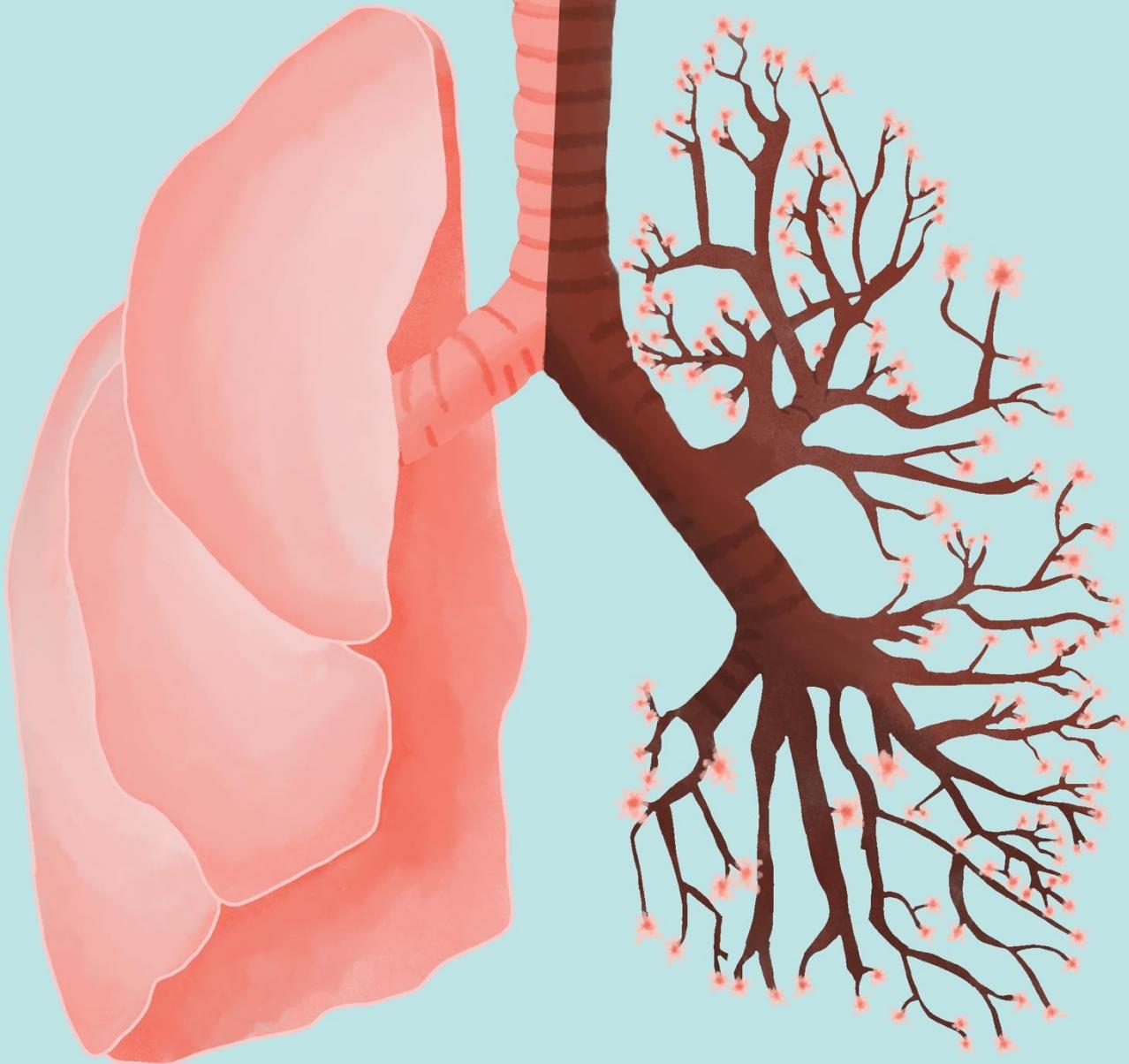


# RESPIRATORY SYSTEM

## MICROBIOLOGY



Title: Sheet 3 – S. Pneumonia, H. Influenza

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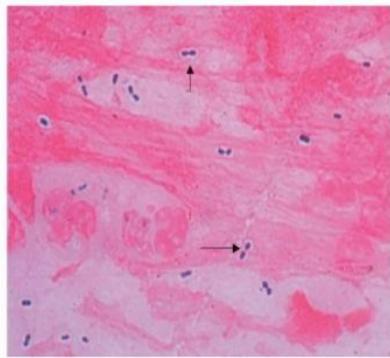
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أولاً  
ثانية  
ثالثة  
رابعة

## \* Streptococcus Pneumoniae



- ◆ 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**. (**poly-shaped**)
- ◆ On blood agar, they produce  **$\alpha$ -hemolysis**. This is a shared feature with **viridans streptococci**.

### How do we differentiate between S. Pneumoniae and S. Viridans?

- ☞ In contrast to S. Viridans:
  - S. Pneumoniae are sensitive to optochin (optochin inhibits their growth).
  - S. Pneumoniae are lysed by bile or deoxycholate (dissolve in bile).
- ↳ We test the organism's bile solubility by adding human bile acid.
- ◆ Since they are gram (+), they have **peptidoglycans**.
- ◆ **All virulent strains have surface capsules**, composed of high-molecular-weight polysaccharide polymers.
- ◆ S. Pneumoniae also have **Pneumolysin** which is a pore-forming toxin that causes  **$\alpha$ -hemolysis**. **The secretion of this toxin is stimulated by the release of Autolysin**.
- ◆ Both S. Pneumoniae and H. Influenza are part of the **normal flora** of the **upper respiratory tract**. The lower respiratory tract is completely sterile.
- ◆ They have a special virulence factor which is the **capsular polysaccharide**. This capsule has more than 90 serotypes.

### ● Pathogenesis:

- ◆ Since S. Pneumonia is part of the normal flora of the **upper** respiratory tract, then most probably the infection caused is of endogenous origin caused by the bacteria moving to the **lower** respiratory tract by aspiration.
- ◆ S. Pneumonia causes a disease derived from its name (pneumonia). **Pneumococcus**; because it elaborate Pneumolysins

Capsules are important because they determine the Antigenicity & virulence of S. Pneumoniae + vaccination

### ● Virulence Factors:

1. **Capsular Polysaccharide:** it's the most important virulence factor for S. Pneumonia and H. Influenza. **Vaccines are easily made for them targeting this capsule (anticapsular antibody)**(antiphagocytic) → **Pneumolysin** to multiply **autolyzed** (autolysis) **and** **phagocytosis** **and** **lysing** **the** **ciliated** **epithelial** **cells** **+ distract** **the** **function** **of** **cilia** **in** **the** **RT**
2. **Lipoteichoic acid:** complement activator, it induces inflammatory cytokine production contributing 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)
3. **Pneumolysin:** the hemolysin that causes  $\alpha$ -hemolysis, may also contribute to pathogenesis (Pneumolysin + it lyses the ciliated epithelial cells+ distract the function of cilia in the RT)

4. **IgA Protease**: pneumococci produce IgA protease that \_ the organism's ability to colonize the mucosa of the upper respiratory tract

### Factors that Predispose People to Pneumococcal Infections:

- ♦ It is worth asking, if *S. Pneumonia* is already part of the normal flora of the upper respiratory tract then how does it causes pneumonia?
  - People become susceptible to pneumococcal infections by factors that lower resistance and predispose persons to pneumococcal infection.
  - These factors either reduce mucus clearing or decrease immune reaction. These include:

1. Anything that can **depress the cough reflex**: alcohol, drug intoxication or other cerebral impairment (geriatrics, cerebrovascular accident {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 obstructions, and respiratory tract injury caused by irritants which disturb the integrity and movement of the mucociliary blanket  
☞ All **prevent clearing of the mucus** and predispose to **community acquired pneumonia** caused by pneumococcus.

3. **Abnormal circulatory dynamics** (e.g., pulmonary congestion and heart failure)  
☞ Blood will congest in the lung → **increase pulmonary secretions** → pneumococcus.

4. **Splenectomy** (spleen clears encapsulated organisms) and certain chronic diseases such as **sickle cell anemia and nephrosis**  
☞ Patients with **sickle cell anemia** auto-infarct their spleen → become functionally asplenic, and are predisposed to **pneumococcal sepsis**.

Non-functional spleen = asplenia

Splenectomy patients highly susceptible to pathogens specially capsulated >>need vaccine + high risk group: diabetic patient as a systemic disease

### 5. Trauma to the head

☞ Causes leakage of spinal fluid through the nose → predisposes to pneumococcal **meningitis**.

### 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 highly communicable** (**endogenous origin**; *it happens from aspiration of your own flora*).

Most accepted theory

person to person transmission  
person to person transmission  
between infected person to susceptible person

البيت الى كله صغاري تكون نسبة الـ S.Pneumonia نورمال فلورا اكتر  
البيت الى كله كبار تكون نسبة يكون عندهم الـ S.Pneumonia نورمال فلورا  
that's an evidence that children exchange strains in their nurseries+daycare center+schools

- ♦ Resistance to infection is **high** in healthy young people, **and disease results most often when predisposing factors are present.**

## ● Diseases Caused by S. Pneumonia (pneumococcus):

- ♦ Streptococcus Pneumonia causes many diseases that vary according to the geographical region. These diseases include: **(S.P leading bacterial cause of :)**

- Pneumonia
- Bacteremia. (followed by sepsis in non-functional spleen patient)
- Meningitis.
- URTIs(upper respiratory tract infection) such as otitis media, mastoiditis, and sinusitis (across all age groups)
- A common cause of Conjunctivitis, especially in children.

اذا اخذنا رجح across of all age groups  
نلقي S.Pneumonia في الامراض البكتيرية top << of bacterial cause  
لهذه الامراض

- ♦ Pneumococci are **the most common cause of community-acquired pneumonia, meningitis, sepsis in splenectomized or non-well-functioning spleen individuals, otitis media, and sinusitis.**

- ♦ Pneumococci are the **leading cause of sepsis in patients without a functional spleen.**

- ♦ 3 types of pneumonia: **community acquired**(infectious cause from your community& the most common cause is S.Pneumonia)\**health care associated**(pneumonia acquired from hospitals بس غالبا ما هي S.Pneumonia و انما بكون سببه Pseudomonas aeruginosa, Klebsiella ,staph, Proteus... )\**ventilator associated** (the top cause is Pseudomonas aeruginosa)

- ♦ S.Pneumonia is invasive: first it could be localized to the lungs-only Pneumonia-,then go to the pleural space(Pyoderma )>lymphatic drainage>circulation>transient Bacteremia>it could then become sepsis with organ failure> meninges (Meningitis)

### A. Pneumonia: -Lower RT- \most common clinical form

- ♦ Str. pneumoniae is the **most frequent cause** of **bacterial pneumonia** with an estimated annual incidence of 1–3 per 1000 of the population, with a **5% case fatality rate**
- ♦ Note that the most common cause of pneumonia is **viral**. However, the most common **bacterial** cause is S. Pneumonia.

Viral Pneumonia	Bacterial Pneumonia
Infiltration of both lungs.	Usually involves only one lobe or a segment of a lobe.

### \* Pathogenesis:

- Pneumococcal pneumonia usually **follows aspiration**; it happens when a person aspires S. Pneumonia from their URT to the bronchial mucosa with subsequent migration through the bronchial mucosa to involve the surrounding lymphatics.
- The inflammatory reaction is focused primarily within the alveolus of **a single lobule or lobe**(right\left lung or fissure), although **multi-lobar disease can also occur.**
- S. Pneumonia as mentioned earlier, **autolyzes** itself. This causes the release of its toxin, pneumolysin, which recruits RBCs and WBCs in the lung. This collection is in

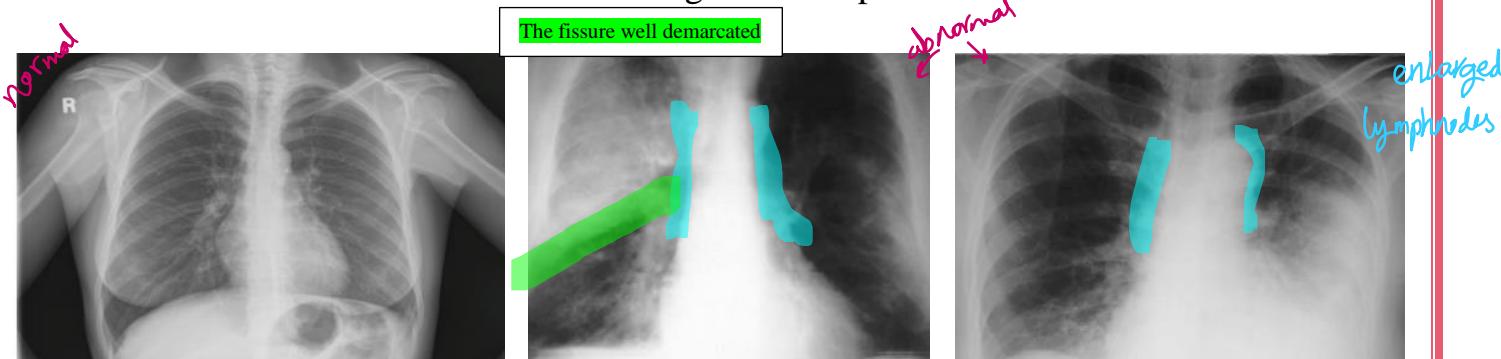
Pneumonia with no structural damage =No volume loss\no atelectasis=the patient can recover completely

the alveolar sac called **consolidation** (lysed bacteria +their extracts+ RBCs+ WBCs +polymorphic nucleated cells +lysed ciliated epithelial cells).

- Most common lobes affected by S.Pneumonia are the **middle right and lower left lobes.**

### \* Complications

- **Opacification** is one of the manifestations of pneumonia. It occurs as a result of gas reduction in the lung due to its replacement by blood / fluids. Opacification is seen as a white shadow on X- Rays.
- Pneumonia causes high fever and chills. Patients also experience chest pain that's usually increased when inhaling.
- Patients have a **productive cough** (cough with sputum). The sputum is cold and rusty due to RBCs. بس هاد بختاف عن
- Contiguous spread commonly results in inflammatory involvement of the pleura; this may progress to **empyema**.
- Pericarditis is an uncommon but well recognized complication.



### \* Clinical Findings (Pneumonia):

- Sudden chill, fever, productive 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**
- Patients start feeling better after taking penicillin
- It is increased by age, underlying disease, bloodstream involvement, metastatic infection and certain types of pneumococci with large capsules (e.g. serotype 3).
- The mortality rate from pneumococcal pneumonia in those admitted to hospital in the UK is approximately 15%.
- Occasionally, lung necrosis and intrapulmonary abscess formation occur with the more virulent pneumococcal serotypes.
- This can result in metastatic involvement of the **meninges**, joints and, rarely, the **endocardium**. *mortality rate ↗*
- Pneumococci are the **leading cause of sepsis in patients** without a functional spleen

Pneumococci are a prominent cause of otitis media, sinusitis, mastoiditis, conjunctivitis, purulent bronchitis, pericarditis, bacterial meningitis, and sepsis.

Red & bulging tympanic membrane

## B. Otitis media & Sinusitis -Upper RT-

Mainly diseases of the children but adults it can be affected especially 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*. Acute otitis media is also called **hot ear disease**.
- ♦ As there are almost 90 serotypes of the capsular polysaccharide, the person that gets infected by *S. Pneumonia* can get re-infected with another strain (a new capsule), which the body has no pre-existing immunity to (there is a constant exchange of pneumococcal strains).
- ♦ The prevalence is highest among children attending kindergarten or primary school

## C. Meningitis -outside the scope of RS-

- ♦ *Str. pneumoniae* is among the three leading causes of bacterial meningitis. Causes of meningitis vary according to geographical regions.
- ♦ It is assumed that invasion arises from the pharynx to the meninges via the blood-stream, as bacteremia usually coexists. it could be extension from a local\focus Pneumonia or without focus(meninges) (يتمن بالرئة مرور بس و بتكم طريقة للدم و بعدها للمنينجيز)
- ♦ 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. → **Meningitis الى Pneumonia** اكتر عرضة لتحول
- ♦ The **fatality** rates are 20% and 30%, respectively, considerably higher than those associated with other types of **bacterial meningitis**. viral meningitis و اعلى من
- ♦ Main symptoms : Vomiting,fever& neck stiffness

### ● Laboratory Diagnosis:

☞ **In sputum:** lancet-shaped\poly-shaped\short chain cocci gram-positive diplococci in Gram-stained smears.(isolation) \*Gold standard to diagnosis\*

☞ If we only want to detect the presence of *S. Pneumonia*, we use the **omnivalent serum**:

- The **omnivalent serum** contains antibodies targeting more than 90 capsular serotypes \\if we want specific type serotype→we put single antiserum for each polysaccharide antigen in the capsule
- We add the serum in addition to methylene blue; the bacteria will appear blue, surrounded by a **hallow** area or capsular swelling (**Quellung reaction**)



☞ **Quellung reaction:** antibody against the capsule which shows swelling of the capsule if contained the antigen for the provided antibody

- Cross-linking reactions between the bacteria can be seen cross linkage between AB تجمعوا لانه بصير في

\*Can be detected by using the quellung reaction with multitype antiserum

\*\*\*\*\*

\*sample could be :blood,sputum,urine, CSF(Cerebrospinal fluid)

We culture it in agar and what we find that the colonies of S.pneumonia look like the colonies of group A beta hemolytic streptococci with some differences in morphology of **S.P (dome shape-deep center +raised rims)**. In addition to that we use during culture optochin to differentiate btw S.Pneumonia (optochin sensitive) and viridans /S.mitidis (resistance to optochin )

☞ **On blood agar:** pneumococci form small  **$\alpha$ -hemolytic** colonies.\***Gold standard to diagnosis\***

- ☞ 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

☞ **Urine test:rapid antigen diagnostic test (antigen C carbohydrate)**

عنوان هیک اذ اطلع (-) ما بکون اکید انه ما عنده فیونو نیا → 70% sensitive

- \* Note: we classify pneumococcus as invasive if it causes meningitis or sepsis, but if it only causes a URTI, we classify it as non-invasive.



## ● Treatment:

Most pneumococci are **susceptible to penicillins** and **erythromycin**, although significant resistance to penicillins has emerged due to abuse.

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 anti-pneumococcal 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  $\beta$ -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 cases should be immunized with the **13-valent pneumococcal conjugate vaccine** (Prevnar 13).

a) **Immuno-compromised:** are given the **13-valent conjugate** pneumococcal vaccine (Prevnar 13) **T-cell-dependent**

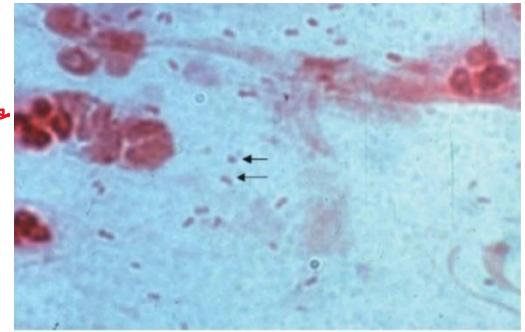
↳ The **immunogen** in this vaccine is the **pneumococcal polysaccharide** of the **13 most prevalent serotypes** conjugated (coupled) to a carrier protein (**diphtheria toxoid**).

↳ Must be given **booster doses every 5 years**.

b) **Healthy individuals age 50 years or older** (they have developed immunity): are given the **unconjugated 23-valent** pneumococcal vaccine (Pneumovax 23) (booster doses at 65) **T-cell-independent**

<b>conjugate</b> → children
<b>unconjugated</b> → adult

- These vaccines are safe and effective and provide long-lasting (at least 5 years) protection



## \* **Hemophilus Influenza**

*blooded* *↳ Living*

- H. influenzae are **gram negative rods (coccobacillary)** {young age culture}, **encapsulated** with a polysaccharide capsule. {In old age: bacillus}
- One of the three important encapsulated pyogenes (pneumococcus and the meningococcus)
- Using serologic methods against the antigen of the polysaccharide capsule, **six serotypes** (A-F) are detected, with serotype B (group B) being the most significant one
- Serotype B is responsible for more **serious illnesses** ( meningitis, epiglottitis, sepsis)
- The type B capsule is **composed** of polyribitol phosphate(**PRP**), 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**

Typeable H.I: {A-F} & B is significant  
Non-typeable H.I: colonizers of normal person  
>> URT+{COPD patient مسؤولين عن الانفلونزا في }

- H. influenzae used to be the leading cause of meningitis in young children, now it's the **third most common**.
- We have 1 representative from each gram reaction and shape that is a respiratory organism (four in total):
  - Pneumococcus G+ve coccus**: capsulated respiratory organism causes meningitis and URTI
  - Meningiococcus G-ve coccus**: capsulated which can colonize the respiratory epithelium
  - The gram-negative ROD, Haemophilus**: also a respiratory capsulated organism that is the **third most common cause of meningitis**.
  - Corynbacterium diphtheriae G+ve ROD**: not capsulated, doesn't cause meningitis
- Note that the three **capsulated** ones are **causative of meningitis** and **have vaccines** made against the capsule

### ○ Pathogenesis & Epidemiology:

- Reservoir**: H. influenzae infects **only humans** with **no animal reservoir**
- Transmission**: 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)

carriage rate of H.I<<< S.P  
لأنه في لها مطاعيم من زمان

- **Virulence Factors:** 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.** {+the capsules the main virulence factor+ immunogenic }
- After becoming established in the upper respiratory tract, the organism can enter the bloodstream (bacteremia) and spread to the meninges
- As mentioned earlier, capsulated strains can 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 Meningococcus)
- Meningitis caused by capsular type B has been greatly **reduced by vaccines** that contain 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>>main Virulence Factors*)

## ● Clinical Findings:

### \* Meningitis:

- ◆ Meningitis caused by H. influenzae produces a clinical picture that is almost identical to pneumococcal or meningococcal meningitis
- ◆ The rapid onset of fever, chills, vomiting, headache, **stiff neck**, (neurological symptoms; drowsiness), is **typical** + emergency

### \* Upper Respiratory Tract Infections:

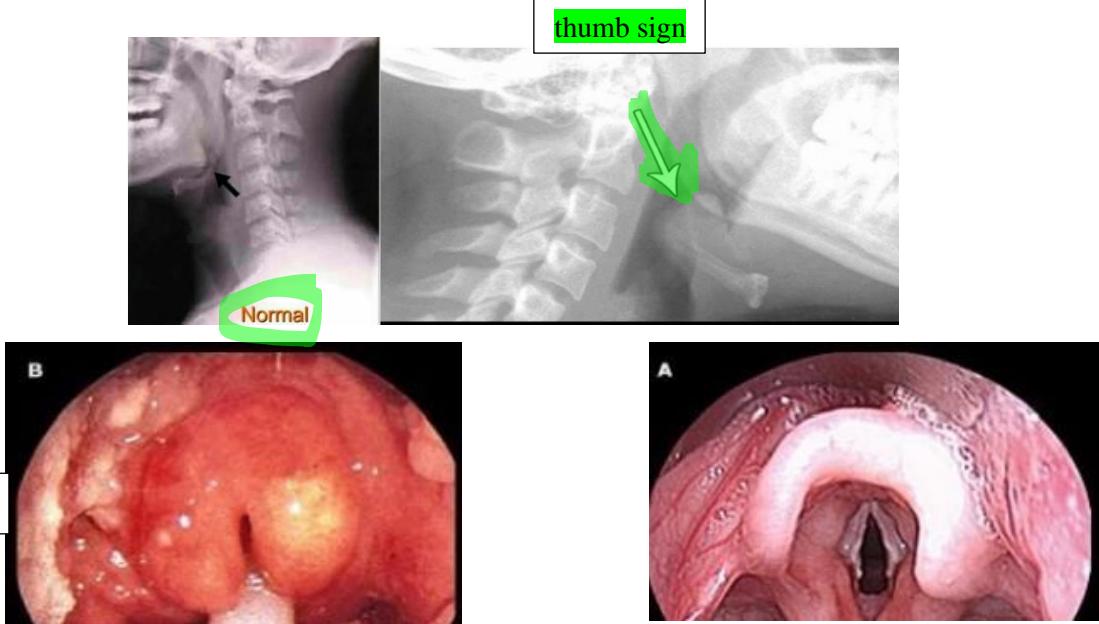
- ◆ Sinusitis and otitis media cause pain in the affected area, opacification of the infected sinus, and redness with bulging of the tympanic membrane
- ◆ H. influenzae is **second** only to the pneumococcus as a cause of these two infections (URTI +meningitis )
- ◆ Other serious infections : septic arthritis, cellulitis, and sepsis (more in asplenic patients, due to the fact that this is a capsulated organism)

### \* Epiglottitis:

- ◆ Rare due to vaccination, 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 (**type B**) ((**endotracheal intubation first then antimicrobial treatment**))
- ◆ Symptoms include, drooling, **stridor** (high pitched breathing noise) and comfort on sitting up.
 

شکست انده عنده  
 don't make any intervention << Epiglottitis  
 laryngospasms  
 لانه سهل يصیر عنده
- Pneumonia in elderly adults, especially those with chronic respiratory disease, can be caused by untypeable(not capsulated) strains of *H. influenzae*

In developed countries the H.I isn't the causative agent of epiglottitis due to vaccination\\the causative: S.P, Staph, GAS  
 but in our countries mainly the bacterial causative agents: H.I followed by S.aureus



### ● Laboratory Diagnosis:

- ◆ Need to isolate the organism to make the diagnosis
- ◆ 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**
- ◆ **Quellung reaction**(Antibody against the capsule which shows clumping + swelling of the capsule if contained the antigen for the provided antibody) and biochemical tests can be used .
- ◆ Additional means of identifying encapsulated strains include fluorescent antibody staining of the organism and counter immune-electrophoresis 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  $\beta$ -lactamase that degrades penicillinase-sensitive  $\beta$ -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-mild-, are treated with either **amoxicillin-clavulanate** or **trimethoprim- sulfamethoxazole**

## ● Prevention:

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

اذا شخصت ولد صغير Hemophilus Meningitis بتطعيه هو و اخوانه الصغار لانهم ... بس الكبار لا غالبا يكونوا not at risk

*A special thanks to Basma AbuMahfouz for her contribution in this sheet*