A streptococcal infections, oral penicillin V can be used.
- In penicillin-allergic patients, erythromycin or one of its long-acting derivatives (e.g., azithromycin) can be used. However, erythromycin-resistant strains of *S. pyogenes* have emerged that may limit the effectiveness of the macrolide class of drugs in the treatment of streptococcal pharyngitis.
- Clindamycin can also be used in penicillin-allergic patients.
- *S. pyogenes* is not resistant to penicillins.

Prevention

- Rheumatic fever can be prevented by **prompt treatment** of group A streptococcal **pharyngitis** with penicillin.
- In susceptible people (previous infection) Prevention of streptococcal infections (usually with benzathine penicillin once each month for several years).
- There is no evidence that patients who have had AGN require similar penicillin prophylaxis.

- **There are no vaccines available against any of the streptococci except *S. pneumoniae***