

Bacterial infections of the Respiratory tract 2

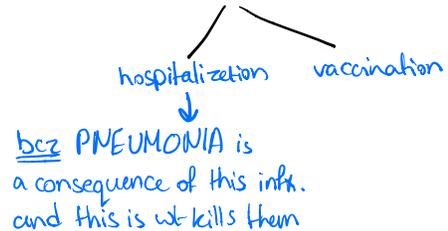
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— : purple for comparison

Someone asked a Q about influenza. Ans: high risk grps are given vaccination and may require hospitalization if they have flu-like symptoms

- in case of epidemics (like current situation in Jordan), you don't need to test for influenza in every patient. ONLY in HIGH RISK GRP, it is a must to confirm H1N1. If confirmed



In this lecture, we will discuss 2 organisms: 1) Strep pneumonia 2) Haemophilus influenza

gram +

gram -

Why grouped together?

- The major virulence factor for both is the capsule
 - Both have vaccines
- usually, capsulated organisms have vaccines.

Microorganisms mentioned in previous lecture and this lecture are extremely important for USMLE and similar exams.

OVERVIEW

Whenever you hear meningitis (in adults/children), pneumonia or UTRI, you should think of 3 organisms; S pneumo, H influenza and Neisseria meningiditis (in case of meningitis).

m/cc of (but it varies according to geography)

Meningitis

- Strep pneumo (in adults)
- H influenza
- Neisseria meng.

Pneumonia

- Strep pneumo (in adults/children)
- H influenza (used to be m/cc but nowadays, its incidence has declined a lot due to vaccination)

URTI (otitis media and sinusitis)

- Strep pneumo
- H influenza
- moraxella catarrhalis

Conjunctivitis

- Strep pneumo

In general, strep pneumonia infx manifests as;

adults → meningitis + pneumonia

children → sinusitis + otitis media + conjunctivitis

α -hemolytic (+)
not applicable for Lancefield

Strep Viridans
op: R bile: not soluble

Strep pneumo
op: S bile: soluble

How to distinguish btw them?

- optochin sensitivity: sensitive if there is a zone of inhibition around optochin disk in the culture
- bile solubility: a drop of human bile acid is added to a specimen taken from the patient or to the colonies

remember: GAS is Optochin R, Bacitracin S

Strep pneumo is part of normal flora and there are certain mechanisms to prevent normal flora from causing disease, if impaired —> risk of endogenous infx and S pn. Infx

Predisposing Factors for S pn.

1. Recent influenza infx: due to epithelial cell dysfunction
2. Impaired cough reflex in alcoholics
3. Impaired phagocytosis in alcoholics: main defense against encapsulated organisms is phagocytosis (and opsonization)
4. Asplenia
 - A. splenectomy after road traffic accident
 - B. Nonfunctional spleen (e.g. sickle cell)
 —> these patients must be vaccinated bcz they are susceptible to overwhelming invasive infx by S pn. (e.g. sepsis)
5. Malnutrition
6. Abnormal circulatory function (e.g. HF)

imp

S pn, H inf and GAS all are part of normal flora of URT but **NOT** LRT (LRT is sterile). So, infx caused by them is most probably **ENDOGENOUS**: aspiration of bacteria into LRT and there the disease starts; m/c form of the disease is pneumonia —> **aspiration pneumonia** and then the bact. may disseminate into blood and cause **meningitis or sepsis !!!**

This doesn't mean that there's no exogenous infx, it indicates that their **communicability is low**

- transmitted to household contact only
- doesn't cause airborne disease
- unlike TB/influenza which cause pandemics and epidemics, Spn. only causes outbreaks but confined outbreaks

communicability is low

in order to transmit infx:

- high inoculum needed
- lowered immunity
- suitable envirm factors of close, prolonged contact

so

↓
in prisons, daycare centers and nursery homes

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. تدل مشها الجرامة)
- All virulent strains have surface capsules, composed of high-molecular-weight polysaccharide polymers.
- 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**.
- Pneumolysin forms pores after release by autolysins



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.)

Since they are gram +, they have peptidoglycans and share a lot of their virulence factors with GAS

Pathogenesis, virulence factors:

(M prot. +100 serotypes)

+90 serotypes

capsular switching in Spn and Hinf. is a new research area (similar to antigenic variation in influenza) NOT FOR OUR LEVEL

- 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. like streptolysin O but pneumolysin isn't released unless there's autolysis
- Pneumococci produce IgA protease that enhances the organism's ability to colonize the mucosa of the upper respiratory tract. Strep pneumo has a tendency for autolysis which augments pneumo-lysin secretion
- Strep pneumo has a choline binding prot (but it's role is still nit well established

Speciall
a major VF

needed to establish infx then adhesin mics start working
ex lipoteichoic acid → Spn.
prot F → GAS

found in H.inf.

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.

again,

→ endogenous infx → aspiration pneumonia, risk of meningitis/sepsis if bacteremia developed

low communicability → ↑ infective dose / ↓ immunity / close contact for prolonged period

→ only confined outbreaks, no epidemics

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.

Bimodal distribution:

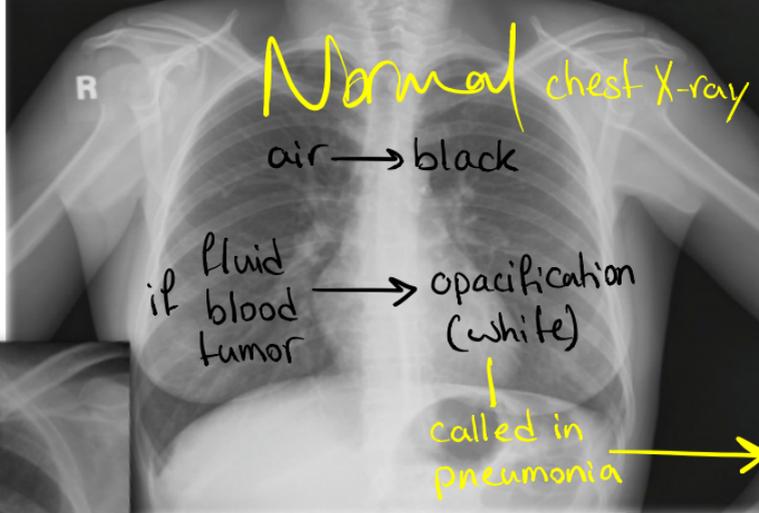
- affects young children <5, in haemophilus <3
- affects old age grp >45 or >65

① Pneumonia

Spn is m/cc in children/adults

- 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.
start multipl. in alveoli but no structural loss (walls still intact)
 - Contiguous spread commonly results in inflammatory involvement of the pleura; this may progress to empyema.
 - Pericarditis is an uncommon but well recognized complication.
no permanent disfigurement of alv
- so RECOVER very QUICKLY after initiating therapy

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



- establish infx
- autolysis
- pneumolysins out
- RBCs and PMNs accumulate

edematous fluid due to local inflam. induced by RBCs/PMNs/Spn.

CONSOLIDATION

m/c affected lobes

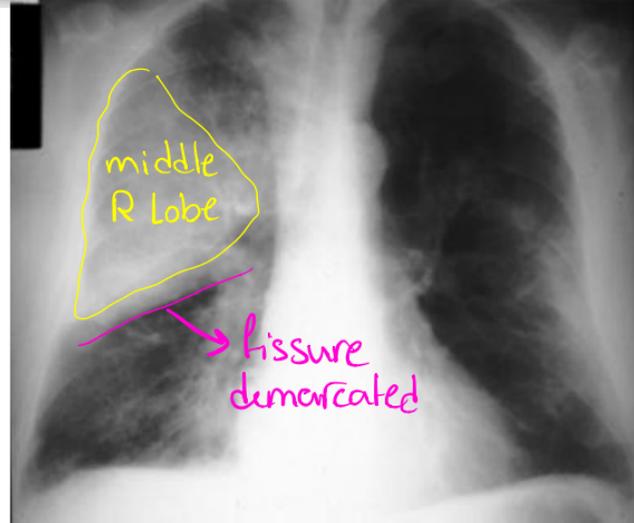
- middle R
- lower L



- viral is m/c of pneum.
- m/c bact. cause is Spn.

bacterial
affects one lobe or a segment (confined)

viral
infiltrates both lungs (diffuse)



- airbronchogram is also used

② Otitis media and sinusitis

not invasive infx

- 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 kindergarten or primary school,
- where there is a constant exchange of pneumococcal strains.

= HOT EAR disease
most childr. experience it many times in their childhood

→ on otoscope: tympanic memb. edematous and red → acute otitis media

③ **Meningitis** invasive infx (along with sepsis)

bcz m/c varies according to geography (Neisseria may be m/c in some areas, same with H. inf)

- 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.

again, 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

↓
if untreated

in H. inf. 90% if untreated so it is more invasive

Clinical Findings

all these are only clues,
and doesn't mean that
these findings can't be
caused by another organism

• Pneumonia:

• sudden chill, fever, cough and pleuritic pain (chest pain that increases with chest movement-breathing).

• Sputum is a red or brown "rusty" color. → bcz of RBCs (pink/rusty)

in pseudomonas org: sputum is green

• 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.

again, • Pneumococci are the leading cause of sepsis in patients without a functional spleen.

sepsis occurs in immuno-compromised or asplenia (nonfunctional / splenectomy)

= organ dysfunction due to bacteremia, seeding to various organs may occur

25-30% of Spn. infected patients have bacteremia (+ve blood cultures)

Laboratory Diagnosis

- blood
- sputum specimens
- CSF

gram +/- shape In sputum: lancet-shaped gram-positive diplococci in Gram-stained smears.

- to confirm
- Can be detected by using the quellung reaction with multitype antiserum.
"capsular swelling test"
 - On blood agar, pneumococci form small α -hemolytic colonies. no Lancefield antigen
 - 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.

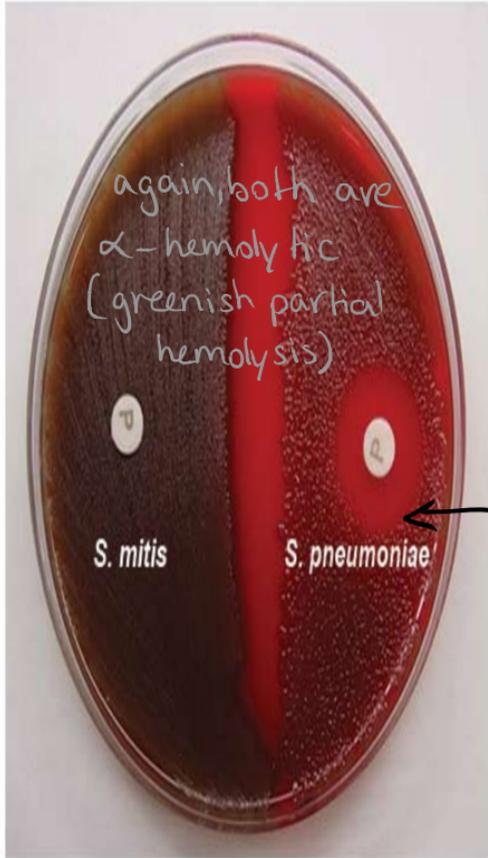
viridans or Spn?

To detect presence of S pn. :

- **Omnivalent serum**: contains +90 polysacch. Abs
- Mix it with the sample taken from the patient and add **methylene blue**
- If present → the capsule appears as a sharply demarcated halo around dark blue stained cell; called **capsular swelling** (see picture below)

Optochin sensitivity

+90 types of "polysaccharide capsule antigens"



Left Side

S. mitis type of viridans

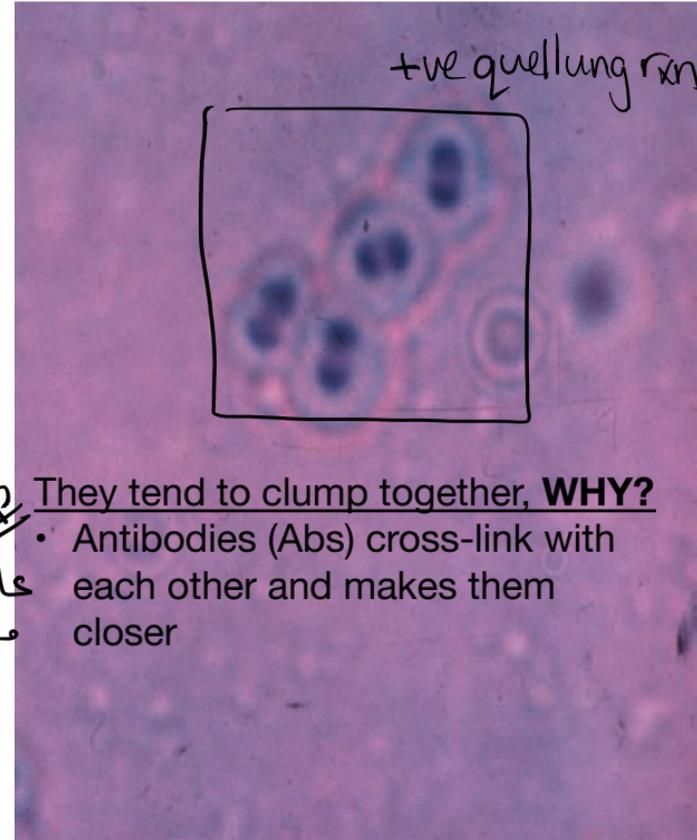
Resistant to optochin

Right Side

S. pneumoniae

Susceptible to optochin

notice zone of inhibition around optochin disk



Quellung reaction

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 any other macrolide 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.

quick recovery (remember: no structural damage)

in US, so in Jordan it is more (but no statistics)

mechanism of resistance is imp

→ H inf produces them

Last year, there were 2 questions about vaccines of S pn and H inf and many didn't answer it. Sooo pay attention

Prevention

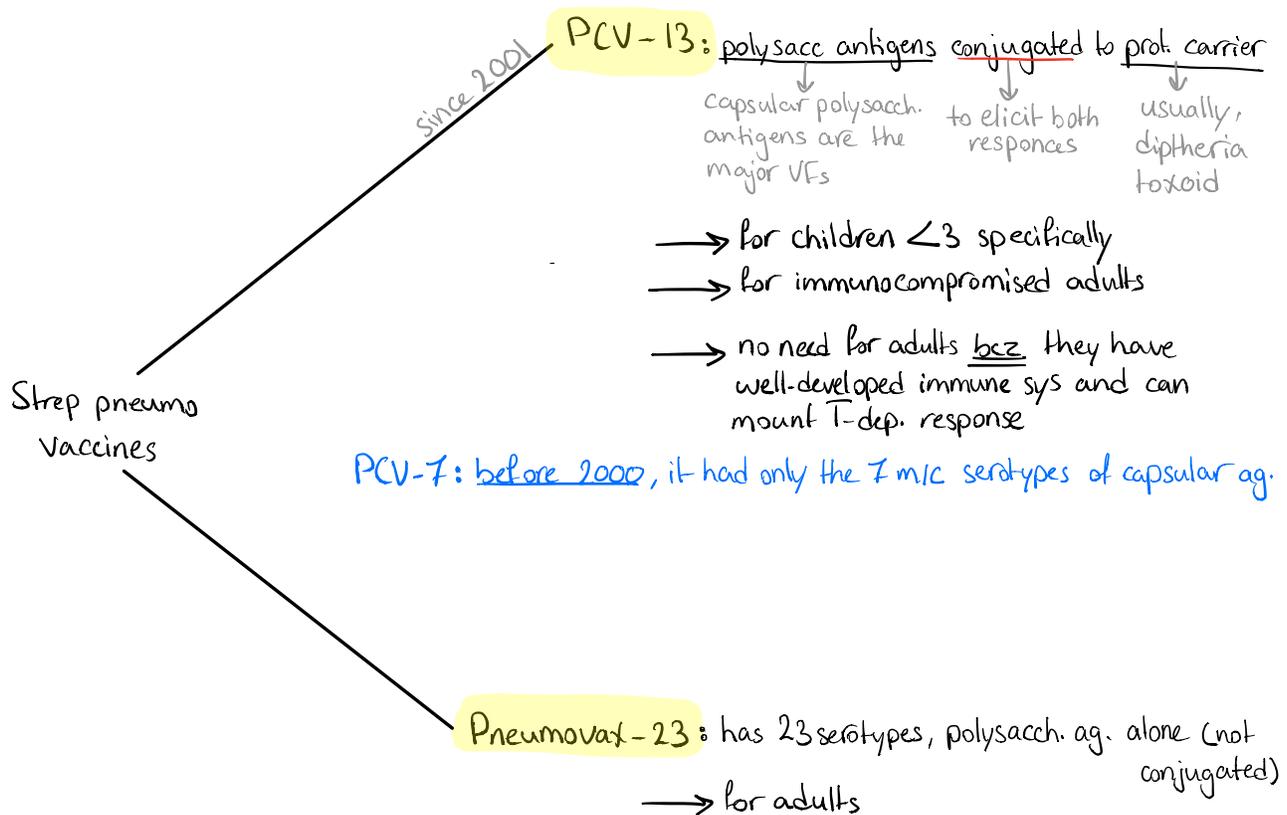
- part of routine vaccination in US, Europe

- not part of " " in Jordan *unlike Hinf*, that's why our children aren't fully vaccinated

- 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) (must be given booster doses every 5 years). *Pcv*
- 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.
- Since most imp VF is the polysacc. capsule, it must be part of the vaccine.

Summary from Dr. Nadur

Note: polysacch antigen → T-independent response
protein antigen → T-dependent response
that's why we conjugate vaccines (to elicit both T-dep and T-indp responses)



How does it work?

- resulting Abs will fight bacteria
- Abs opsonize bacteria → help phagocytes to spot them → complement activation

Asem asked a Q. Ans is: there's no evidence supporting prophylaxis in case of strep pneumonia (neither in children nor in immunodeficient adults)

HAEMOPHILUS important Properties

remember
Spn. is diplococci

★ Coccobacillary: they are bacilli but very short and with a curved end so they look like cocci

- 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 .
→ polyribitol polysaccharide capsule PRP
- 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.

★ : the Dr. said to focus on them

Major VF is capsule

S pn → +90 serotypes

H inf → divided into



Typable

- Possess a polysaccharide capsule
 - → virulent and invasive
- Divided into 6 serotypes A-F
- Cause significant disease
 - Epiglottitis
 - Sepsis
 - Meningitis
- m/c is B
 - most invasive
 - most responsible for mortality
 - H inf vaccine only contains serological type B capsular ag (called PRP)

Non-typable

- No capsule
- Mainly cause URTI
- As well as LRTI but not invasive
 - COPD patients may have superimposed infection “acute exacerbation”; non-typable H influenza is part of the ddx.

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^① and have vaccines made against the capsule.^②
- Pneumococcus G+ve coccus = capsulated respiratory organism causes Strep pneum. meningitis and URTI
- Meningococcus G-ve coccus also capsulated which can colonize the respiratory epithelium *Neisseria mening.*
- and now the Gram negative ROD, Haemophilus is also a respiratory capsulated organism that is the third most common cause of meningitis. *H. influenzae*
- The fourth is *Corynebacterium diphtheriae*, not capsulated, doesn't cause meningitis.

resp.
baet.

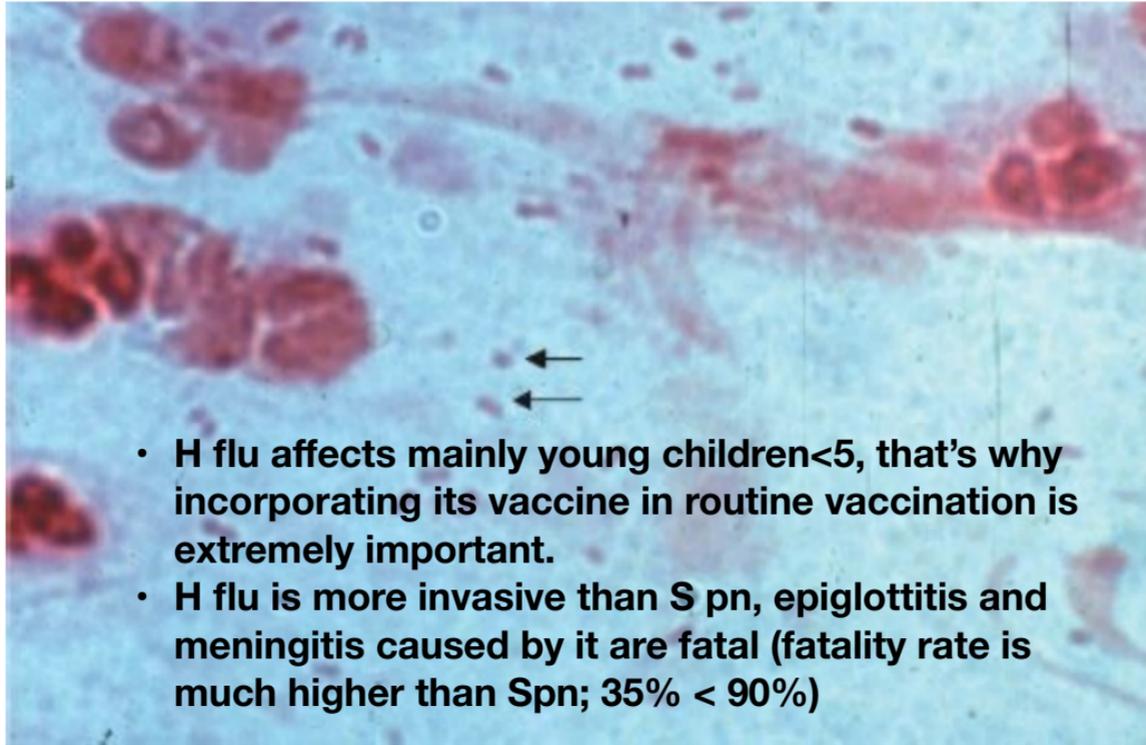


FIGURE 19–1 *Haemophilus influenzae*—Gram stain. Arrows point to two small “coccobacillary” gram-negative rods. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

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 Meningococcus)
- 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)

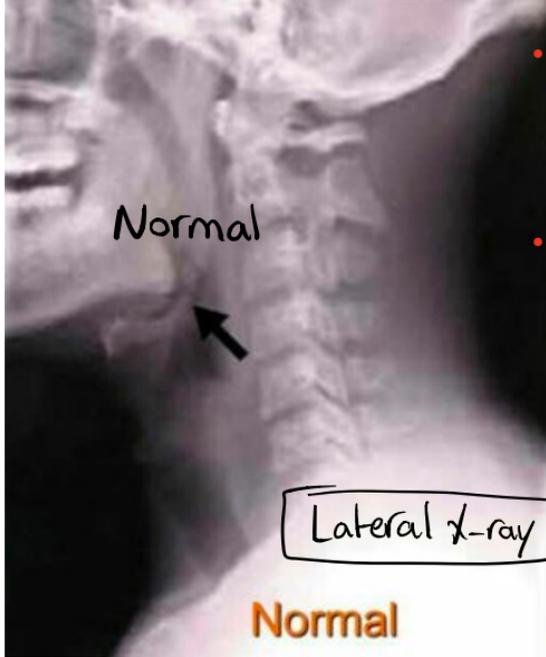
Typable serotypes healthy carriers % declined a lot.

Non-typable serotypes healthy carriers can reach up to 90%

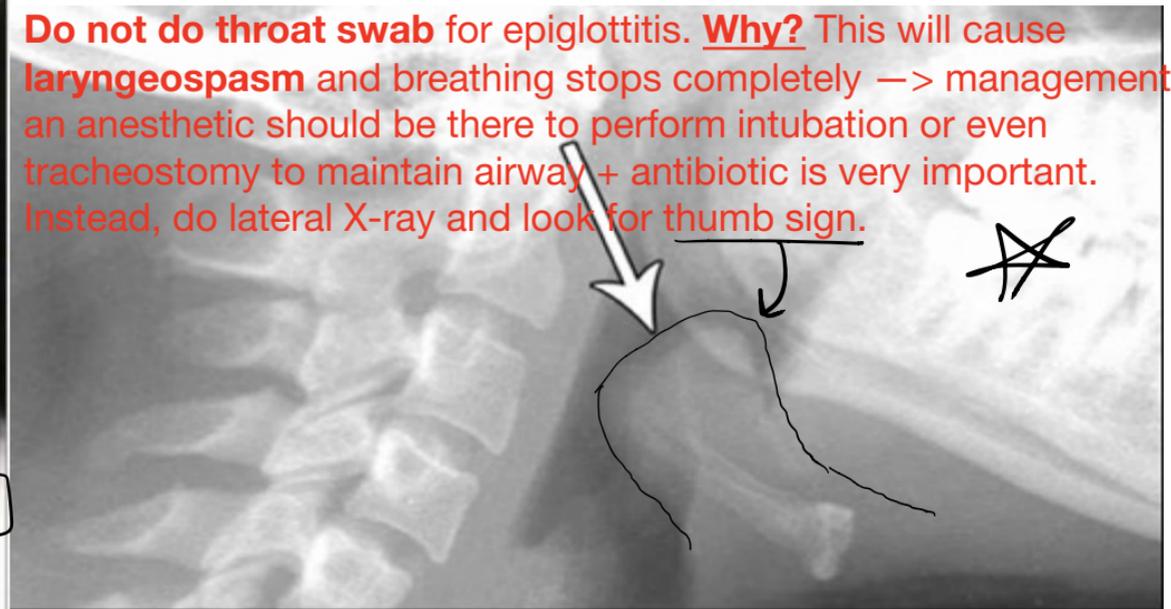
Clinical Findings

- 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" epiglottitis 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 discomfort on sitting up.
- Pneumonia in elderly adults, especially those with chronic respiratory disease, can be caused by untypeable strains of *H. influenzae*.

bcz
part of
routine
vaccination

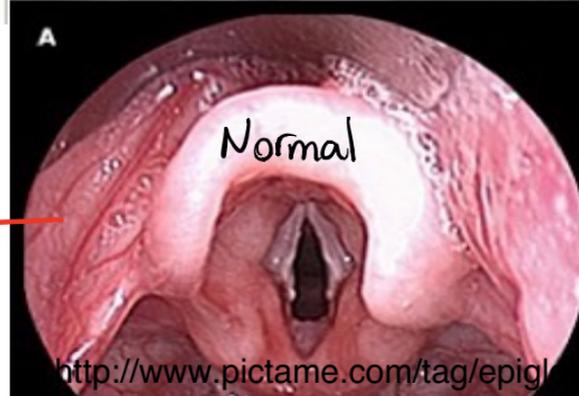


- **Do not do throat swab** for epiglottitis. **Why?** This will cause **laryngospasm** and breathing stops completely → management: an anesthetic should be there to perform intubation or even tracheostomy to maintain airway + antibiotic is very important.
- **Instead, do lateral X-ray and look for thumb sign.**



Medical
EMERGENCY!

كلو ٣ مرات



Laboratory Diagnosis

- Gram -
- 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. *so use these characteristics to distinguish it from others*
- **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 fluorescent antibody staining of the organism and counter immunoelectrophoresis or latex agglutination tests, which detect the capsular polysaccharide.
- In case of epiglottitis, no throat swab. Only lat x-ray

Bcz they are FASTIDIOUS



Culture
★

to confirm capsule presence

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. *Spn \rightarrow alter PBP*
- 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.

*again,
more
invasive*

H inf is more invasive, more serious. You don't wait to see whether penicillin works or not since resistance is high. However, penicillin still works in many cases

Prevention

- The vaccine is only against type B (doesn't cover A or non-typable)
- vaccine* • Capsule= vaccine, so the vaccine contains the capsular polysaccharide of H. influenzae type b conjugated to diphtheria toxoid or other carrier protein. *given for children*
- Depending on the carrier protein, it is given some time between the ages of 2 and 15 months. *remember why*
- 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.
- prophylaxis* • 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
- Prophylaxis is given for all children and unvaccinated or immunocompromised adults in the household of the infected person.

The vaccine is given in 4 doses;

- 1st dose: 2nd mn
- 4th dose: 1- 1 1/2 yrs

if the booster dose isn't given, the person considered unvaccinated

Fortunately

- Incidence of H inf decreased a lot bcz of vaccines.
- Non-typable ones are still common, but at least they didn't cause fatal diseases.

The End