

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 next table.
- All none *streptococcus pneumoniae* will be discussed first, followed by a separate topic for *S. pneumoniae* the most important streptococcus.
- unlike staphylococci, streptococci (especially those of medical importance) are many, and thus we use a classification system and we diagnose disease by classification 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



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.)

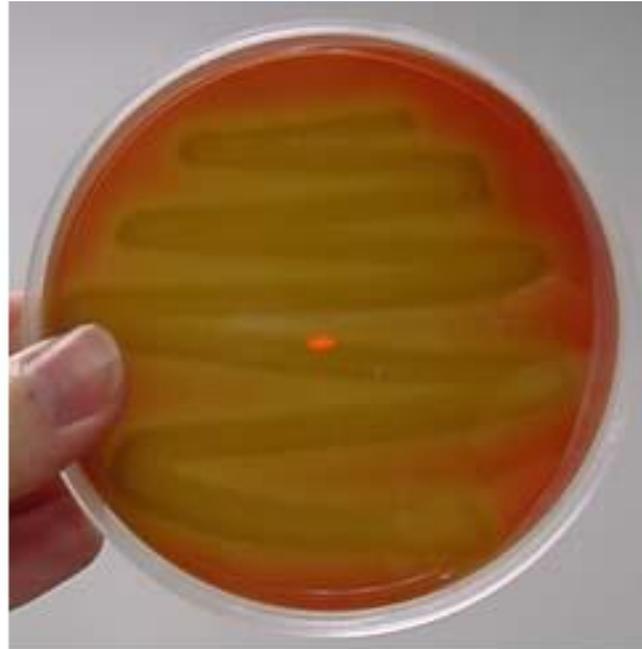
Lancefield Grouping

- 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

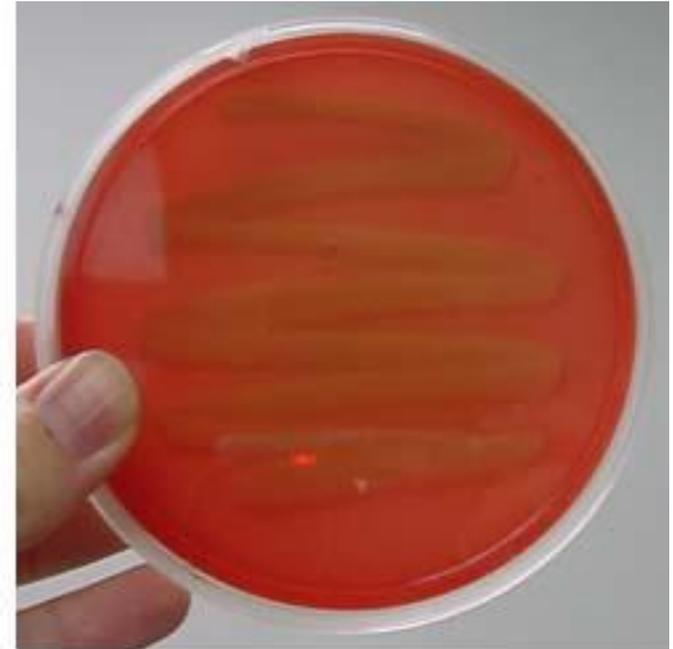
One of the most important characteristics for identification of streptococci is the type of hemolysis



Beta Hemolysis



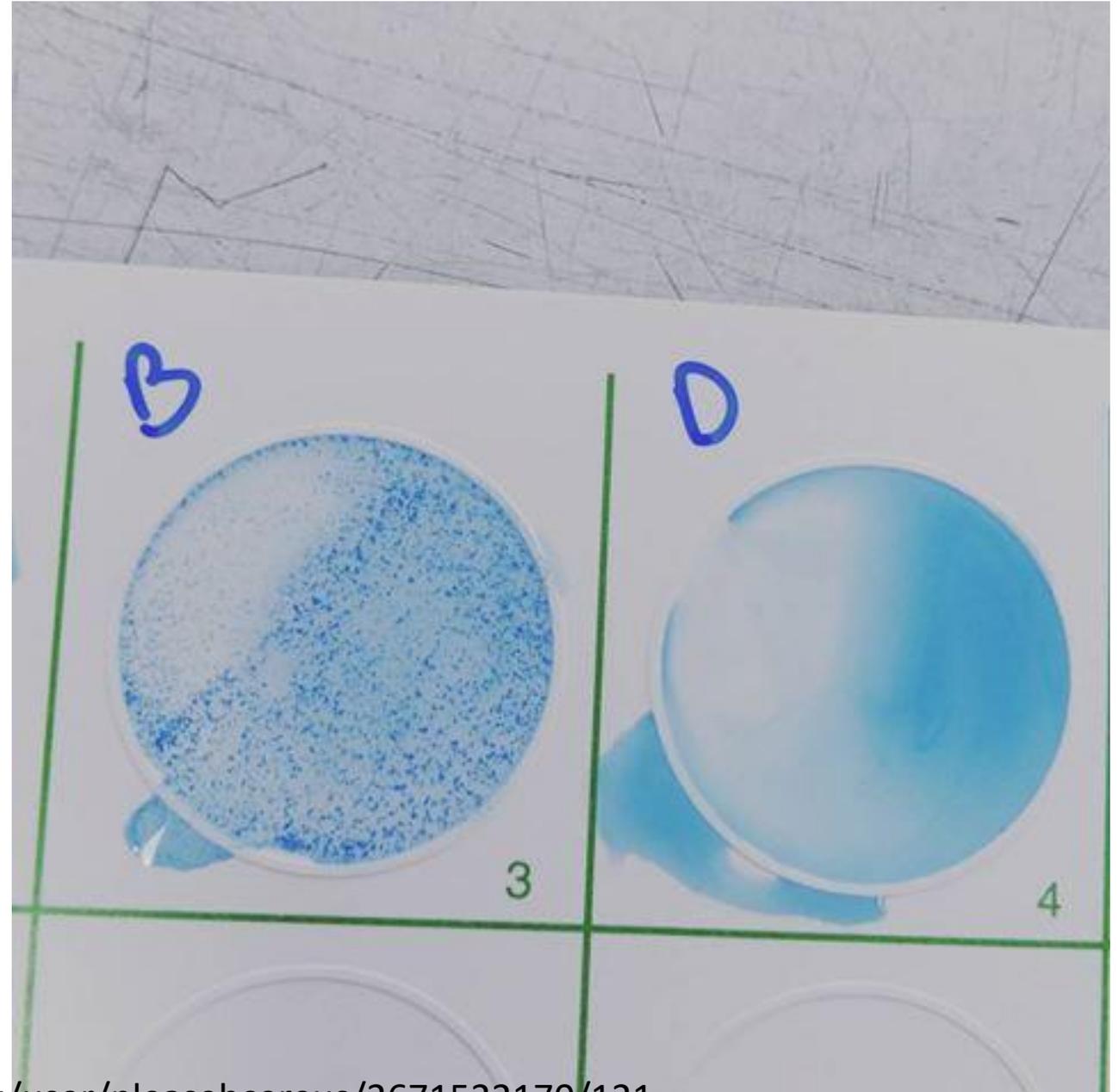
Alpha Hemolysis



Gamma Hemolysis

- (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).

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



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

¹All streptococci are catalase-negative.

²Both *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.

⁴NA, not applicable.

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

Diseases

- Streptococci cause a wide variety of infections.
- Lancefield, group A streptococcus (*S. pyogenes*) is the **leading** bacterial cause of **pharyngitis and cellulitis** (soft tissue infection).
- It is an important cause of **impetigo** (similar to S.a.), as well as **necrotizing fasciitis, and streptococcal toxic shock syndrome (similar toxin to that present in S.a.)**.
- Even though Kawasaki isn't proven to be caused by an immunologic reaction to Staph, there are two immunologic reactions that are proven to be caused by streptococci (**rheumatic fever –which also affects the heart- and acute glomerulonephritis- affect the kidney**).

- *Streptococcus agalactiae* (group B streptococcus) is the leading cause of **neonatal sepsis and meningitis.**
- *Enterococcus faecalis* is an important cause of hospital-acquired **urinary tract infections and endocarditis. 1**
- Viridans group streptococci are the most common cause of **endocarditis. 2**
- *Streptococcus bovis* also causes **endocarditis. 3**



FIGURE 15-9 Cellulitis. Note erythema and swelling of the dorsum of the foot. *Streptococcus pyogenes* is the most common cause of cellulitis. (Courtesy of Richard P.

If left untreated, can be fatal.



FIGURE 15-8 Pharyngitis. Note erythema of soft palate, uvula, and posterior pharynx and swelling of the uvula. The most common bacterial cause of pharyngitis is *Streptococcus pyogenes*. Note: The curved white lines on the uvula and the palate are artifacts of photography. (Source: Centers for Disease Control and Prevention. CDC #6323.)

- There are two important antigens of β -hemolytic streptococci:
- (1) **C carbohydrate** determines the **group** of β -hemolytic streptococci. It is located in the **cell wall**, and its specificity is determined by an amino sugar.
- (2) M protein is the most important virulence factor and determines **the type** of group A β -hemolytic streptococci.
- It protrudes from the outer surface of the cell and interferes with ingestion by phagocytes (i.e., it is antiphagocytic).

- Antibody to M protein provides ONLY type-specific immunity.
- This is because there are approximately 80 serotypes based on the M protein, hence, you can get multiple infections with *S. pyogenes* from different serotypes.
- Strains of *S. pyogenes* that produce certain homologue of the M protein types are found to be rheumatogenic (i.e., cause primarily rheumatic fever), whereas other strains of *S. pyogenes* that produce other M protein types are more nephritogenic (i.e., cause primarily acute glomerulonephritis).
- Although M protein is the main antiphagocytic component of *S. pyogenes* (it prevents complement activation), the organism also has a polysaccharide capsule that works similar to other capsules (negative charge).

Classification of Streptococci

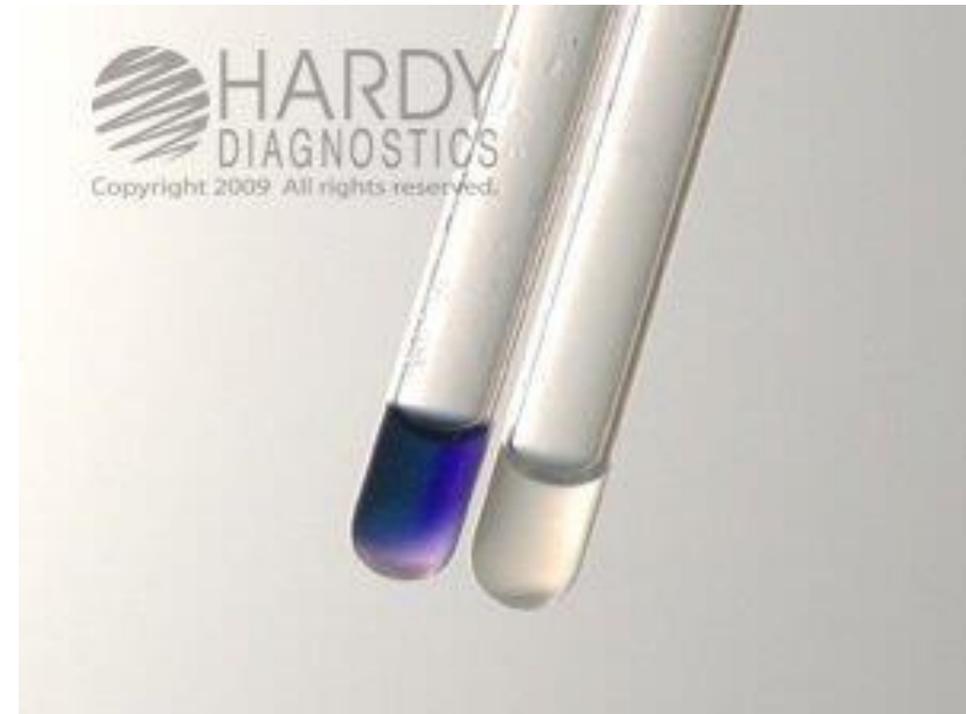
β-Hemolytic Streptococci

- These are the ones that are arranged into groups A–U (Lancefield groups) on the basis of antigenic differences in C carbohydrate.
- In the clinical laboratory, the group is determined by precipitin tests with specific antisera or by immunofluorescence.
- Group A streptococci (*S. pyogenes*) are one of the most important human pathogens, these are the most common bacterial cause of pharyngitis and one of the very common causes of skin infections.
- They possess two factors that allow them to adhere to pharyngeal epithelium via pili composed of lipoteichoic acid and the M protein.
- Many strains have a hyaluronic acid capsule that is antiphagocytic.
- The growth of *S. pyogenes* is differentiated from other beta hemolytic streptococci by its sensitivity to bacitracin (an antibiotic) added to the agar- complete hemolysis + bacitracin = non *S. pyogenes*



Bacitracin test for *Streptococcus pyogenes*

- Group B streptococci (*S. agalactiae*) has a different disease profile, it colonizes the genital tract of some women and can cause neonatal meningitis and sepsis (when the baby passes through the birth canal). (*Staph saprophyticus* –only 5%)
- They are usually bacitracin-resistant. They hydrolyze (break down) hippurate, an important diagnostic criterion.
- When hippurate is hydrolysed
- by an organism glycine and benzoic acid are formed, which are Detected by a color indicator.
-



Group D streptococci

- These are the classical enteric Gram positive cocci → enterococci (e.g., *E. faecalis* and *Enterococcus faecium*)
- Nonenterococci group D → (e.g., *S. bovis*).
- *Enterococci* are members of the colon normal flora, they are known to be opportunistic pathogens in the urinary, biliary, and cardiovascular infections.
- They are very hardy organisms; they can grow in hypertonic (6.5%) saline or in bile and are not killed by penicillin G.
- This is why we utilize the synergistic combination of penicillin and an aminoglycoside (e.g., gentamicin) to kill enterococci.
- Vancomycin can also be used, but vancomycin-resistant enterococci (VRE) have emerged and become an important and much feared cause of life-threatening nosocomial infections.
- More strains of *E. faecium* are vancomycin resistant than are strains of *E. faecalis*.

Nonenterococcal group D streptococci

- The classic human pathogen is *S. bovis*, can cause similar infections to the enterococci, but are not strong as enterococci (e.g., they are inhibited by 6.5% NaCl and killed by penicillin G).
- Note that the hemolytic reaction of group D streptococci is variable: most are α -hemolytic, but some are β -hemolytic, and others are nonhemolytic.

Non- β -Hemolytic Streptococci

- Some streptococci produce no hemolysis; others produce α -hemolysis.
- The **two major α -hemolytic organisms** are 1) *S. pneumoniae* (pneumococci) and 2) the **viridans group of streptococci** (which includes, *Streptococcus mitis*, *Streptococcus sanguinis*, and *Streptococcus mutans*).
- Pneumococci and viridans streptococci are distinguished in the clinical laboratory by two main criteria:
- (1) **The growth of pneumococci is inhibited by optochin**, whereas the growth of viridans streptococci is not inhibited; and
- (2) **colonies of pneumococci dissolve when exposed to bile (bile-soluble)**, whereas colonies of viridans streptococci do not dissolve.
- *Streptococcus intermedius* and *Streptococcus anginosus* (also known as the *S. anginosus-milleri* group) are usually α -hemolytic or nonhemolytic, but some isolates are β -hemolytic, They are **found primarily in the mouth and colon**.

Viridans Group

- Those are the streptococci that remain once we exclude Beta hemolytic ones (*S. pyogenes* and *S. agalactiae*), *S. pneumoniae* and *enterococci*.
- Hemolysis (Beta) is the first exclusion criteria, they are (usually) alpha hemolytic (see later) – as in they do not cause complete hemolysis of the blood agar, but cause partial hemolysis with a remaining distinctive GREEN color-
- Viridans means green in latin
- The other exclusion criteria between the two alpha hemolytics (pneumococcus and viridans group, is the sensitivity to optochin by pneumococcus)
- Several species that are usually commensal (non pathogens in immune competent patients) but are opportunistic in immune compromised patients.

- They are the main cause of dental caries as mentioned before and are a major cause of endocarditis.
- *Since its such a major group, the identification and taxonomy is still under controversy (even alpha hemolysis!)*
- **Major differences between them and *streptococcus pneumoniae*, is their ability to resist optochin AND being bile insoluble (they don't get lysed by bile salts)**
- Enterococci are usually selected by growth on NaCl 6.5% (7.5% and above will select Staph and micrococci) and grow on Bile esculin agar
- Viridans streptococci are part of the normal flora of the human pharynx and intermittently reach the bloodstream to cause infective endocarditis.
- *S. mutans* synthesizes polysaccharides (dextrans) that are found in dental plaque and lead to dental caries
- **Biofilm formation and fermentation of sugars and production of acids is the main mechanism that causes destruction of enamel**

Peptostreptococci

- These grow under anaerobic or microaerophilic conditions and produce variable hemolysis.
- Peptostreptococci are members of the normal flora of the gut, mouth, and female genital tract and participate in mixed anaerobic infections.
- The term mixed anaerobic infections refers to the fact that these infections are caused by multiple bacteria, some of which are anaerobes and others are facultatives.
- For example, peptostreptococci and viridans streptococci, both members of the oral flora, are often found in brain abscesses following dental surgery.
- *Peptostreptococcus magnus* and *Peptostreptococcus anaerobius* are the species frequently isolated from clinical specimens.

Transmission

- Transmission is usually from the source of colonization, in this case the human throat, skin, and intestines or when producing disease when they gain access to tissues or blood.
- Viridans streptococci and *S. pneumoniae* are found chiefly in the oropharynx;
- *S. pyogenes* is found on the skin and in the oropharynx in small numbers;
- *S. agalactiae* occurs in the vagina and colon;
- enterococci and anaerobic streptococci are located in the colon.

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;
 - (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.

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

- The M protein of *S. pyogenes* is its most important antiphagocytic factor, but its capsule, composed of hyaluronic acid, is also antiphagocytic, antibodies are not formed against the capsule because hyaluronic acid is a normal component of the body (self protein).
- **Group A streptococci- *S. pyogenes***- produce three important inflammation-related –Invasion related factors: think of it as the *S. aureus* equivalent in strep
- (1) **Hyaluronidase**, this degrades hyaluronic acid, which is the ground substance of subcutaneous tissue (helps with invasion), this is why Hyaluronidase is known as spreading factor since it facilitates the rapid invasion of *S. pyogenes* in skin infections (cellulitis).
- (2) **Streptokinase (fibrinolysin)** activates plasminogen to form plasmin, which dissolves fibrin in clots, thrombi, and emboli, It can be used to lyse thrombi in the coronary arteries of heart attack patients.
- (3) **DNase (streptodornase)** degrades DNA in exudates or necrotic tissue. Antibody to DNase B develops during pyoderma; this can be used for diagnostic purposes.
- **Streptokinase–streptodornase** mixtures applied as a skin test give a positive reaction in most adults, indicating normal cell-mediated immunity.

- Similar to *S.a*, group A streptococci produce five important EXOtoxins and hemolysins:
- (1) Erythrogenic toxin causes the rash seen in scarlet fever (erythema marginatum). Its mechanism of action is similar to that of the TSST of *S. aureus* (acts as a superantigen).
- It is produced only by certain strains of *S. pyogenes* lysogenized by a bacteriophage carrying the gene for the toxin.
- The injection of a skin test dose of erythrogenic toxin (Dick test) gives a positive result in persons lacking antitoxin (i.e., susceptible persons).

Scarlet fever



Scarlet fever



Diphtheria

- (2) Streptolysin O is a hemolysin – breaks down RBCs, also similar to S.a, it is inactivated by oxygen (oxygenlabile), and this is why β -hemolysis only when colonies grow **under** the surface of a blood agar plate.
- It is antigenic, and antibody to streptolysin O (anti-ASO) develops after group A streptococcal infections. The titer of these antibodies can be important in the diagnosis of rheumatic fever.
- (3) Streptolysin S is a hemolysin that is not inactivated by oxygen (oxygenstable).
- It is **not** antigenic but is responsible for β -hemolysis when colonies grow on the surface of a blood agar plate.

- (4) Pyrogenic exotoxin A
- the toxin responsible for most cases of streptococcal toxic shock syndrome. It has the same mode of action as does staphylococcal TSST (i.e., it is a superantigen that causes the release of large amounts of cytokines from helper T cells and macrophages).
- (5) Exotoxin B is a protease that rapidly destroys tissue and is produced in large amounts by the strains of *S. pyogenes*, the so-called “flesh-eating” streptococci that cause necrotizing fasciitis.



- Pathogenesis by **group B streptococci** (*S. agalactiae*) is based on the ability of the organism to induce **an inflammatory response**.
- However, unlike *S. pyogenes*, no cytotoxic enzymes or exotoxins have been described, and there is no evidence for any immunologically induced disease.
- **Group B streptococci** have a **polysaccharide** capsule that is antiphagocytic, and anticapsular antibody is protective.
- Pathogenesis by *S. pneumoniae* and the viridans streptococci is uncertain, **as no exotoxins or tissue-destructive enzymes have been demonstrated**.
- The main virulence factor of *S. pneumoniae* is its antiphagocytic polysaccharide capsule.
- **Many of the strains of viridans streptococci that cause endocarditis produce a glycocalyx** that enables the organism to adhere to the heart valve
- **(viridans = biofilm, pneumococcus= capsule, GAS = exotoxins and invasive enzymes, GBS = inflammatory)**

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.



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

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

- 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.



FIGURE 15–14 Erysipelas. Note well-demarcated border of the inflamed area. *Streptococcus pyogenes* is the most common cause of erysipelas. (Reproduced with permission from Longo DL et al (eds): *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill, 2012. Copyright © 2012 by The McGraw-Hill Companies, Inc.)

<http://diseasespictures.com/wp-content/uploads/2013/01/Lymphangitis-2.jpg>

- Pregnant women are usually susceptible to these bugs, Group A streptococci can cause endometritis (puerperal fever, infection of the uterine lining), which may progress into sepsis, if the causing GAS is of the M protein type that can cause AGN, it will develop in these patients (Immune-mediated poststreptococcal AGN).
- GBS on the other hand, causes neonatal sepsis and meningitis, this happens in women who are colonized with GBS, and have had PROM (prolonged rupture of the membrane), the delay in birth and the exposure of the fetus predisposes them to the infection.
- **Premature children** (born prior to 37 weeks' gestation) or their mothers have had no antibodies to **GBS are at a greatly increased risk of disease.**
- Group B streptococci are an important cause of neonatal pneumonia as well.

- Although group B streptococcal (GBS) infections commonly seen in neonates, GBS is still capable of causing infections in adults (such as pneumonia, endocarditis, arthritis, cellulitis, and osteomyelitis).
- **Postpartum endometritis** also occurs (infection of the lining of uterus after birth) why after birth? This is a skin pathogen, opening of the usually closed environment of the uterus during birth and manipulation by hospital staff (who are colonized with these bugs).
- **Diabetes is the main predisposing factor for adult group B streptococcal infections** (how come?)- there are theories, the most accepted is that the rise of sugar in blood reduces the function of the immune system, also causes reduction in blood flow (recruitment of WBCs) and nerve damage (also prevents proper immune function).

- **Viridans streptococci (e.g., *S. mutans*, *S. sanguinis*, *S. salivarius*, and *S. mitis*) are the most common cause of infective endocarditis.**
- **They TYPICALLY enter the bloodstream (bacteremia- bacteria in blood) from the oropharynx after dental surgery.**
- Signs of endocarditis: *are fever (teichoic acid), heart murmur (vegetation and destruction of heart valves), anemia, and embolic events (emboli in the blood) that cause symptoms such as splinter hemorrhages, subconjunctival petechial hemorrhages, and Janeway lesions (see next slide).*
- The vegetation of the heart valves is 100% fatal unless effectively treated with antimicrobial agents!
- About 10% of endocarditis cases are caused by enterococci, but any organism causing bacteremia may settle on already deformed valves.
- **At least three blood cultures are necessary to ensure recovery of the organism in more than 90% of cases.**



<http://www.healthgala.info/2017/08/Jane-way-lesion-Pictures-Definition-Symptoms-Causes-Treatment.html>

<https://www.healthline.com/health/splinter-hemorrhages#overview1>

- Viridans streptococci, especially *S. anginosus*, *S. milleri*, and *S. intermedius*, are also a cause of brain abscesses, as mentioned before these are usually multi-pathogenic and are seen often in combination with mouth anaerobes (a mixed aerobic–anaerobic infection).
- **Dental surgery** is an important predisposing factor to **brain abscess (so as a dentist you have access to the heart and brain with the bugs in the mouth!!!)**- dental surgery provides a portal for the viridans streptococci and the anaerobes in the mouth to enter the bloodstream (bacteremia) and spread to the brain.
- Viridans streptococci are involved in mixed aerobic–anaerobic infections in other areas of the body as well (e.g., lung abscesses and abdominal abscesses).

- Enterococci (GDS): Cause urinary tract infections (enteric bacteria, and thus has close proximity to the ureter) especially in hospitalized patients (this is due to the use of catheters combined with bed pans- contamination is imminent).
- Thus → Indwelling urinary catheters and urinary tract instrumentation are important predisposing factors.
- Enterococci also cause endocarditis, particularly in patients who have undergone gastrointestinal or urinary tract surgery or instrumentation , this is why they are not common, **we do a lot more dental procedures and introduce viridans group that we do GI or UT surgery.**
- They also cause intra-abdominal and pelvic infections, typically in combination with anaerobes (the same as other streptococci, if given the access and chance they will cause abscess).
- *S. bovis*, a nonenterococcal group D streptococcus, causes **endocarditis, especially in patients with carcinoma of the colon** (how?), This association is so strong that when we find patients with *S. bovis*, bacteremia, or endocarditis , these patients should be investigated for the presence of colonic carcinoma!
- Peptostreptococci are one of the most common bacteria found in brain, lung, abdominal, and pelvic abscesses.

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 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 polyarthritits
 - 3-Carditis, may develop.
- 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.
- **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.

Rheumatic fever-diagnosis



*Erythematous patches
with central clearing*

Erythema marginatum

- 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 polyarthritits), 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%.

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 (sensitive 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.

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

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

¹All streptococci are catalase-negative.

²Both *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.

⁴NA, not applicable.

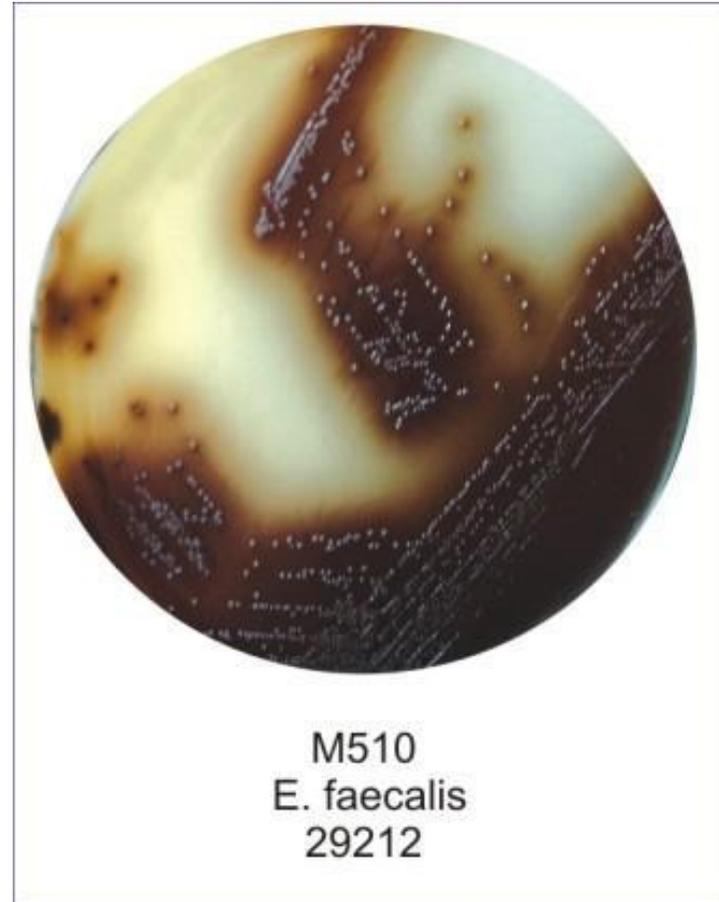
⁵Viridans group streptococci include several species, such as *S. sanguinis*, *S. mutans*, *S. mitis*, *S. gordonii*, *S. salivarius*, *S. anginosus*, *S. milleri*, and *S. intermedius*.



Bacitracin test for *Streptococcus pyogenes*

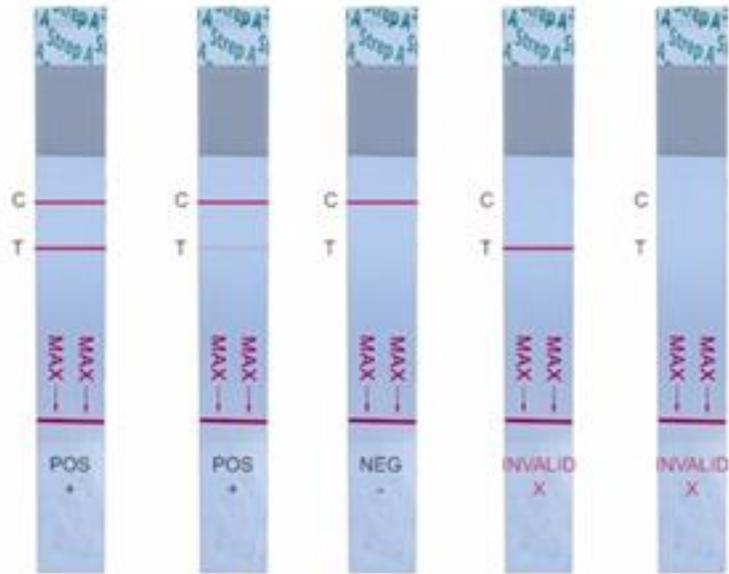


Bile esculin : *e. faecalis*



- 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)



- A rapid test is also available for the detection of **group B streptococci in vaginal and rectal samples**.
- It detects the DNA of the organism, and results can be obtained in **approximately 1 hour**.
- Viridans group streptococci form α -hemolytic colonies on blood agar and must be distinguished from *S. pneumoniae* (pneumococci), which is also α -hemolytic.
- Viridans group streptococci are **resistant to lysis by bile** and will grow in the **presence of optochin (RESIST)**, whereas pneumococci will not.
- The various viridans group streptococci are classified into species by using a variety of biochemical tests

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.

- Endocarditis caused by most viridans streptococci is curable by **prolonged penicillin treatment**.
- However, enterococcal endocarditis (remember these are hardy organisms and live in the gut) can be eradicated only by **a penicillin or vancomycin combined with an aminoglycoside**.
- Enterococci resistant to multiple drugs (e.g., penicillins, aminoglycosides, and vancomycin) have emerged. Resistance to vancomycin in enterococci is mediated by a cassette of genes that encode the enzymes that substitute D-lactate for D-alanine in the peptidoglycan. The same set of genes encodes vancomycin resistance in *S. aureus*.
- VREs are now an important cause of nosocomial infections; there is no reliable antibiotic therapy for these organisms. At present, two drugs are being used to treat infections caused by VRE: **linezolid (Zyvox) and daptomycin (Cubicin)**.
- Nonenterococcal group D streptococci (e.g., *S. bovis*) are not highly resistant and can be treated with penicillin G.
- The drug of choice for group B streptococcal infections is **either penicillin G or ampicillin**.
- Some strains may require higher doses of penicillin G or a combination of penicillin G and an aminoglycoside to eradicate the organism. Peptostreptococci can be treated with penicillin G.

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.
- In patients with damaged heart valves who undergo invasive dental procedures, endocarditis caused by viridans streptococci can be prevented by using amoxicillin PREoperatively. Again **PRE OPERATIVELY**
- To avoid unnecessary use of antibiotics, it is recommended to give amoxicillin prophylaxis only to those patients who have the highest risk of severe consequences from endocarditis (e.g., those with **prosthetic heart valves or with previous infective endocarditis**) and who are undergoing high-risk dental procedures, such as manipulation of gingival tissue.

- As for GBS, the incidence of neonatal sepsis can be reduced by a combination of two approaches:
 - (1) Screening of ALL pregnant women at 35 to 37 weeks' gestation by doing vaginal and rectal cultures (RST). If cultures are positive, then penicillin G (or ampicillin) should be administered intravenously at the time of delivery.
 - (2) If the patient has not had cultures done, then penicillin G (or ampicillin) should be administered intravenously at the time of delivery to women who experience prolonged (longer than 18 hours) rupture of membranes, whose labor begins before 37 weeks' gestation, or who have a fever at the time of labor. If the patient is allergic to penicillin, either cefazolin or vancomycin can be used.
 - *Oral ampicillin given to women who are vaginal carriers of group B streptococci does not eradicate the organism.* Rapid screening tests for group B streptococcal antigens in vaginal specimens can be insensitive, and neonates born of antigen-negative women have, nevertheless, had neonatal sepsis. Note, however, that as group B streptococcal infections have declined as a result of these prophylactic measures, neonatal infections caused by *E. coli* have increased.
- **There are no vaccines available against any of the streptococci except *S. pneumoniae***

STREPTOCOCCUS PNEUMONIAE

- Diseases
- *Streptococcus pneumoniae* (pneumococcus) causes 1) pneumonia 2) bacteremia 3) meningitis, and 4) URTI (upper respiratory tract infections)- such as otitis media, mastoiditis, and sinusitis.
- Pneumococci are the **most common cause** of community-acquired pneumonia, meningitis, sepsis in splenectomized individuals(?), otitis media, and sinusitis.
- They are a common cause of conjunctivitis, especially in children.
- Important Properties:
- Pneumococci are gram-positive lancet-shaped cocci arranged in pairs (diplococci) or short chains (The term lancet-shaped means that the diplococci are oval with somewhat pointed ends rather than being round.)
- On blood agar, they produce α -hemolysis, In contrast to viridans streptococci, they are lysed by bile or deoxycholate, and they are sensitive to optochin

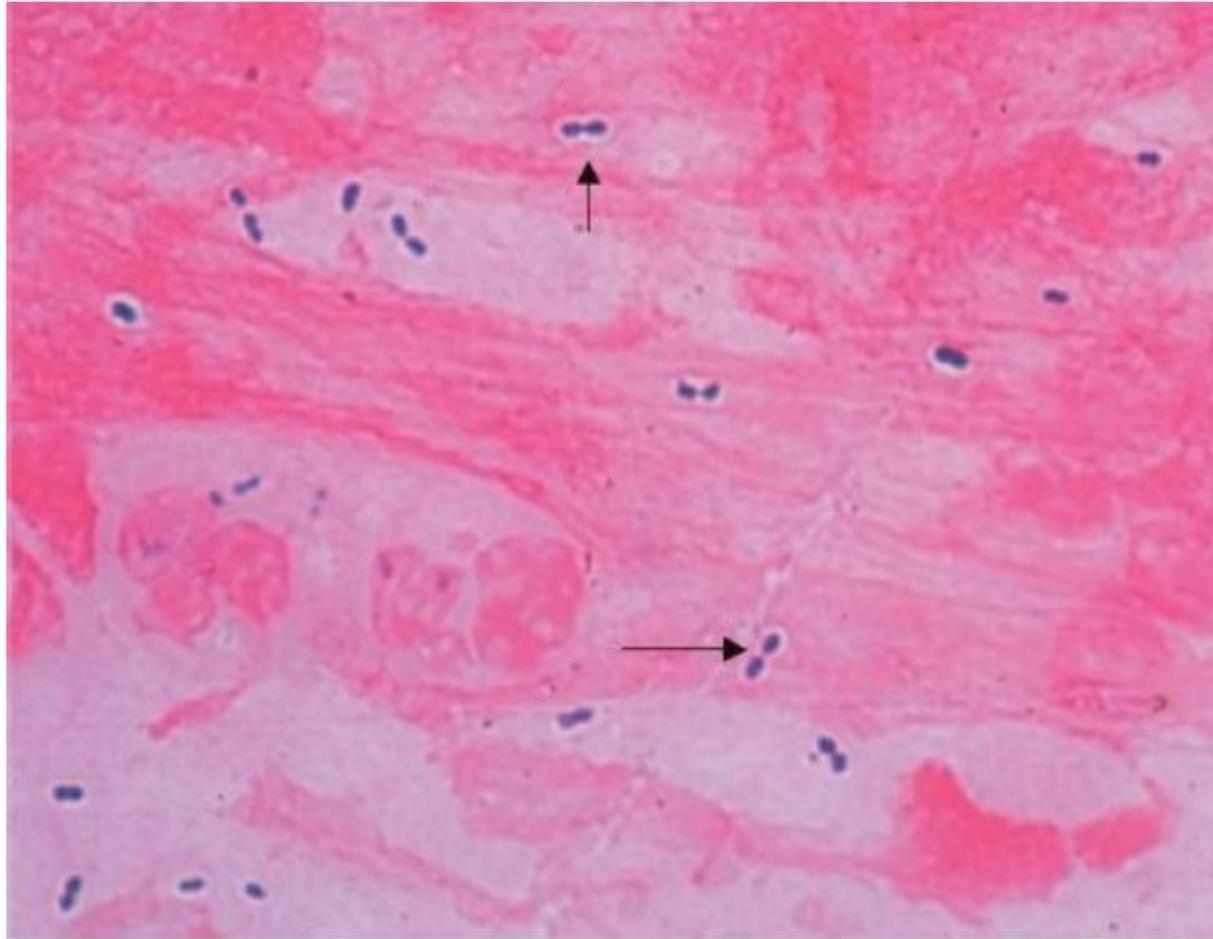
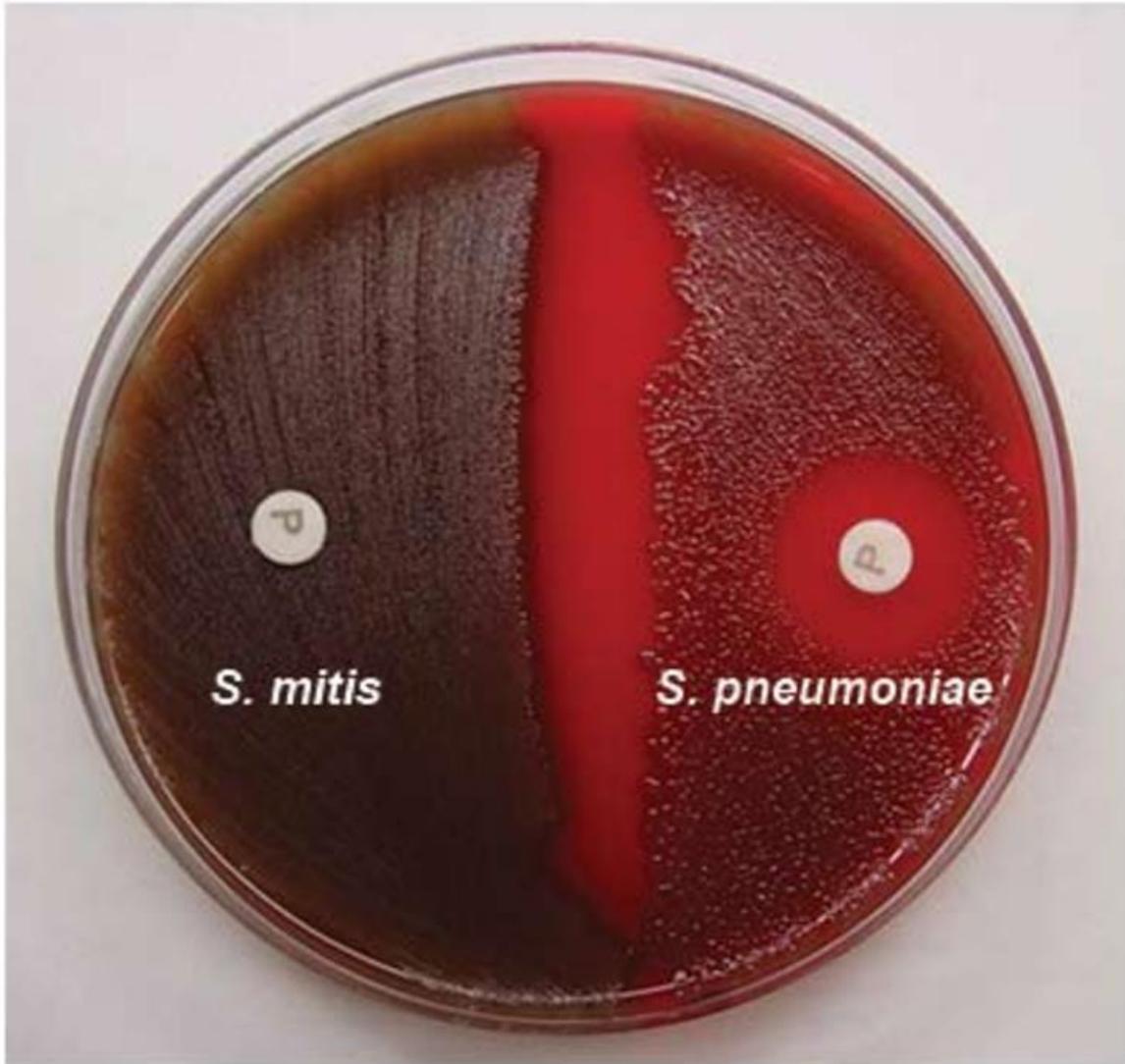


FIGURE 15–15 *Streptococcus pneumoniae*—Gram stain. Arrows point to typical gram-positive diplococci. Note that the clear area around the organism is the capsule. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)



Left Side

S. mitis

Resistant to optochin

Right Side

S. pneumoniae

Susceptible to optochin

- Pneumococci possess **polysaccharide capsules** (thus splenectomy patients cant clear this organism) , it has more than **85 antigenically distinct types according to the polysaccharide capsule.**
- With type-specific antiserum, **capsules swell (quellung reaction),** and this can be used to identify the type.
- Specific antibody to the capsule opsonizes the organism, **facilitates phagocytosis, and promotes resistance.** Such antibody develops in humans as a result either of infection (asymptomatic or clinical) or of **administration of polysaccharide vaccine.**
- Capsular polysaccharide elicits primarily a **B-cell (T-independent) response.**

- Another important surface component of *S. pneumoniae* is a teichoic acid in the cell wall called C-substance (also known as C-polysaccharide).
- Its medical importance is that it is used in the lab measurement of C reactive protein, because it reacts with C-reactive protein (CRP) (which is a normal serum protein).
- CRP is an “acute-phase” protein that is elevated as much as 1000-fold in acute inflammation.
- CRP is a nonspecific indicator of inflammation and is elevated in response to the presence of many organisms, (not just *S. pneumoniae*).
- This is where the clinical importance of C substance comes in, CRP in human serum is measured in the laboratory by its reaction with the carbohydrate of *S. pneumoniae*.
- The medical importance of CRP is that an elevated CRP appears to be a better predictor of heart attack risk than an elevated cholesterol level.

Transmission

- Humans are the natural hosts for pneumococci; there is no animal reservoir.
- Because a proportion (5%–50%) of the healthy population harbors virulent organisms in the oropharynx, pneumococcal infections are not considered to be communicable (it happens from your own flora).
- Resistance is high in healthy young people, and disease results most often when predisposing factors are present.

Pathogenesis, virulence factors:

- The most important virulence factor is **the capsular polysaccharide**, and **anticapsular antibody is protective**.
- Lipoteichoic acid: complement activator, it induces **inflammatory cytokine production contributes** to the inflammatory response and to **the septic shock syndrome** that occurs in some immunocompromised patients (a bit similar to protein A in LPS in Gram negatives).
- Pneumolysin, **the hemolysin that causes α -hemolysis**, may also **contribute to pathogenesis**.
- Pneumococci **produce IgA protease that enhances the organism's ability to colonize the mucosa of the upper respiratory tract**.

- Factors that lower resistance and predispose persons to pneumococcal infection include (factors that reduce mucus clearing or factors that decrease immune reaction)
- (1) anything that can depress the cough reflex: alcohol or drug intoxication or other cerebral impairment , all contribute to an increase aspiration of secretions (and thus pneumonia)
- (2) abnormality of the respiratory tract (e.g., viral infections), pooling of mucus, bronchial obstruction, and respiratory tract injury caused by irritants (which disturb the integrity and movement of the mucociliary blanket) all prevent clearing of mucus and predispose to community acquired pneumonia caused by pneumococcus.
- (3) abnormal circulatory dynamics (e.g., pulmonary congestion and heart failure)- will congest the blood in the lung, increase pulmonary secretions → pneumococcus
- (4) splenectomy (capsule, reduces immunity) and certain chronic diseases such as sickle cell anemia and nephrosis, patients with sickle cell anemia autoinfarct their spleen, become functionally asplenic, and are predisposed to pneumococcal sepsis.
- Trauma to the head that causes leakage of spinal fluid through the nose predisposes to pneumococcal meningitis.

Clinical Findings

- Pneumonia:
- sudden chill, fever, cough, and pleuritic pain (chest pain that increases with chest movement-breathing).
- Sputum is a red or brown “rusty” color.
- Bacteremia occurs in 15% to 25% of cases.
- Spontaneous recovery may begin in 5 to 10 days and is accompanied by development of anticapsular antibodies.
- Pneumococci are a prominent cause of otitis media, sinusitis, mastoiditis, conjunctivitis, purulent bronchitis, pericarditis, bacterial meningitis, and sepsis.
- Pneumococci are the **leading cause of sepsis in patients** without a functional spleen.

Laboratory Diagnosis

- In sputum lancet-shaped gram-positive diplococci in Gram-stained smears.
- Can be detected by using the quellung reaction with multitype antiserum.
- On blood agar, pneumococci form small α -hemolytic colonies.
- The colonies are bile-soluble (i.e., are lysed by bile), and growth is inhibited by optochin.
- Blood cultures are positive in 15% to 25% of pneumococcal infections.
- Culture of cerebrospinal fluid is usually positive in meningitis. Rapid diagnosis of pneumococcal meningitis can be made by detecting its capsular polysaccharide in spinal fluid using the latex agglutination test. A rapid test that detects urinary antigen is also available for the diagnosis of pneumococcal pneumonia and bacteremia. The urinary antigen is the C polysaccharide (also known as the C substance), not the capsular polysaccharide. Because of the increasing numbers of strains resistant to penicillin, antibiotic sensitivity tests must be done on organisms isolated from serious infections.

Treatment

- Most pneumococci are susceptible to penicillins and erythromycin, although significant resistance to penicillins has emerged
- In severe pneumococcal infections, penicillin G is the drug of choice, whereas in mild pneumococcal infections, oral penicillin V can be used.
- A fluoroquinolone with good antipneumococcal activity, such as levofloxacin, can also be used.
- In penicillin-allergic patients, erythromycin or one of its long-acting derivatives (e.g., azithromycin) can be used.
- An increasing percentage of isolates, ranging from 15% to 35% depending on location, show high-level resistance, which is attributed to multiple changes in penicillin binding proteins.
- They do not produce β -lactamase. Vancomycin is the drug of choice for the penicillin-resistant pneumococci, especially for severely ill patients.
- Ceftriaxone or levofloxacin can be used for less severely ill patients.

Prevention

- Despite the efficacy of antimicrobial drug treatment, the mortality rate of pneumococcal infections is high in immunocompromised (especially splenectomized) patients and children under the age of 5 years. Such persons should be immunized with the 13-valent pneumococcal conjugate vaccine (Pneumovax 13).
- The immunogen in this vaccine is the pneumococcal polysaccharide of the 13 most prevalent serotypes conjugated (coupled) to a carrier protein (diphtheria toxoid). The unconjugated 23-valent pneumococcal vaccine (Pneumovax 23) should be given to healthy individuals age 50 years or older.
- These vaccines are safe and effective and provide long-lasting (at least 5 years) protection. Immunization of children reduces the incidence of pneumococcal disease in adults because children are the main source of the organism for adults and immunization reduces the carrier rate in children.

- A booster dose is recommended for
- (1) people older than 65 years who received the vaccine more than 5 years ago and who were younger than 65 years when they received the vaccine, and
- (2) people between the ages of 2 and 64 years who are asplenic, infected with human immunodeficiency virus (HIV), receiving cancer chemotherapy, or receiving immunosuppressive drugs to prevent transplant rejection.
- A potential problem regarding the use of the pneumococcal vaccine is that of serotype replacement. Will the vaccine reduce the incidence of disease caused by the serotypes in the vaccine but not the overall incidence of pneumococcal disease because other serotypes that are not in the vaccine will now cause disease?
- In fact, an increase in invasive pneumococcal disease caused by serotype 19A, which was not in the previously used 7-valent vaccine, occurred. This led to the production of the current conjugate vaccine containing 13 serotypes, including 19A.