Pharmaceutical microbiology

Chapter 4

Streptococci

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Lecture 11

01/11/2020

Pathogenesis and Clinical Findings

- **A. Diseases Attributable to Invasion by *S. pyogenes***
- **β-Hemolytic Group A Streptococci**
- **1. Erysipelas .....** If the portal of entry is the skin, erysipelas results, with **massive brawny edema** and a rapidly advancing margin of infection.
- **2. Cellulitis .....** Streptococcal cellulitis **is an acute, rapidly spreading infection of the skin and subcutaneous tissues**. It follows infection associated with **mild trauma, burns, wounds, or surgical incisions**. **Pain, tenderness, swelling, and erythema** occur.

- **Cellulitis** is differentiated from **erysipelas** by two clinical findings:

- In cellulitis,
- **The lesion is not raised,**
- **and the line between the involved and uninvolved tissue is indistinct.**

Erispelas and cellulitis

- **3. Necrotizing fasciitis (streptococcal gangrene)**

- There is **extensive and very rapidly spreading necrosis of the skin, tissues, and fascia.** Bacteria other than *S. pyogenes* can also cause necrotizing fasciitis. The group A streptococci **that cause necrotizing fasciitis have sometimes been termed flesheating bacteria**.

- **4. Puerperal fever**..... If the streptococci **enter the uterus after delivery, puerperal fever develops, which is essentially a septicemia originating in the infected wound (endometritis).**

5. Bacteremia or sepsis

- Infection of traumatic or surgical wounds with streptococci results in bacteremia, which can rapidly be fatal.
- *S. pyogenes* bacteremia can also occur with skin infections, such as cellulitis and rarely pharyngitis.

Necrotizing fasciitis (streptococcal gangrene)

B. Diseases Attributable to Local Infection With *S. pyogenes* and Their Byproducts

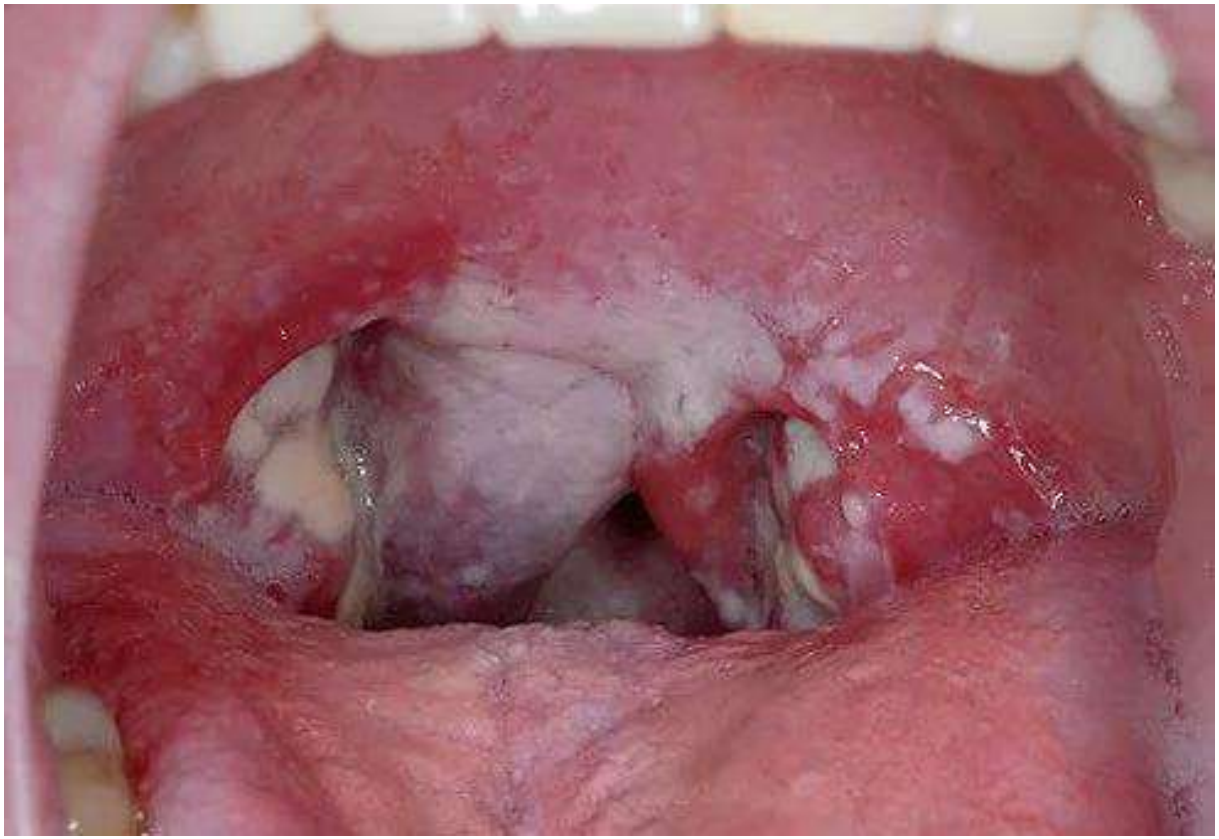
1. Streptococcal sore throat

The most common infection caused by β-hemolytic *S pyogenes* is streptococcal sore throat or pharyngitis.

S. pyogenes adhere to the pharyngeal epithelium by means of lipoteichoic acid–covered surface pili and by means of hyaluronic acid in encapsulated strains.

The glycoprotein fibronectin (MW, 440,000) on epithelial cells probably serves as lipoteichoic acid ligand.

Streptococcal sore throat



2. Streptococcal pyoderma

- Local infection of **superficial layers of skin, especially in children, is called impetigo.**
- It consists of **superficial vesicles that break down. It spreads by continuity and is highly communicable, especially in hot, humid climates.**

- **3- scarlet fever** Pyrogenic exotoxins A–C also cause in association with *S pyogenes* pharyngitis or with skin or soft tissue infection.

- The pharyngitis may be severe. The rash appears on the trunk after 24 hours of illness and spreads to involve the extremities.

C. Poststreptococcal Diseases (Rheumatic Fever, Glomerulonephritis)

1. Acute glomerulonephritis

- This sometimes develops 1–4 weeks after *S pyogenes* skin infection (pyoderma, impetigo) or pharyngitis. Some strains are particularly nephritogenic, principally with M types 2, 42, 49, 56, 57, and 60 (skin).

- Other nephritogenic M types associated with throat infections and glomerulonephritis are 1, 4, 12, and 25. After random streptococcal skin infections, the incidence of nephritis is less than 0.5%.

2. Rheumatic fever

- This is the most **serious sequela of *S. pyogenes* because it results in damage to heart muscle and valves.** Certain strains of group A streptococci contain cell membrane antigens that cross-react with human heart tissue antigens.

- The onset of rheumatic fever is often preceded by *S pyogenes* pharyngitis 1–4 weeks earlier, although the infection may be mild and may not be detected. In general, however, **patients with more severe streptococcal sore throats have a greater chance of developing rheumatic fever.**

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- Typical symptoms and signs of rheumatic fever include **fever, malaise, a migratory nonsuppurative polyarthritis, and evidence of inflammation of all parts of the heart** (**endocardium, myocardium, and pericardium**).
- It is therefore **important to protect such patients from recurrent *S pyogenes* infections by prophylactic penicillin administration.**

Diagnostic Laboratory Tests

A. Specimens

- Specimens to be obtained depend on the nature of the streptococcal infection. A throat swab, pus, or blood is obtained for culture. Serum is obtained for antibody determinations.

B. Smears

- Smears from pus often show single cocci or pairs rather than definite chains. Smears of throat swabs are rarely contributory because viridans streptococci are always present and have the same appearance as group A streptococci on stained smears.

C. Culture

- Specimens suspected of containing streptococci are cultured on blood agar plates. If anaerobes are suspected, suitable anaerobic media must also be inoculated. Incubation in 10% CO2 often speeds hemolysis. Slicing the inoculum

- **D. Antigen Detection Tests**

- Several commercial kits are available for rapid detection of group A streptococcal antigen from throat swabs.
- These kits use enzymatic or chemical methods to extract the antigen from the swab, then use enzyme immunoassay (EIA) or agglutination tests to demonstrate the presence of the antigen.

- **E. Serologic Tests**

- A rise in the titer of antibodies to many group A streptococcal antigens can be estimated. Such antibodies include **ASO, particularly I respiratory disease; anti-DNase B and antihyaluronidase, particularly in skin infections; antistreptokinase; anti-M type-specific antibodies**; and others. Of these, the anti-ASO titer is most widely used.

Treatment

- All *S pyogenes* are susceptible to penicillin G. Macrolides, such as erythromycin and clindamycin, have often been recommended for penicillin allergic patients and for patients with necrotizing fasciitis.
- Antimicrobial drugs have no effect on established glomerulonephritis and rheumatic fever.
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- Doses of penicillin or erythromycin that result in effective tissue levels for 10 days usually accomplish this.
- Antimicrobial drugs are also very useful in preventing reinfection with β-hemolytic group A streptococci in patients with rheumatic fever.

Epidemiology, Prevention, and Control

- Many other streptococci (eg, viridans streptococci, enterococci) are members of the **normal microbiota of the human body**. They **produce disease only when established in parts of the body where they do not normally occur (eg, heart valves).**

- 1. **Detection and early antimicrobial therapy of respiratory and skin infections with group A streptococci.**

- Prompt eradication of streptococci from early infections can effectively prevent the development of poststreptococcal disease.

- This requires maintenance of adequate penicillin levels in tissues for 10 days (eg, benzathine penicillin G given once intramuscularly). Erythromycin is an alternative drug, although many S. pyogenes are now resistant.

- 2. Antistreptococcal chemoprophylaxis in persons who have suffered an attack of rheumatic fever. This involves giving one injection of benzathine penicillin G ... IM every 3–4 weeks or
- daily oral penicillin or oral sulfonamide.
- The first attack of rheumatic fever infrequently causes major heart damage; however, such persons are particularly susceptible to reinfections with streptococci that precipitate relapses of rheumatic activity and give rise to cardiac damage.

Concept Checks

- Streptococci are a large group of gram-positive organisms that are catalase negative and tend to grow in pairs and long chains. Major classifications include **the type of hemolysis (α, β, or no hemolysis [γ]), conditions for growth, and capacity to cause disease**.

- **S pyogenes (group A β-hemolytic streptococcus) is the most virulent pathogen in the Streptococcus family.** It elaborates numerous proteins, **hemolysins, enzymes, and toxins responsible for the broad range of suppurative (eg, cellulitis) and immunologic diseases** (poststreptococca GN, RF) associated with this organism.

Streptococcus agalactiae

- **These are the group B streptococci.** They **typically are β-hemolytic.** Group B streptococci are **part of the normal vaginal flora and lower gastrointestinal tract in 5–30% of women**.

- **Group B streptococcal infection during the first month of life may present as fulminant sepsis, meningitis, or respiratory distress syndrome.**

Viridans Streptococci

- The viridans streptococci are **the most prevalent members of the normal microbiota of the upper respiratory tract and are important for the healthy state of the mucous membranes there.**
- They may reach the bloodstream as a result of trauma and are a principal cause of endocarditis on abnormal heart valves.
- **(eg, *S mutans*) synthesize large polysaccharides such as dextrans or levans from sucrose and contribute importantly to the genesis of dental caries.** Some viridans streptococci

- **Subacute endocarditis** often involves abnormal valves (congenital deformities and rheumatic or atherosclerotic lesions)., subacute endocarditis is most frequently caused by members of the normal microbiota of the respiratory or intestinal tract that have accidentally reached the blood.
- **After dental extraction, at least 30% of patients have viridans streptococcal bacteremia.**

Streptococcus pneumoniae

- **The pneumococci (*S. pneumoniae*) are gram-positive diplococci, often lancet shaped or arranged in chains, possessing a capsule of polysaccharide that permits typing with specific antisera.**
- Pneumococci are normal inhabitants of the upper respiratory tract of 5–40% of humans and can cause **pneumonia, sinusitis, otitis, bronchitis, bacteremia, meningitis, and other infectious processes**.

Treatment

- Because pneumococci are susceptible to many antimicrobial drugs, early treatment usually results in rapid recovery, and antibody response seems to play a much diminished role.
- Penicillin G has been the drug of choice. Some penicillin-resistant strains are resistant to cefotaxime.Resistance to tetracycline, erythromycin, and fluoroquinolones also occurs. Pneumococci remain susceptible to vancomycin. Because resistance profiles are not predictable, routine susceptibility testing should be performed for all pneumococcal infections

Concept Checks

- **Viridans streptococci** and **enterococci** are **part of the normal microbiota of the human oral and gastrointestinal tracts**, but **they can be associated with serious infections**, such as **bacteremia and endocarditis under certain conditions.**
- ***S pneumoniae* is α-hemolytic; optochin susceptible**; **and virulent largely** because of its polysaccharide capsule, which inhibits phagocytosis.
- ***S pneumoniae* is the major cause of community-acquired pneumonia** but can also disseminate via the bloodstream to the central nervous system.
- Invasive disease is preventable through vaccination

Pharmaceutical microbiology

Chapter 5

G-ve cocci

Nessieria

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Lecture 12

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Neisseria

- The genus ***Neisseria*** **consists of Gram-negative, aerobic,nonsporing, nonmotile cocci, typically arranged in pairs (diplococci)**
- The **bacteria belonging to this genus are oxidase positive and mostly catalase positive.** They **ferment sugars with production of acid but no gas.**

- The genus *Neisseria* consists of 10 species. *Neisseria gonorrhoeae* and *Neisseria meningitidis* are the two important species that cause human infections.
- These **two species are strictly pathogens for humans, whereas the other *Neisseria* species are commensals of the mouth and upper respiratory tract, and hence cause opportunistic infections.**

(A)Neisseria gonorrhoeae

- *N. gonorrhoeae* is a strict human pathogen. It is the causative agent of **gonorrhea**, one of the most common sexually transmitted disease worldwide.
- Gonococci when transmitted non sexually from the mother's genital tract to the newborn during birth cause ophthalmia neonatorum.

Gonorheae ophthalmia neonatorum.

- The cell wall of *N. gonorrhoeae* like any other Gram-negative bacteria consists of three layers:
- outer cell surface,
- middle peptidoglycan layer, and
- inner cytoplasmic membrane

Cell wall of N. gonorrhoeae

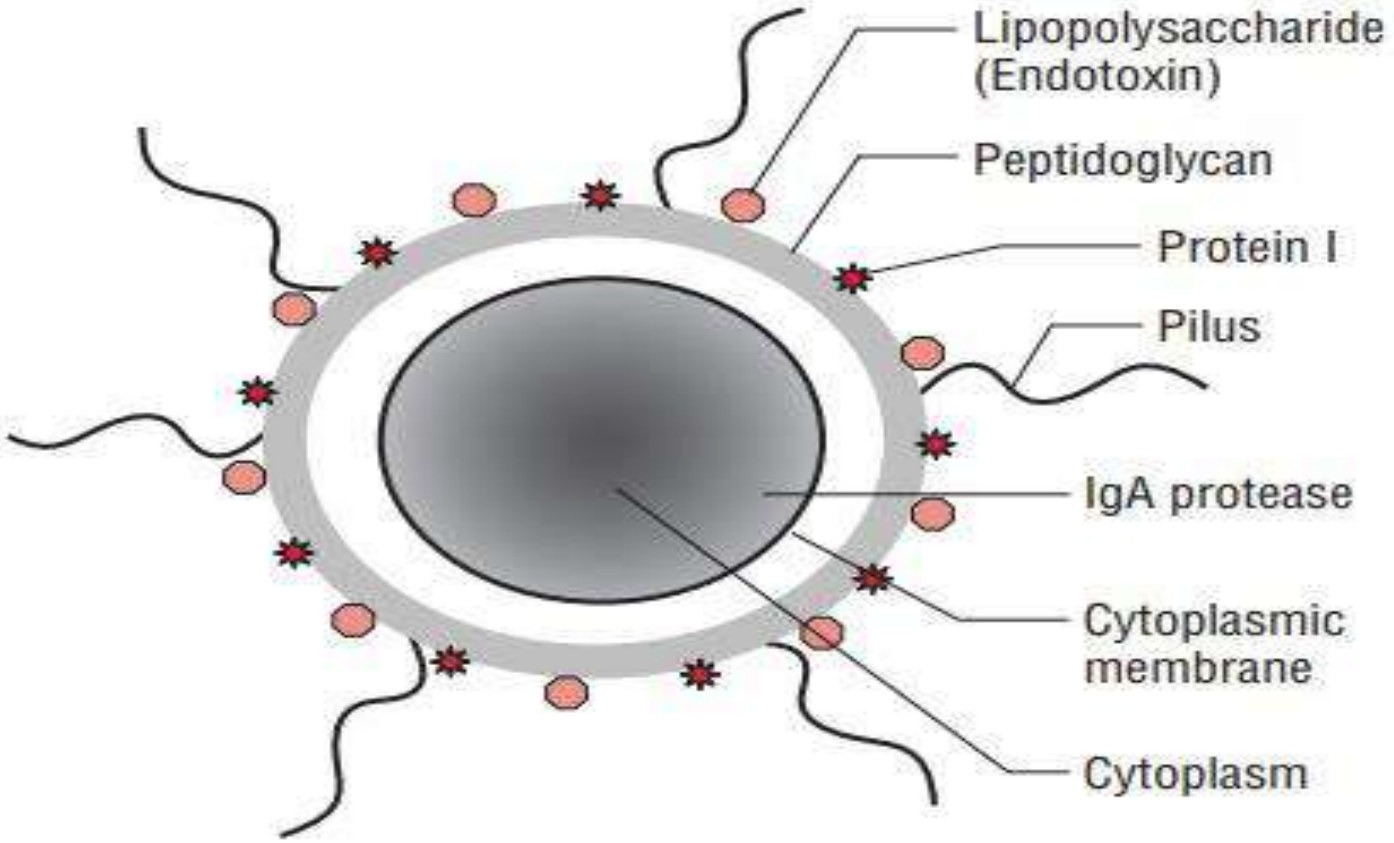
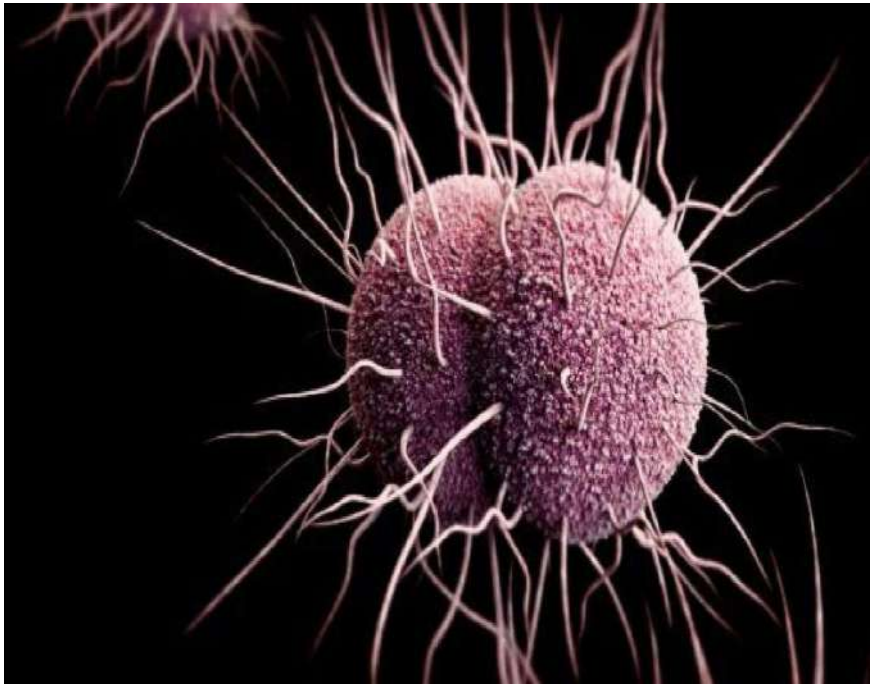


FIG. 26-1. Schematic diagram of *Neisseria gonorrhoeae*.

Neisseria gonorrhoeae



Pathogenesis and Immunity

- **N. gonorrhoeae causes disease** both **by multiplying in tissues and by causing inflammation**.

- **Virulence factors**

- **Capsule:**

- ***N. gonorrhoeae* does not form a true carbohydrate capsule unlike *N. meningitidis***. **Instead, it forms a polyphosphate capsule, which is loosely associated with its cell surface.**. **It prevents phagocytosis of the gonococci.**

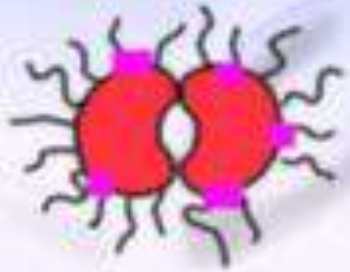
- **Pili:**

- Pili are hair-like structures that extend from the cytoplasmic membrane through the outer membrane. **The pili are composed of the proteins known as pilins, which are repeating protein subunits.**

Pathogenisis

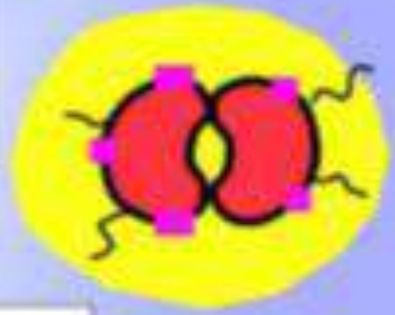
Pathogenesis

N. gonorrhoeae



Virulence Factors
Similar, but –
Differences
In utilization

N. meningitidis



LOS
IgA1 protease
iron-binding proteins

PILI
Outer Membrane Proteins
(Por,Opa, Rmp proteins)

LOS
Capsule
IgA1 protease
iron-binding proteins
PILI
Outer Membrane Proteins

- The expression of protein pilin is controlled by P gene complex. The **pilins** of all the strains of gonococci are **antigenically different.** There is a marked antigenic variation in gonococcal pili as a result of chromosomal rearrangement.
- More than 100 serotypes are known.
- The pili are important virulence factors:

■ They play an important role in the virulence of the bacteria.

They mediate attachment of gonococci to nonciliated epithelial cells.

■ They also contribute to virulence by **preventing ingestion and killing of gonococci by neutrophils.**

- **Other virulence factors:** These include:

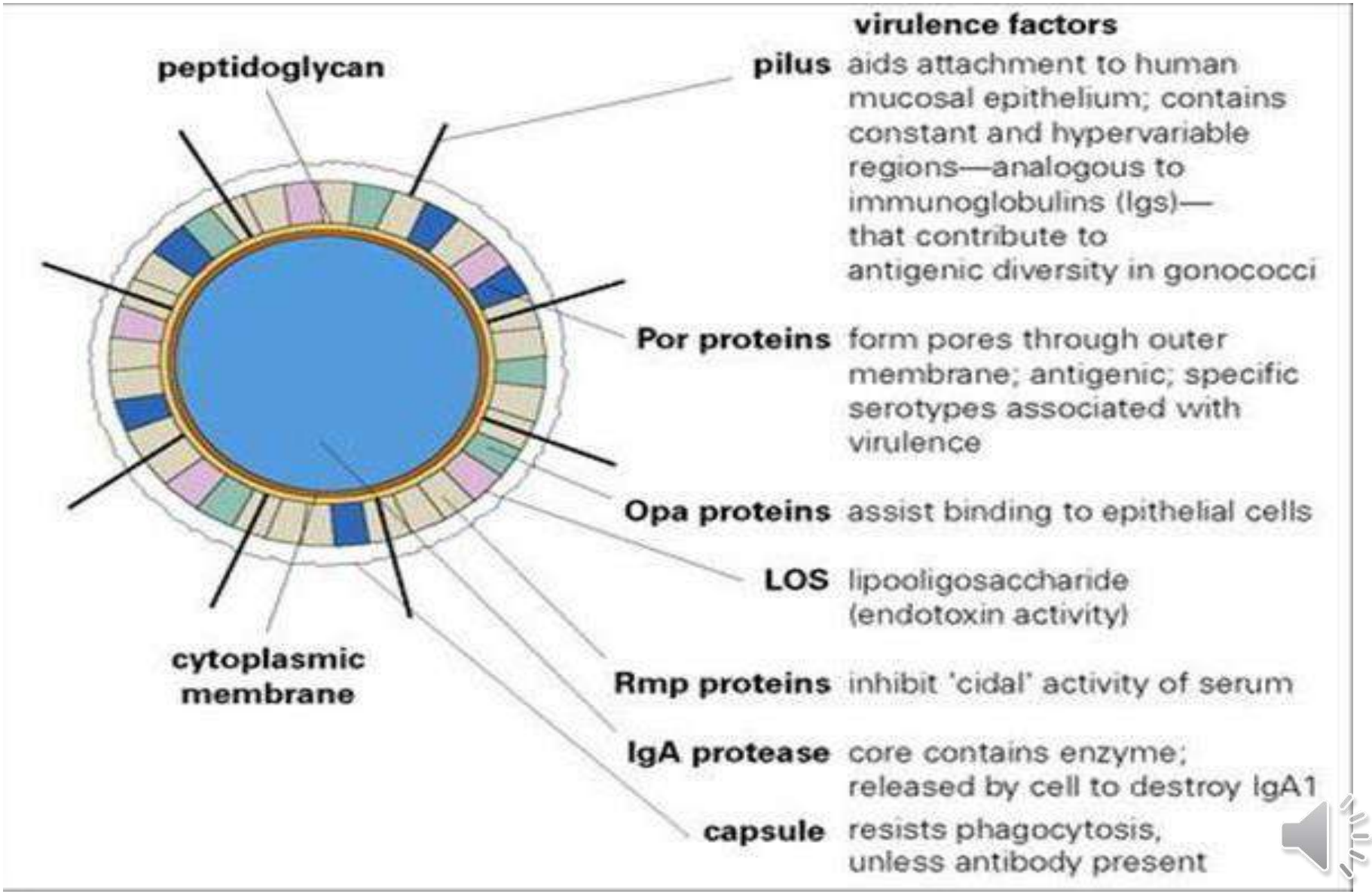
■ **Opa proteins** mediate **bacterial adherence of bacteria to each other and to the eukaryotic cells.**

■ **Por protein** of outer membrane protein (OMP) **confers resistance to serum killing of gonococci** by **preventing fusion of phagolysosome in neutrophils.**

■ **Rmp proteins** produce **antibodies that block serum bactericidal activity against gonococci.**

Lipo-oligosaccharide of the bacteria possesses endotoxic activity.

Proteins of N.gonorheae



Clinical Syndromes

Gonorrhea

- **Gonorrhea is a sexually transmitted disease.** It is **primarily a genital infection restricted to the urethra in men and cervix in women.** The **incubation period varies from 2 to 8 days.**
- **Gonorrhea in men: A symptomatic acute infection is seen in approximately 95% of all infected men**. Urethritis is the major clinical manifestation,
- **Gonorrhea in women:** In women, **endocervix is the primary site (80–90%) of infection because gonococci invade only the endocervical columnar epithelial cells. Pelvic inflammatory disease (PID)** is **the most important complication in females following gonococcal infection.**

Treatment

- **Sulfonamides** were used as early as in 1935 for treatment of gonorrhea. In the beginning, all the strains of gonococci were sensitive to sulfonamides but subsequently, they developed resistance to these antibiotics.
- **Penicillin** is the drug of choice for penicillin-sensitive strains of *N. gonorrhoeae.*

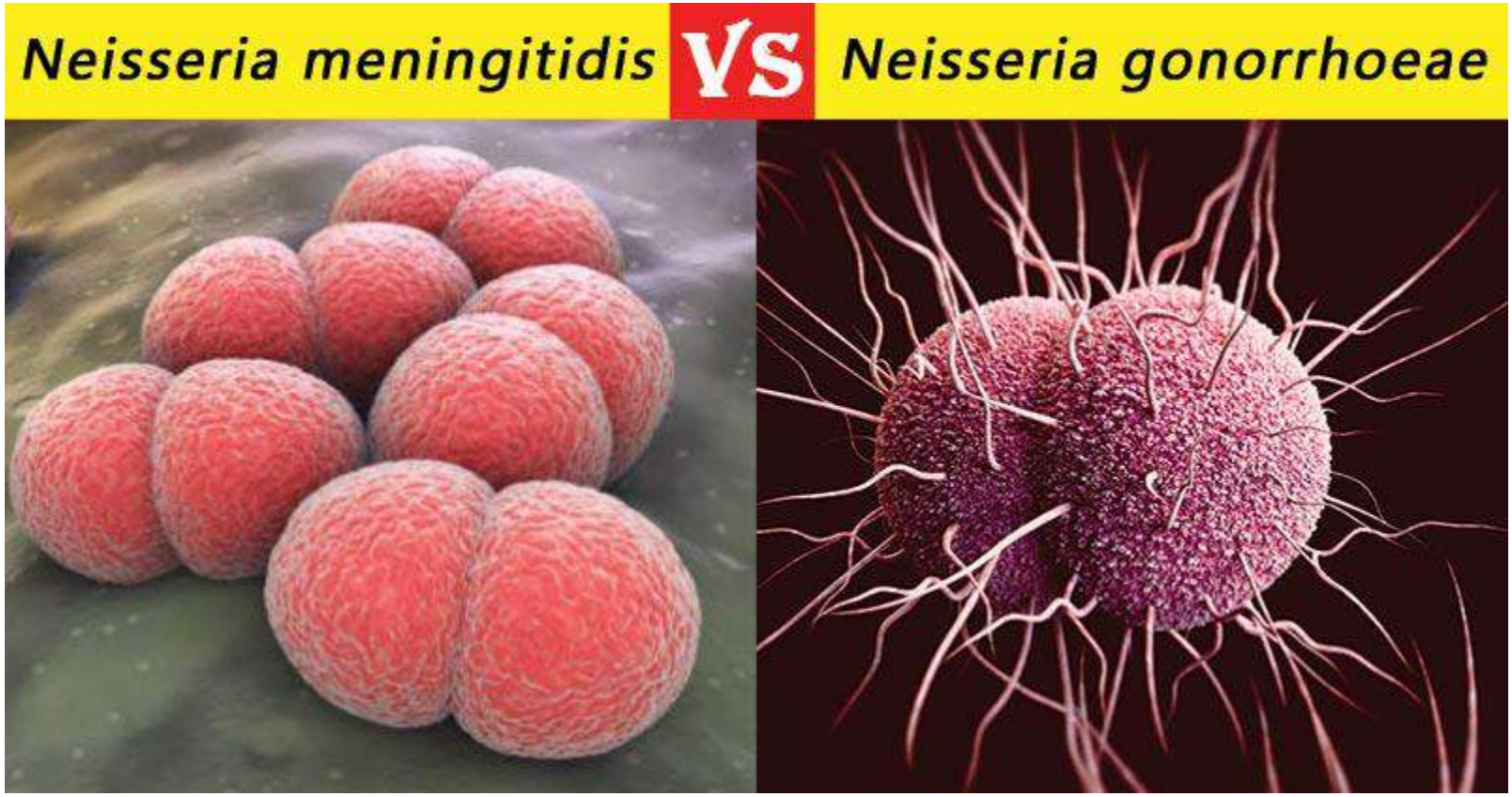
Prevention and Control

- Currently, there is **no effective vaccine available against *N. gonorrhoeae*. Chemoprophylaxis by the prophylactic use of penicillin is also ineffective** and may promote the development of resistant strains.
- Therefore,
- **(*a*) health education,**
- **(*b*) early detection of cases,**
- **(*c*) tracing of contacts, and**
- **(*d*) follow-up of screening of sexual contacts is important in the prevention of gonorrheal epidemics**.
- Furthermore, the prevention of gonorrhea involves the promotion of safe sex and individual counseling.

(B) Neisseria meningitidis (Meningitis, Sepsis)

- Morphology and culture.
- Meningococci are Gram-negative, coffee-beanshaped cocci.
- They are nonmotile and feature a polysaccharide capsule.
- Growing meningococci in cultures requires mediums containing blood.
- Antigen structure.
- Serogroups A, B, C, D, etc. (a total of 12) are differentiated based on the capsule chemistry.
- Epidemics are caused mainly by strains of Serogroups are divided into serovars based on differences in the outer membrane protein antigens.

N.Meningitidis

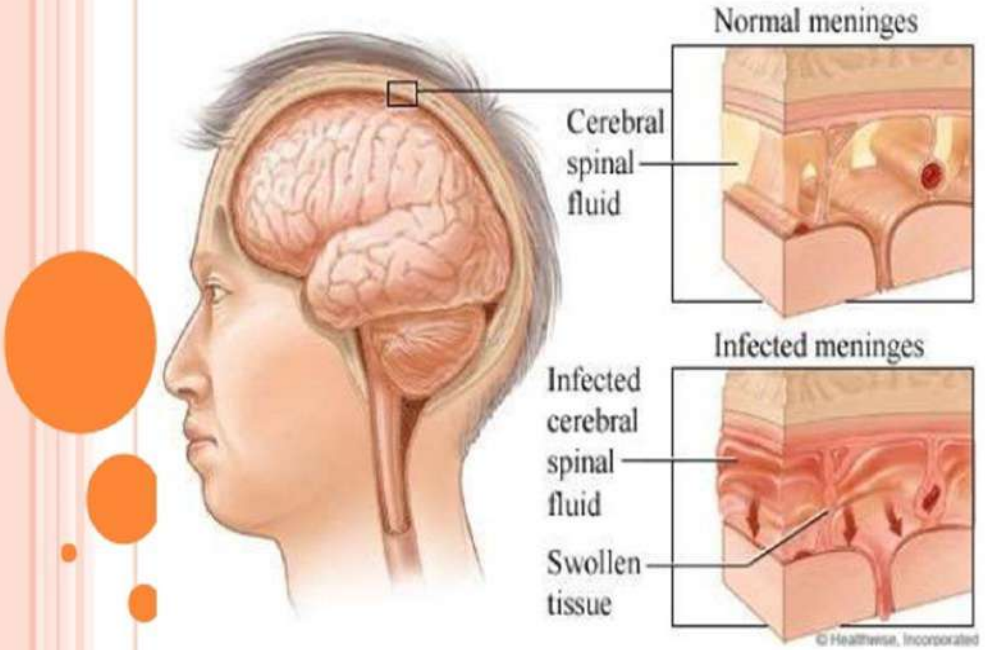


Pathogenesis and clinical picture.

- Meningococci are parasites of the nasopharynx.
- **These microorganisms are carried by 5–10% of the population. If virulent meningococci colonize the nasopharyngeal mucosa of a host lacking the antibodies, pathogen invasion of the mucosa by means of "parasite directed endocytosis" becomes possible .**

- Onset of the meningitis is usually sudden, after an incubation period of two to three days, with severe headache, fever, neck stiffness, and severe malaise.

WHAT IS MENINGITIS



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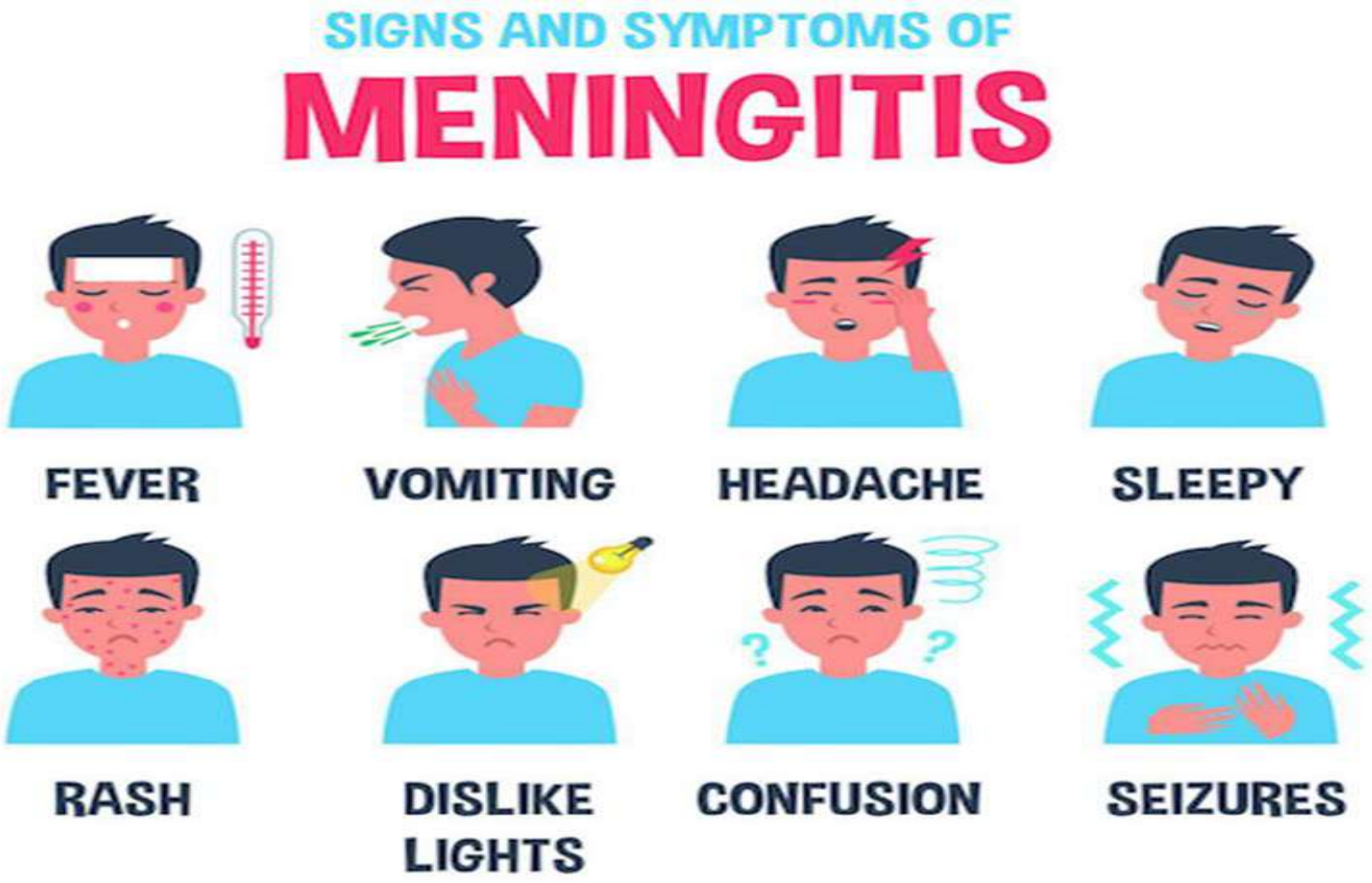
Signs and symptoms of meningitis



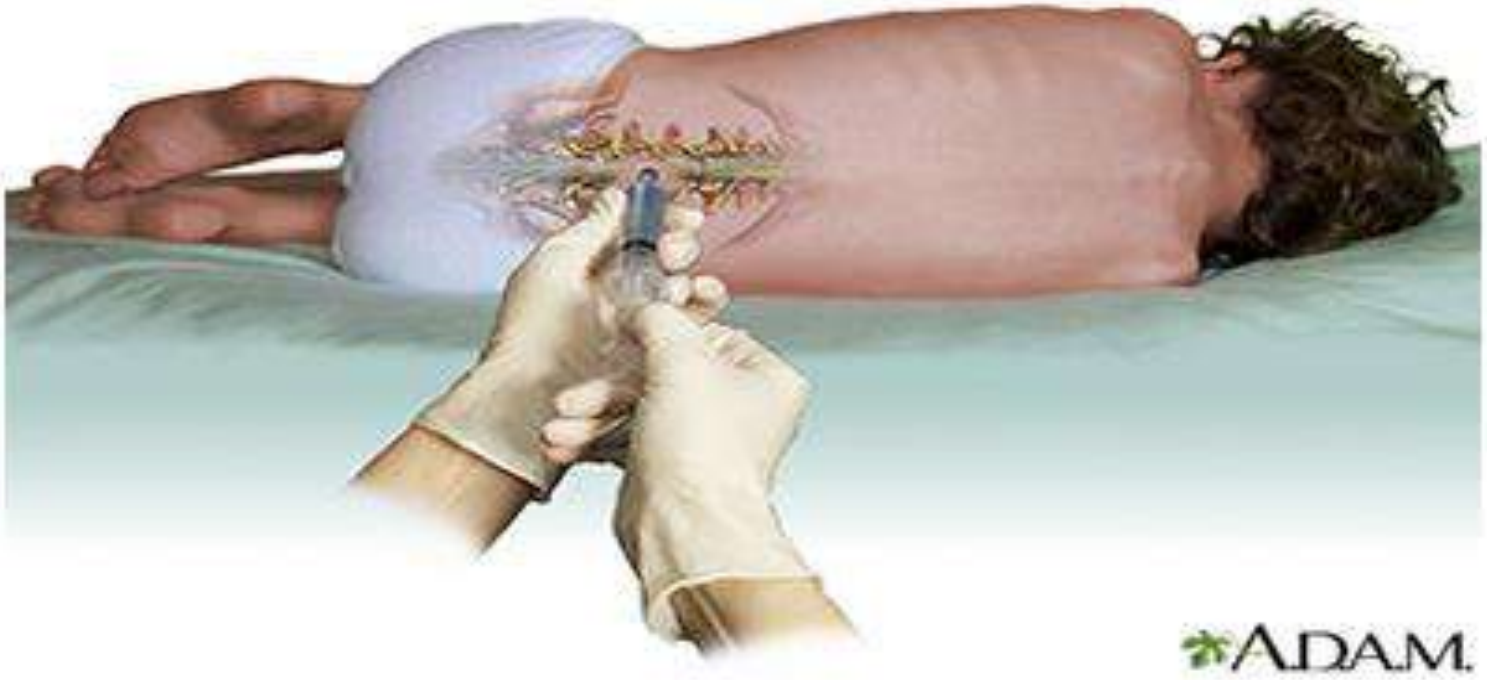
Meningitis in children

Diagnosis

- Diagnosis requires detection of the pathogen in cerebrospinal fluid or blood by means of microscopy and culturing techniques.
- The slide agglutination test is used to determine the serogroup.
- Latex agglutination or coagglutination can be used for direct antigen detection in cerebrospinal fluid.

Lumbar puncture

Cerebrospinal fluid drawn
from between two vertebrae



Therapy.

- The antibiotic of choice is penicillin G.
- Very good results have also been obtained with third-generation cephalosporins, e.g., cefotaxime or ceftriaxone.
- It is important to start treatment as quickly as possible to prevent delayed damage.
- The advantage of cephalosporins is that they are also effective against other meningitis pathogens due to their broad spectrum of action (with the exception of Listeria monocytogenes).

Epidemiology and prevention.

- Meningococcal infections are more frequent in the winter and spring months.
- Transmission of meningococci is by droplet infection.
- Humans are the only pathogen reservoir.
- Sources of infection include both carriers and infected persons with manifest disease.
- Prophylactic antibiosis is indicated for those in close contact with diseased persons(e.g., in the same family).