

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

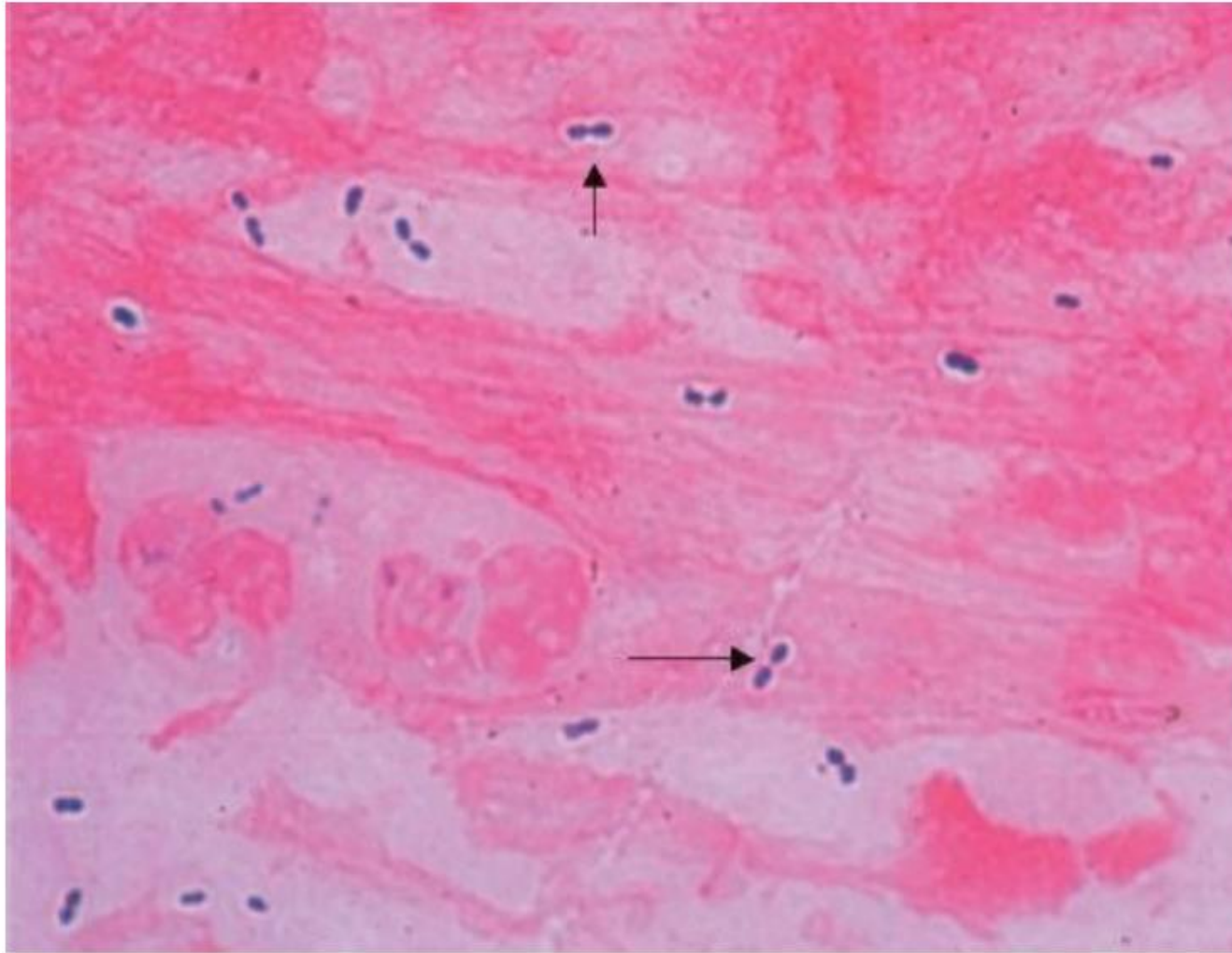
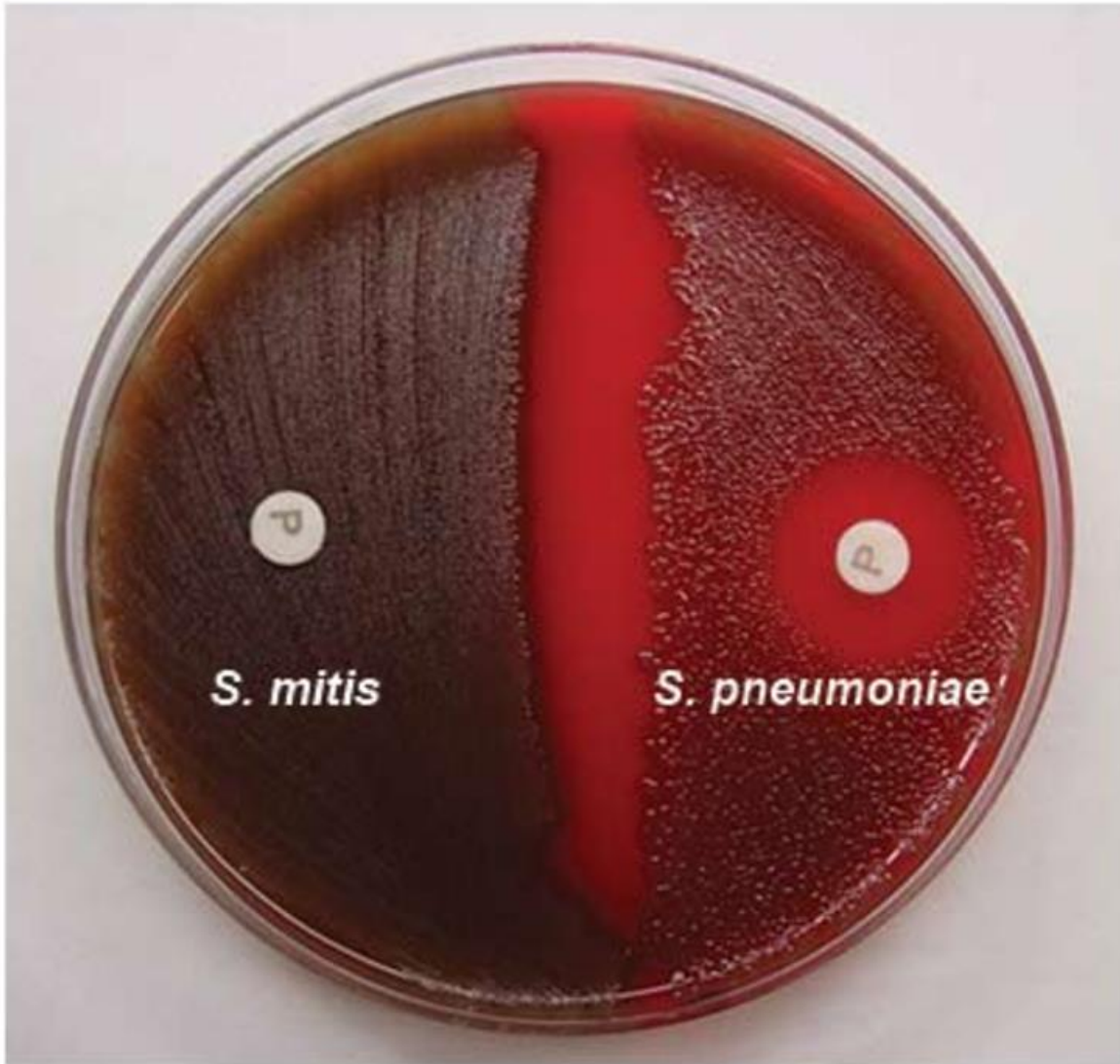


FIGURE 15–15 *Streptococcus pneumoniae*—Gram stain. Arrows point to typical gram-positive diplococci. Note that the clear area around the organism is the capsule. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)



Left Side

S. mitis

Resistant to optochin

Right Side

S. pneumoniae

Susceptible to optochin

- 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.**
- Canakinumab vs ibuprofen

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(geriatrics ,CVA, mental 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.

Pneumonia

- *Str. pneumoniae* is the most frequent cause of pneumonia with an estimated annual incidence of 1–3 per 1000 of the population, **with a 5% case fatality rate.**
- Pneumococcal pneumonia usually follows aspiration (!) with subsequent migration of through the bronchial mucosa to involve the surrounding lymphatics.
- The inflammatory reaction is **focused primarily within the alveolus of a single lobule or lobe, although multilobar disease can also occur.**
- Contiguous spread commonly results in inflammatory involvement of the pleura; this may progress to empyema.
- Pericarditis is an uncommon but well recognized complication.
-

- Occasionally, lung necrosis and intrapulmonary abscess formation occur with the more virulent pneumococcal serotypes.
- Bacteraemia may complicate pneumococcal pneumonia in up to 15% of patients.
- This can result in metastatic involvement of the meninges, joints and, rarely, the endocardium.
- The mortality rate from pneumococcal pneumonia in those admitted to hospital in the UK is approximately 15%.
- It is increased by age, underlying disease, bloodstream involvement, metastatic infection and certain types of pneumococci with large capsules (e.g. serotype 3).

Otitis media and sinusitis

- Middle ear infections (otitis media) affect approximately half of all children between the ages of 6 months and 3 years; approximately one-third of cases are caused by *S. pneumoniae*.
- Disease occurs after acquisition of **a new strain to which** there is no pre-existing immunity.
- The prevalence is highest among children attending kinder garten or primary school,
- where there is a constant exchange of pneumococcal strains.

Meningitis

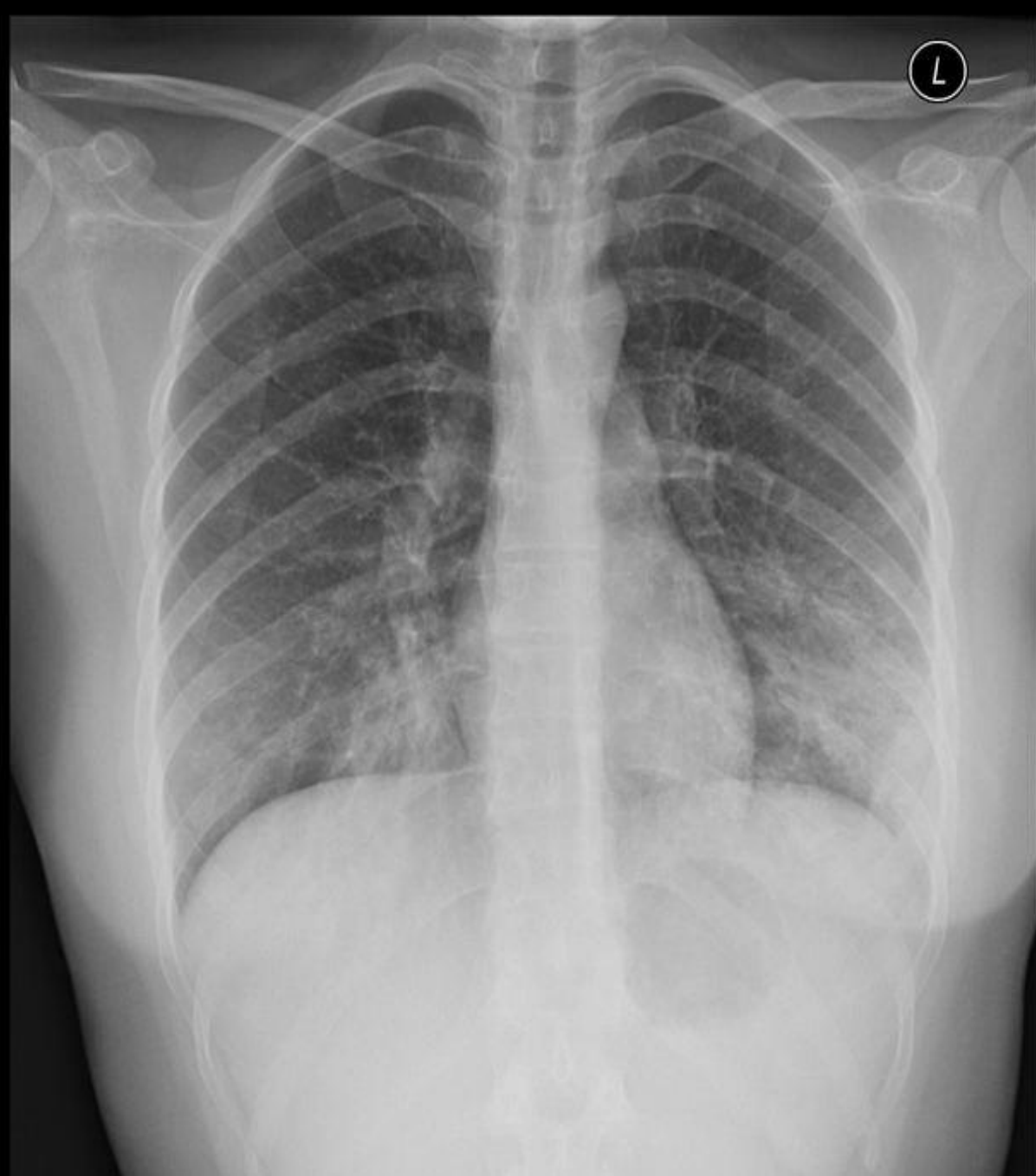
- *Str. pneumoniae* is among the three leading causes of bacterial meningitis. It is assumed that invasion arises from the pharynx to the meninges via the blood- stream, as bacteraemia usually coexists. Meningitis may occasionally complicate pneumococcal infection at other sites, such as the lung and middle ear.
- The incidence of pneumococcal meningitis is bimodal and affects children less than 3 years of age and adults of 45 years and above.
- **The fatality rates are 20% and 30%**, respectively, considerably higher than those associated with other types of bacterial 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.



<http://www.chestx-ray.com/index.php/education/normal-cxr-module-train-your-eye>



<https://radiopaedia.org/articles/atypical-pneumonia>

Pneumococcal pneumonia





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.

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 (Prevnar 13) (must be given booster doses every 5 years).
- 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 (booster doses at 65)**.
- These vaccines are safe and effective and provide long-lasting (at least 5 years) protection.

Hib, Bordetella, and diphtheria

Gram-Negative Rods Related to the Respiratory Tract

Species	Major Diseases	Laboratory Diagnosis	Factors X and V Required for Growth	Vaccine Available	Prophylaxis for Contacts
<i>H. influenzae</i>	Meningitis ¹ ; otitis media, sinusitis, pneumonia, epiglottitis	Culture; capsular polysaccharide in serum or spinal fluid	+	+	Rifampin
<i>B. pertussis</i>	Whooping cough (pertussis)	Fluorescent antibody on secretions; culture	-	+	Azithromycin
<i>L. pneumophila</i>	Pneumonia	Serology; urinary antigen; culture	-	-	None

¹ In countries where the *H. influenzae* b conjugate vaccine has been deployed, the vaccine has greatly reduced the incidence of meningitis caused by this organism.

- *H. influenzae* and *B. pertussis* are found only in humans, whereas *L. pneumophila* is found primarily in environmental water sources.

HAEMOPHILUS

- Diseases *H. influenzae* used to be the leading cause of meningitis in young children
- Note we have 1 representative from each Gram reaction and shape that is a respiratory organism, the three capsulated ones are causative of meningitis and have vaccines made against the capsule:
- Pneumococcus G+ve coccus = capsulated respiratory organism causes meningitis and URTI
- Meningococcus G-ve coccus also capsulated which can colonize the respiratory epithelium
- and now the Gram negative ROD, Haemophilus is also a respiratory capsulated organism that is the third most common cause of meningitis.
- The fourth is Corynebacterium diphtheriae, not capsulated, doesn't cause meningitis,

Back to haemophilus

- A conjugated vaccine against the capsule has greatly reduced the incidence of meningitis caused by this organism.
- However, It is still an important cause of upper respiratory tract infections (otitis media, sinusitis, conjunctivitis, and epiglottitis) and sepsis in children.
- The most significant and dangerous disease that can be life threatening especially in children is epiglottitis (caused by group B *H. influenzae* –HiB)
- *Haemophilus* can also cause pneumonia in adults, particularly in those with chronic obstructive lung disease.

Important Properties

- *H. influenzae* G-ve ROD encapsulated with a polysaccharide capsule
- one of the three important encapsulated pyogens (pneumococcus and the meningococcus).
- Using serologic methods against the antigen of the polysaccharide capsule, six serotypes are detected, with serotype B (group B) being the most significant one.
- Serotype B is the one most responsible for the more serious illnesses (meningitis, epiglottitis, sepsis)
- The type B capsule is composed of polyribitol phosphate, promotes anti-phagocytosis and invasiveness .
- Unencapsulated strains are less invasive but can cause disease usually limited to the upper respiratory tract (sinusitis and otitis media).
- Growth of the organism on laboratory media requires the addition of two components, heme (factor X) and NAD (factor V), for adequate energy production.

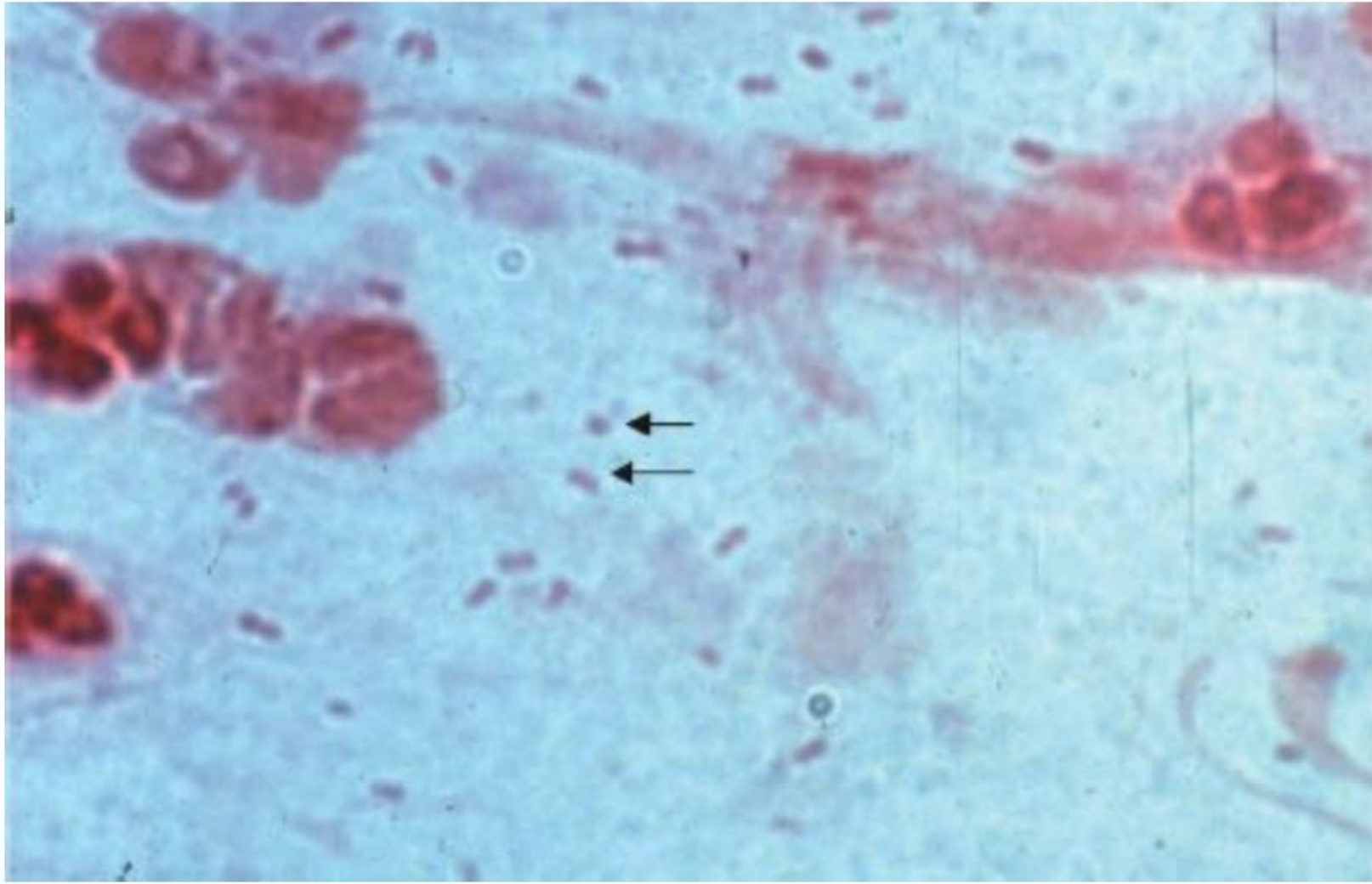


FIGURE 19–1 *Haemophilus influenzae*—Gram stain. Arrows point to two small “coccobacillary” gram-negative rods. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

Give COCCOBACILLUS



http://microbe-canvas.com/admin/uploads/image/bacterien/haemophilus-influenzae/haemophilus-influenzae_005_bk_cult_gram-2_ff-350x220.jpg

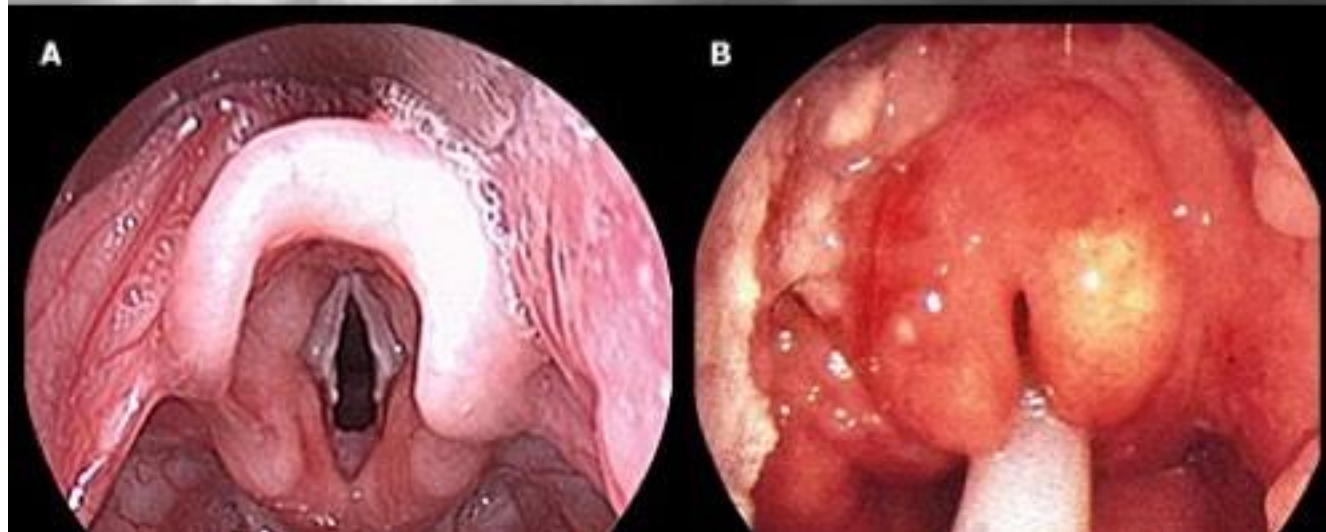
Pathogenesis & Epidemiology

- *H. influenzae* **infects only humans with no animal reservoir.**
- Similar to other respiratory pathogens, it is transmitted by the inhalation of airborne droplets into the respiratory tract, this can result in **asymptomatic colonization or infection** (otitis media, sinusitis, pneumonia).
- Also like all respiratory pathogens, to be able to survive in this environment, the organism produces an **IgA protease** that degrades secretory IgA which would otherwise inhibit its attachment to the mucosa.
- After becoming established in the upper respiratory tract, the organism can enter the **bloodstream (bacteremia) and spread to the meninges.**
- As mentioned, capsulated strains cause meningitis (they have to have antiphagocytic capability to survive the trip through the blood to reach the meninges, this is true *for Pneumococcus and Meningioccus*)
- meningitis caused by capsular type b has been greatly reduced by vaccine contains the type b polysaccharide as the immunogen.
- Similar to pneumococcus and meningococcus, the pathogenesis of *H. influenzae* is pyogenic with no exotoxin production (capsule and endotoxin based)

- Age group most affected is children from **6m to 6y**, the peak occurs from 6m-1y.
- This is significant due to the fact that symptoms would be harder to determine especially that of meningitis (fever stiff neck) or epiglottitis (inability to swallow, regurgitation of fluids)
- The peak occurs post 6 month mark due to the decline of the protective 6 month window provided by maternal IgG, in addition children from 6m-2 year have reduced ability to produce antibodies (which are needed to clear this organism due to the presence of the capsule)

Clinical Findings

- Meningitis caused by *H. influenzae* produces a clinical picture that is almost identical pneumococcal or meningococcal meningitis.
- Meningitis → The rapid onset of fever, headache, **stiff neck**, (neurological symptoms; drowsiness), is typical.
- URTI → Sinusitis and otitis media cause pain in the affected area, opacification of the infected sinus, and redness with bulging of the tympanic membrane.
- *H. influenzae* is second only to the pneumococcus as a cause of these two infections.
- Other serious infections : septic arthritis, cellulitis, and sepsis(more in asplenic patients, due to the fact that this is a capsulated organism).
- **Epiglottitis** → rare, but can obstruct the airway and **CAN BE FATAL**. Upon inspection, a swollen “cherry-red” epiglottis is seen. This life-threatening disease of young children is caused almost exclusively by *H. influenzae*. Symptoms include, drooling, stridor (high pitched breathing noise) and comfort on sitting up.
- Pneumonia in elderly adults, especially those with chronic respiratory disease, can be caused by untypeable strains of *H. influenzae*



<http://www.pictame.com/tag/epiglottitis>

Laboratory Diagnosis

- Need to isolate the organism to make the Dx, inactivated blood must be used (chocolate agar, to remove inhibitors of growth in the blood) **enriched** with two growth factors required for bacterial respiration (chocolate agar +factor x and factor V).
- An organism that grows on Chocolate+Factors X and V is assumed to be *H. influenzae*; other species of *Haemophilus*, such as *Haemophilus parainfluenzae*, do not require both factors.
- Quelling reaction (Antibody against the capsule which shows swelling of the capsule if contained the antigen for the provided antibody) can be used, also biochemical tests.
- Additional means of identifying encapsulated strains include fluorescentantibody staining of the organism and counter immunoelectrophoresis or latex agglutination tests, which detect the capsular polysaccharide.

Treatment

- For **meningitis and serious systemic infections** (remember these are more invasive and aggressive) caused by *H. influenzae* the treatment of choice is **ceftriaxone (3rd gen)**.
- From 20% to 30% of *H. influenzae* type b isolates produce a β -lactamase that degrades penicillinase-sensitive β -lactams such as ampicillin but not ceftriaxone.
- It is important to institute antibiotic treatment promptly, because the incidence of neurologic sequelae (subdural empyema) is high.
- Untreated *H. influenzae* meningitis has a fatality rate of approximately 90%.
- *H. influenzae* upper respiratory tract infections (such strains as mentioned are less aggressive and less invasive), that cause otitis media and sinusitis, are treated with either amoxicillin-clavulanate or trimethoprim-sulfamethoxazole.

Prevention

- Capsule= vaccine, so the vaccine contains the capsular polysaccharide of *H. influenzae* type **b** conjugated to diphtheria toxoid or other carrier protein.
- Depending on the carrier protein, it is given some time between the ages of **2 and 15 months**.
- This vaccine is much more effective in young children than the unconjugated vaccine and has reduced the incidence of meningitis caused by this organism by approximately 90% **in immunized children**.
- Meningitis in close contacts of the patient can be prevented by rifampin.
- Rifampin is used because it is secreted in the saliva to a greater extent than ampicillin. Rifampin decreases respiratory carriage of the organism, thereby reducing transmission

BORDETELLA

- Disease:
- *B. pertussis* is the cause of whooping cough (pertussis).
- It is still seen especially in infants under 2 months (received no or little protection from mother, usually typical whooping cough is seen)
- Important Properties
- *B. pertussis* is a Gram negative rod, also small coccobacillus shape, **encapsulated**

Pathogenesis & Epidemiology

- *B. pertussis* infects only humans (this is a recurring pattern in many URT pathogens) and is transmitted by respiratory droplets from infected individuals (usually through coughing).
- Once it finds its way to the epithelium of the upper respiratory tract, it attaches itself (without invading the tissue) and causes reduction (and eventually death of) the ciliated epithelial cells (= no more clearing of mucus).
- Mainly affects children and young adults, it is similar to other respiratory pathogens a highly infective disease, but it is more so than most.
- This is why this organism is one of the targeted organisms in scheduled vaccines, the vaccine was successful in reducing worldwide destruction of pertussis
- Lapse in vaccination due to wars or trends, but also due to waning(reduced overtime) immunity of the vaccine has caused outbreaks of pertussis during the years 2005, 2010, and 2012 , has raised concerns and is pushing forward for additional vaccine boosters.

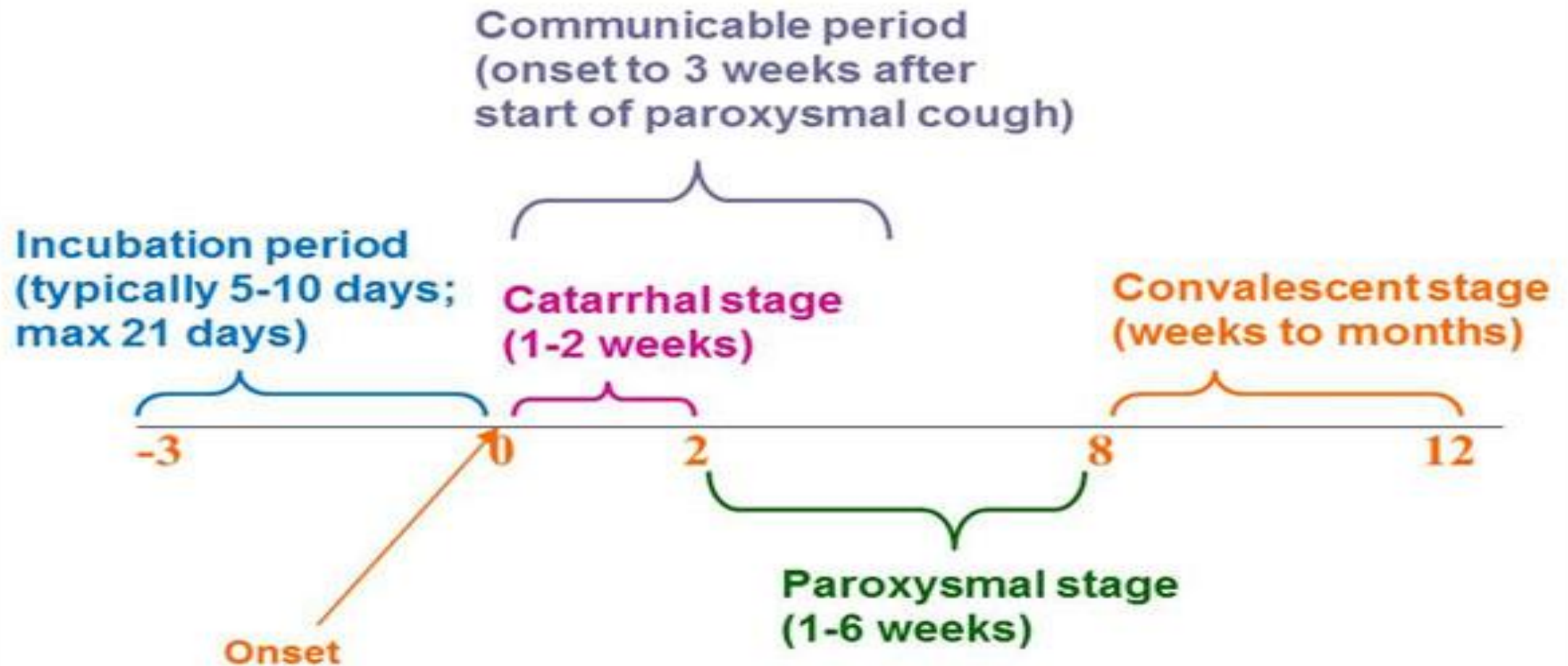
- Pathogenesis, due to virulence factors:
- (1) Filamentous hemagglutinin, is the protein the bacterium uses to attach itself to the cilia of the epithelial cells, damages these cells as well (antibodies against this protein are protective). (no cilia= no more clearing of mucus)
- (2) Pertussis toxin stimulates increase (by enzymatic ADP ribosylation of G proteins) of the intracellular cAMP, once cAMP rises it causes (similar to the diarrhea mechanism by cholera) increase extracellular secretions (now a lot more respiratory secretions are being produced).
- no more clearing of mucus from (1) + a lot more mucus is being produced
- (2) Both contribute to the severe PROLONGED severe cough of pertussis (the only mechanism left to clear airways is to forcefully cough it out)
- The pertussis toxin is part of the DTaP vaccine (all three components of this vaccines are A-B configuration toxins)

- Patients with pertussis exhibit a high number of lymphocytes in their blood (*lymphocytosis), this is due to Pertussis toxin inhibition of signal transduction (by ribosylation with ADP on G proteins) of chemokines, which in turn causes an inhibition of lymphocytes entering the lymph tissue and remaining in the blood.
- (3) The organisms also synthesize and export adenylate cyclase. This enzyme, when taken up by phagocytic cells can inhibit their bactericidal activity. Bacterial mutants that lack cyclase activity are avirulent(bug stops cilia, causes extra secretions and now also evaded immune cell destruction).
- (4) Tracheal cytotoxin is a fragment of the bacterial peptidoglycan, this toxin, acts alongside with endotoxin to induce nitric oxide, which kills the ciliated epithelial cells.

Clinical Findings

- Whooping cough begins with mild symptoms (sneezing, coughing, low grade fever) then develops into an acute tracheobronchitis followed by a severe paroxysmal (sudden outbursts) cough, which lasts from 1 to 4 weeks.
- The paroxysmal pattern is characterized by : a series of hacking coughs, production of large amounts of mucus (productive/wet), ended by inspiratory (trying to catch their breath) whoops , the characteristic noise is due to narrowing of the glottis.
- the organism is restricted to the respiratory tract and blood cultures are negative, but with pronounced leukocytosis with up to 70% lymphocytes.
- Although central nervous system anoxia and exhaustion can occur as a result of the severe coughing, **death is due mainly to pneumonia.**
- The classic picture of whooping cough described above occurs primarily in young children.

Clinical Course (in weeks)



Clinical findings in adults

- *B. pertussis* infection often manifests as a paroxysmal cough of varying severity lasting weeks.
- The characteristic whoop is often absent, leading to difficulty in recognizing the cough as caused by this organism (larger airways).
- In the correct clinical setting, adults with a cough lasting several weeks (often called the 100-day cough) should be evaluated for infection with *B. pertussis*

Laboratory Diagnosis

- The organism can be isolated from nasopharyngeal swabs taken during the paroxysmal (cough) stage.
- Bordet-Gengou medium used for this purpose contains a high percentage of blood (20%–30%) to inactivate inhibitors in the agar.
- The organism is then identified (from the above growth medium) by detecting its antigens (either by agglutination or by fluorescent antibody stains)
- The reason for depending on antigen detection is due to the slow nature of growth for this organism, rapid diagnosis is mandated and thus direct fluorescent-antibody staining of the nasopharyngeal specimens can be used for diagnosis.
- Polymerase chain reaction–based tests are highly specific and sensitive and should be used if available.
- In patients with prolonged cough, the antigen can actually be detected from the patients own serum (antibody test).

Treatment

- Azithromycin (macrolide) is the drug of choice.
 - It is essential to treat early, Azithromycin will reduce the bacterial load and reduce the chance of complications, otherwise it will have little effect on progression of the disease once it has reached further stages (the toxin already caused damage to the mucosa).
- Supportive care (e.g., oxygen therapy and suction of mucus) during the paroxysmal stage is important, especially in infants.

Prevention

- Vaccine based : either an acellular one (contains 5 purified antigen proteins, no cells, this is the most used vaccine) or killed vaccine containing inactivated *B. pertussis* organisms.
- The main immunogen in acellular vaccine is the inactivated pertussis toxin (pertussis toxoid) the toxoid in the vaccine is pertussis toxin that has been inactivated genetically by introducing two amino acid changes, which eliminates its ADP-ribosylating activity but retains its antigenicity.
- It is the first vaccine to contain a genetically inactivated toxoid.
- The other antigens in the acellular vaccine are filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3.
- The acellular vaccine has fewer side effects than the killed vaccine but has a shorter duration of immunity

- The pertussis vaccine is usually given combined with diphtheria and tetanus toxoids (DTaP) in three doses beginning at 2 months of age.
- A booster at 12 to 15 months of age and another at the time of entering school are recommended (this is the typical schedule with minor differences, we give the three doses by 12-18 months and a booster before school age (3-4 years)).
- A push second dose for DTaP is gaining support due to outbreaks (in teenagers).
- To protect newborns, pregnant women should receive pertussis vaccine, antipertussis IgG from the mother will protect newborn the first few months of life.
- (the killed vaccine has side effects, encephalopathy in 1/1000000 jabs)
- Azithromycin is useful in prevention to exposed individual (immunized under 4 years –their immunity will not protect them 100% due to the still not fully developed immune system or also azithromycin should be given to the unimmunized who are exposed in the unimmunized)

Diphtheria

NON-SPORE-FORMING GRAM-POSITIVE RODS

- There are two important pathogens in this group:
- 1 *Corynebacterium diphtheriae*
- 2 *Listeria monocytogenes*

Organism	Type of Pathogenesis	Typical Disease	Predisposing Factor	Mode of Prevention
<i>C. diphtheriae</i>	Toxigenic	Diphtheria	Failure to immunize	Toxoid vaccine
<i>L. monocytogenes</i>	Pyogenic	Meningitis; sepsis	Neonate; immunosuppression	No vaccine; pasteurize milk products

CORYNEBACTERIUM DIPHTHERIAE

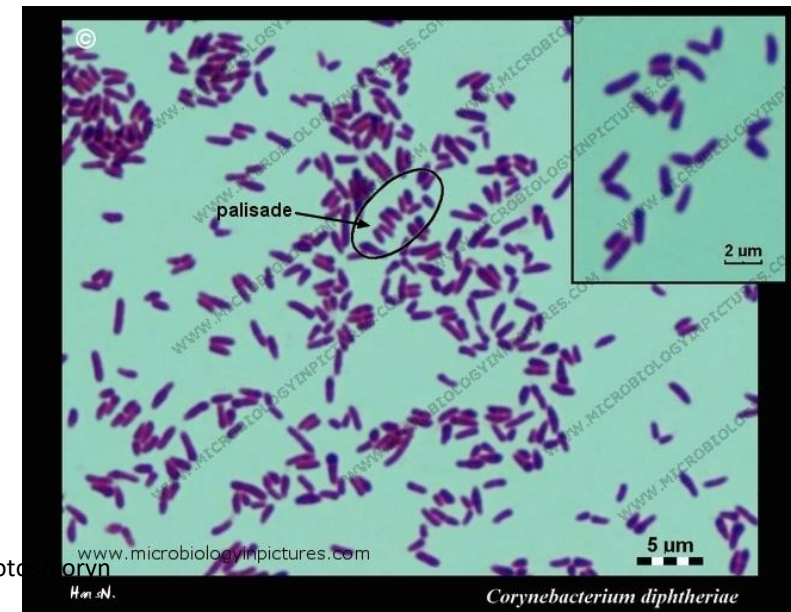
- *C. diphtheriae* causes diphtheria
- Other Corynebacterium species (diphtheroids) are implicated in opportunistic infections.



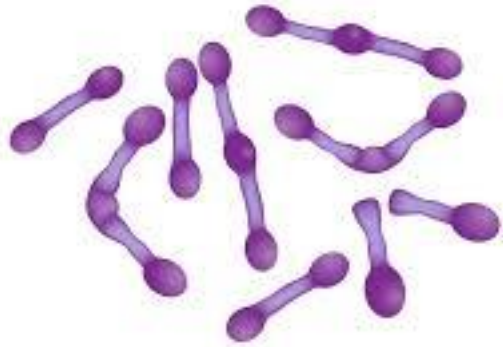
FIGURE 17–7 Diphtheria. Note whitish-gray pseudomembrane covering posterior pharynx and marked inflammation of palate and pharynx. Caused by diphtheria toxin, an exotoxin that inhibits protein synthesis by inhibiting elongation factor-2. (Courtesy of Dr. Peter Strebel.)

Important Properties

- Corynebacteria , club shaped Gram positive rods (wider at one end) and are arranged in palisades or in V- or L-shaped formations (or chinse letters)
- The rods have a beaded appearance. The beads consist of granules of highly polymerized polyphosphate—a storage mechanism for high-energy phosphate bonds.
- The granules stain metachromatically (i.e., a dye that stains the rest of the cell blue will stain the granules red).



Club Shaped G+Ve rods



Corynebacterium diphtheriae



Transmission

- Humans are the only natural host of *C. diphtheriae*
- Both toxigenic and nontoxigenic organisms reside in the upper respiratory tract and are transmitted by airborne droplets (similar to other respiratory pathogens).
- The organism can also infect the skin at the site of a preexisting skin lesion.
- This occurs primarily in the tropics but can occur worldwide in indigent persons with poor skin hygiene.

Pathogenesis

- Mainly exotoxin mediated (similar to other G+ve rods), however, the bug must establish itself in the throat first (invasiveness) prior to exotoxin production.
- Diphtheria toxin inhibits protein synthesis by ADP-ribosylation of elongation factor-2 (EF-2) used to maintain elongation of the peptide chain = no protein synthesis in eukaryotic cell.
- Similar to other toxins it is formed in an A- B fashion (active/binding)
- As mentioned, the toxin is encoded on a gene transmitted by transduction on a temperate phage

- The host response to *C. diphtheriae* consists of the following:
 - (1) A local inflammation in the throat which forms fibrinous exudate that gives the characteristic tough, adherent, gray pseudomembrane
 - (2) Antibody production against the exotoxin , which hinders the exotoxin activity by blocking the interaction of the binding domain (the B in the A-B config) with the receptors (no binding = no cell entry)

Clinical Findings/complications

- Diphtheria is rare now thanks to vaccines, however we should be aware of the thick throat pseudomembrane
- The other aspects are nonspecific: fever, sore throat, and cervical adenopathy. There are three prominent complications:
- (1) Extension of the membrane into the larynx and trachea, causing airway obstruction.
- (2) Myocarditis accompanied by arrhythmias and circulatory collapse.
- (3) Nerve weakness or paralysis, especially of the cranial nerves.

- Paralysis of the muscles of the soft palate and pharynx can lead to regurgitation of fluids through the nose.
- Peripheral neuritis affecting the muscles of the extremities also occurs.
- Cutaneous diphtheria causes ulcerating skin lesions covered by a gray membrane.
- These lesions are often indolent and often do not invade surrounding tissue. Systemic symptoms rarely occur.

Laboratory Diagnosis

- For diphtheria we need to show the presence of the **organism and production of the toxin** (due to presence of atoxigenic strains).
- Due to the quick nature of toxin mediated disease, the decision to treat with an antitoxin should be clinical and not wait for lab confirmation.
- A throat swab should be cultured on Loeffler's medium (cream colored colonies are shown in the slant) , a tellurite plate (black colonies seen as tellurium salt that is reduced to elemental tellurium within the organism thus black colored colonies), and a blood agar plate.
- The typical gray-black color of tellurium in the colony is a telltale diagnostic criterion.
- If *C. diphtheriae* is recovered from the cultures then we can confirm toxin (either animal inoculation, antibody-based gel diffusion precipitin test or PCR test for the presence of the gene).



<http://www.medical-labs.net/wp-content/uploads/2014/05/b350-3-Corynebacterium-diphtheriae-on-tellurite.jpg>

- Smears of the throat swab should be stained with both Gram stain and methylene blue.
- Although the diagnosis of diphtheria cannot be made by examination of the smear, the finding of many tapered, pleomorphic Gram-positive rods can be suggestive.
- The methylene blue stain is excellent for revealing the typical metachromatic granules (the club shape is due to these granules).

Treatment

- 1)ANTITOXIN) The treatment of choice is **antitoxin**, which should be given **immediately** on the basis of **clinical impression** (not on lab confirmation, this takes while to get both isolation of organism and detection of toxin)
- The need for immediate treatment with antitoxin is due to the toxin's RAPID and IRREVERSIBLE action on cells, thus antitoxin will work on unbound toxin in the blood only
- 2) ANTIBIOTICS) Treatment with penicillin G or erythromycin is **also recommended** with antitoxin but not as a substitute.
- Antibiotics will reduce bacterial count and this toxin production, they will also reduce the chance of a carrier state

Prevention

- Diphtheria is now rare in the world due to its inclusion in the scheduled vaccine regiment (DTaP) with diphtheria toxoid.
- **In warzones or areas with lapse in immunization, reemergence (and atypical symptoms) are on the rise**
- formaldehyde treatment of the toxin, destroys the toxin but leaves intact the antigenicity
- Immunization consists of three doses given at 2, 4, and 6 months of age, with boosters at 1 and 6 years of age.
- Because immunity wanes, a booster every 10 years is recommended.
- Immunization does not prevent nasopharyngeal carriage of the organism.