Chapter 18 - The **Gram Positive** and **Gram Negative** Cocci of Medical Importance*

*Lecture notes are to be used as a *study guide* only and *do not* represent the comprehensive information you will need to know for the exams.

The most common infectious species of **pyogenic cocci**\(^1\) belong to the four genera: *Staphylococcus*, *Streptococcus*, *Enterococcus*, and *Neisseria*. **Pyoderma** is a diagnostic term used for any acute inflammatory infection of the skin with **purulent** (pus-containing) **exudates** (substance that has oozed into the tissues). Pyoderma can be caused by a primary invasion by pathogens or as a secondary infection caused by an opportunistic pathogen. The majority of lesions or abscesses are caused by *Staphylococcus aureus*.

### 18.1 General Characteristics of the Staphylococci

Members of the genus *Staphylococcus* are **Gram-positive**, nonmotile cocci about 1µm in diameter (fig. 18.1). They form clusters of cells as they divide. Common inhabitants of the skin and mucous membranes. As a group, *Staphylococci* do not have spores or flagella, but may form capsules. They grow well on routine laboratory media and are facultative anaerobes. Species from the Staphylococcus genus (usually *S. aureus*) are responsible for approximately 13% of nosocomial infections reported each year and implicated in nearly 80,000 deaths nationwide. Typically known as “staph” infections.

Important human pathogens are: *S. aureus*, *S. capitis*, *S. epidermidis*, and *S. hominis* (Table 18.2). Of these, *S. aureus* in the most serious.

### Growth and Physiological Characteristics of *Staphylococcus aureus*

*S. aureus* produces round, opaque colonies at 37°C. Its growth is enhanced in the presence of O\(_2\) and CO\(_2\). Most strains are metabolically versatile. *S. aureus* can withstand high salt up to a 10% concentration, extremes in pH and temperature. It can withstand dry environments, disinfectants and antibiotics.

### Virulence Factors of Staphylococcus aureus

Different strains of *Staphylococcus aureus* produce a variety **virulence factors** (enzymes and toxins) harmful to their human hosts (Table 18.1):

**Exoenzymes:**

1. **Coagulases** are enzymes that clot plasma and blood. The presence of this enzyme indicates the pathogenic potential of the strain (coagulase test - fig. 18.6).
2. \(\beta\)-**lactamases** break down penicillin and cephalosporins, making these antibiotics useless.
3. **Hyaluronidase** breaks down hyaluronic acid, that holds cells together in connective tissue; thus facilitates the spread of bacteria.
4. **Lipases** hydrolyze host cellular membrane fats and lipids, causing lysis of host cells. Found in *Staphylococcus* strains that cause pimples and boils.

**Exotoxins** found in *Staphylococcus aureus* are often responsible for the symptoms of the disease.

1. **Leukocidin** is a cytolytic toxin that disrupts the plasma membrane of polymorphonuclear leukocytes (e.g. neutrophils) and macrophages. It attacks the phospholipids in the cell membrane.
2. **Hemolysins** are toxins that destroy RBCs (fig. 18.2).
3. **Exfoliative toxin** – causes epidermis to separate from dermis; skin peels away in scalded skin syndrome.
4. **Enterotoxins** – exotoxins that act on the gastrointestinal tract inducing nausea, vomiting, and diarrhea; one of the top causes of food born illness.
5. **Toxic Shock Syndrome Toxin** (TSST) – exotoxin present in some strains that leads to a characteristic and potentially fatal condition known as toxic shock syndrome.

---

\(^1\) **pyogenic cocci** are bacteria that tend to stimulate pus formation.
Epidemiology and Pathogenesis of S. aureus

*S. aureus* is part of the normal human flora. It can be isolated from fomites. Carriage occurs in the nose, skin and nasopharynx, and intestine. Those who tend to become infected may have poor hygiene and nutrition, tissue injury, diabetes, and immunodeficiency. It is a common infection in newborn and nursery wards.

A more serious strain has arisen in the community called MRSA. It spreads by contact with skin lesions and it can be difficult to treat and control.

The Scope of Staphylococcal Disease

Staphylococcal Infections

Like many invading organisms, Staphylococci can begin as a local infection of the skin and then spread systemically, leading to much more severe conditions. A local staph infection can cause an abscess (fig. 18.3a).

Localized Cutaneous Infections (fig. 18.3):

1. **folliculitis** – a mild, superficial inflammation of hair follicles
2. **impetigo** – characterized by bubble like epidermal swellings that can break and peel away (fig. 18.5a).
3. **Boils (furuncles)** result when the inflammation of a single hair follicle or sebaceous gland progresses into a large, red, and tender abscess or pustule. A cluster of furuncles is referred to as a **carbuncle** (fig. 18.3).
4. **scalded skin syndrome (SSSS)** – exfoliative toxin in local infections causes blistering and peeling away of outer skin layers (fig. 18.5bc).

Miscellaneous Systemic Infections:

1. **endocarditis** - inflammation of the heart lining and or valves. Bacterial endocarditis usually affects the heart valves. Clinical symptoms: severe weakness, persistent fever, chills, sweats, difficulty breathing, lesions on lower legs, and an enlarged spleen and heart. The heart becomes unable to pump blood efficiently. This results in interstitial fluids not being collected and returned to the heart, but accumulating in tissues (edema). Patients who have had heart valve replacement surgery are particularly susceptible. Other etiological agents of endocarditis include *Streptococcus pyogenes, Enterococcus faecalis, Neisseria gonorrhoeae,* and *Pseudomonas aeruginosa.* It can result from dental surgery, tooth decay, ulcers, cancers, boils and wounds.

2. **osteomyelitis** – inflammation of bone and marrow or bone marrow (fig. 18.4).

3. **bacteremia** – bacteria found in the blood. Can be asymptomatic or **septicemia** = high degree of bacterial sepsis in blood; infection with symptoms (fever, chills, low blood pressure, shock). It can be caused by a natural progression of localized infection to systemic disease or by invasive medical procedures. Staphylococcal bacteremia causes a high mortality rate among hospital patients with chronic disease.

4. **arthritis** - inflammation of the joints.

5. **pneumonia** – infection and inflammation of the lung. Although staphylococci are responsible for only a small percentage of pneumonias, the fatality rate is 50%. (See section on pneumonia below.)

6. **meningitis** - inflammation of meninges. As for pneumonia, staphylococci only account for a small percentage of meningitis cases, but this form is severe. (See section on meningitis below.)

Toxigenic Staphylococcal Disease
TSS, toxic shock syndrome
When infections are caused by toxigenic strains, diseases such as toxic shock syndrome can result. **Toxic shock syndrome** is characterized by hypotension (low blood pressure), shock, fever, rash, sore throat, conjunctiva infection, muscle aches and other symptoms (diarrhea, vomiting). Rashes resembling scarlet fever followed by peeling of hands and feet. It can occur in anyone, but is found primarily in menstruating females. It has been associated with the use of super-absorbent tampons (Making Connections 18.1).

The causative agent appears to be *Staphylococcus aureus* and 3 toxins: enterotoxins C and F – account for about 50% of non-menstrual related TSS – and **toxic shock syndrome toxin (TSST)** - responsible for all menstrual cases.

**Treatment**: Fluid and electrolyte replacement to reverse hypotension and shock. Drain abscesses and use antibiotics (β-lactamase-resistant penicillins and cephalosporins).

8. **Childbed fever or puerperal sepsis**
During childbirth the tissues lining the uterus and vagina can be damaged allowing both normal flora and true pathogens to penetrate into the circulatory system. This can result in **childbed fever or puerperal sepsis**. In the early 19th century, childbed fever cases ran as high as 50% among birthing mothers with a 5-15% mortality rate. Joseph Lister and Ignaz Semmelweis encouraged hand washing and instrument sterilization. By the late 1800s, the rate for childbed fever was reduced to 15% with 0.5% mortality rate (500 deaths/100,000 births). Usually it is caused by *Streptococcus* or *Staphylococcus* (both G+ bacteria). Current statistics: 300,000 cases/year with a death rate between 300-600/year (0.1-0.2% mortality rate).

9. **Gastroenteritis:**
Exotoxins that affect the GI tract in humans are referred to as **enterotoxins**. The signs and symptoms associated with enterotoxins are nausea, vomiting, and diarrhea. **Staphylococcal gastroenteritis** is caused by ingesting food containing *Staphylococcus aureus* enterotoxins. It is characterized by rapid onset of nausea, vomiting, and diarrhea about 1-6 hours after consumption. Severity depends on amount and type of enterotoxin. The toxins do not noticeably alter the food’s taste or smell. Food culprits include custards, hams, hollandaise sauce, and creamy fruit salads (tuna, chicken and macaroni salads). Large amounts of enterotoxins can be produced in foods left at room temperature for several hours. The toxins are not easily destroyed by cooking (inactivation requires 100ºC for at least 30 minutes). Generally self-correcting within 24 hours, Staphylococcal gastroenteritis is usually not treated.

**Staphylococcus in Hospitals**

Staphylococcal infections outside the hospital (community-acquired infections) are treated with penicillin and penicillin derivatives as the drug of choice. Hospital-acquired infections (**nosocomial infections**2) are often penicillin resistant, making treatment difficult. In those strains producing β-lactamase, lincomycin, erythromycin and novomycin are used.

According to the Center for Disease Control, an estimated 10% of all hospital patients acquire some type of nosocomial infection. Certain types of operations (amputations, intestinal surgeries) are accompanied by an infection rate approaching 30%.

A hospital is a high-density community of susceptible individuals. Pathogenic bacteria are prevalent and new ones are introduced by incoming patients. The use of antimicrobial agents creates an environmental that selects for the growth of resistant strains, and staff members are often carriers of these strains. The immune system of patients is often stressed by surgery, radiation therapy for cancer, immunsuppressant medications, and in-dwelling apparatuses such as catheters and IV tubes.

**Host Defenses Against S. aureus**

Humans have a well-developed defense against staph infections. Unbroken skin is a good defense against staph. Specific antibodies are produced against staph, but they are not very effective. Neutrophils and macrophages serve as the better defense. Abscess formation helps to prevent the spread of staph in the body.

---

2 **Nosocomial** infections are infections acquired while in a hospital.
Other Important Staphylococci

Coagulase-negative staphylococci (fig. 18.6)

1. *Staphylococcus epidermidis* – normal skin flora and mucous membranes; also *S. hominis* lives near apocrine glands, *S. capitis* lives on the face, scalp and external ear. Each bacterium is able to enter breaks in the skin at their location and cause infection.
2. *S. saprophyticus* – a common urinary tract infection in sexually active young women.

Identification of *Staphylococcus* Isolates in Clinical Samples

Staphylococci can be isolated from body fluids and infected tissues. Can use sheep’s blood agar and/or mannitol salt agar. It is Gram positive with irregular clusters of cocci cells. Differentiate from streptococci by a catalase test (fig. 18.6a), and other cocci by biochemical tests (fig. 18.7). *S. aureus* is differentiated from other staph species by the production of coagulase where *S. aureus* produces coagulase (fig. 18.6b). PCR can also be used to identify *S. aureus*. See table 18.2 for the different characteristics of the clinically relevant staphylococci.

Clinical Concerns in Staphylococcal Infections

MRSA carry multiple antibiotic drug resistance genes. HA-MRSA are hospital acquired; CA-MRSA are community acquired.

Treatment of Staphylococcal Infections

Treatment: 95% of *S. aureus* strains have acquired penicillinase resistance. MRSA (methicillin-resistant *S. aureus*) strains are increasing; they show broad resistance to methicillin, gentamicin, cephalosporins, tetracycline, and erythromycin. Vancomycin has been used as a last alternative, but resistant strains (VRSA) have also appeared. Proper identification of the infectious strain may allow combinatorial drug therapy. See also CLINICAL CONNECTIONS – Acronyms and Antibiotic Resistance.

Prevention of Staphylococcal Infections

Humans are the principal reservoir of pathogenic staphylococci. WASH YOUR HANDS!!!!!!!

See also Pathogen Profile #1 *Staphylococcus aureus*

18.2 General Characteristics of the Streptococci and Related Genera

There are several pathogenic species of *Streptococcus*. They are all Gram-positive, catalase negative, non-spore forming, non-motile, facultative aerobic cocci arranged in chains and pairs (fig. 18.8). The most important pathogens are *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and *Streptococcus mutans* and *Enterococcus faecalis*. (fig. 18.9)

They are classified into Lancefield groups, based on their surface antigens; in this case, surface polysaccharides (A-H, J & K) (Table 18.3). Group A & B contain the most important human pathogens. An alternative classification is based on their hemolytic activity.

---

3 According to the text, up to 80% of the Staphylococcal strains responsible for nosocomial infections have acquired multi-drug resistance, i.e. they are virtually untreatable with current antibiotics.
Beta-Hemolytic Streptococci: *Streptococcus pyogenes*

The most serious streptococcal pathogen is *Strep. pyogenes*, a Group A strep. It is a strict pathogen that inhabit the throat, nasopharynx, and occasionally the skin of humans.

Streptococcal pathogenicity resides in **virulence factors** including: M-protein, hemolysins and erythrogenic toxins:

1. **The M-protein** of Group A is a fimbria protein that inhibits phagocytosis and helps the bacterial cell bind to respiratory epithelial cells (fig. 18.10).
2. **C-carbohydrates**, specialized polysaccharides found on the cell wall (fig. 18.10).
3. **Lipoteichoic acid** contributes to the adherence on epithelial cells in the skin and pharynx.
4. **Capsule made of hyaluronic acid (HA).**
5. **CSa protease** catalyzes a protein in the complement system.

**Major Extracellular Toxins:**

6. **Erythrogenic toxins** are toxins that damage blood vessels beneath the skin and result in the characteristic rash of scarlet fever.
7. **Streptolysins** are **hemolysins** (destroy blood cells). Two types:
   - **Streptolysin O** (SLO) is an oxygen-sensitive enzyme produced by Group A streptococci. SLO affects leukocytes and myocardial (heart) cells.
   - **Streptolysin S** is an oxygen-tolerant enzyme that contributes to beta^4^ hemolysis.
8. **Superantigens** cause an over stimulation T cells which leads to **tumor necrosis factor**.

Like the Staphylococci, Streptococcal species also cause a broad range of diseases. These conditions can start as local infections and spread systemically.

**Major Extracellular Enzymes**

1. Streptokinase will digest fibrin clots.
2. Hyaluronidase breakdown connective tissue.
3. Streptodornase is a DNAse that hydrolyzes DNA.

**Epidemiology and Pathogenesis of Streptococcus pyogenes**

Humans are the only significant reservoir. It gains access to the human host when immune resistance is low or there is a break in the skin. Children tend to be the most susceptible group in the population.

**Skin Infections - Streptococcal Cutaneous Infections**

Streptococcal infections also cause pyogenic lesions. They result from invasion of skin through scratches, insect bites, cuts or sores. Occasionally, superficial streptococcal infections can result in complications.

1. **Streptococcal impetigo** – a crusty, flaking of the epiderms, is caused by β-hemolytic Group A streptococci (fig 18.11a).

2. **Erysipelas** is an acute febrile (fever-related) disease with inflammation, redness of the skin, head and face lesions accompanied by headache, nausea and vomiting (fig 18.11b). Untreated infections can result in septicemia, abscesses, nephritis or rheumatic fever as the result of toxins.

---

^4^ **Alpha** hemolytic Streptococci break down red blood cells in blood agar and cause a zone of green discoloration around the colonies. **Beta** hemolytic Streptococci produce a clear zone of hemolysis around the colony. “**N**” hemolytic Streptococci produce no hemolysis. Fig. 18.9, pg 544
3. **Necrotizing fasciitis** – extensive necrosis of skin, and underlying connective tissue associated with *S. pyogenes* infections. The so-called “flesh eating disease”. Starts as normal infection. Enzymes digest connective tissue and toxins poison epidermal and dermal tissue. As the flesh is killed (necrosis), it separates and sloughs off, forming a pathway for deeper microbial invasion. (18.2 MAKING CONNECTIONS)

**Throat Infections**

**Pharyngotonsillitis** (“strep throat”) is inflammation of the pharynx accompanied by fever, malaise, throat pain and post nasal secretions (fig. 18.12). The throat is scarlet red with pus-containing material. Primary cause: Group A, $\beta$-hemolytic *Streptococcus pyogenes*.

"Strep throat" is common in school-age children (5-15 years) during the winter months. It is transmitted by aerosols and occasionally food.

**Systemic Infections**

1. **Scarlet fever** – a fine, red "sandpaper" rash resulting from the action of erythrogenic toxins on blood vessels. A complication of streptococcal pharyngotonsillitis. Begins with a rash on the chest which spreads to other parts of the body. Fever, vomiting, and prostration accompany the rash.

**Long-Term Complications of Group A Infections**

1. **Rheumatic fever** or rheumatic heart disease causes 10-20,000 deaths each year (about 3% of human streptococcal infections develop into rheumatic fever). It is characterized by arthritis and carditis (including permanent scarring and distortion of heart valves), fever and inflammation of small blood vessels (fig. 18.13).

2. **Acute glomerulonephritis** is an acute inflammation of the glomeruli in the kidney. It is characterized by blood in the urine (hematuria) and hypertension.

3. **Acute epiglottitis** is grave inflammation of the epiglottis. The disease progresses quickly causing fever, sore throat, extreme difficulty in swallowing and a continuing enlargement of the epiglottis. If the airway becomes blocked, apnea and death will follow. Other etiologic agents include *Haemophilus influenzae*, *Streptococcus pneumoniae*, streptococci, staphylococci, and viruses.

See also Pathogen Profile #3 *Streptococcus pyogenes*

**Group B: Streptococcus agalactiae**

*Streptococcus agalactiae* represents the group B streptococci (GBS), a potential normal flora of the human vagina, pharynx, and large intestine. GBS is transferable to infants during delivery and is the most prevalent cause of **neonatal pneumonia**, **sepsis**, and **meningitis** in the U.S. and Europe. Approximately 19,000 babies a year acquire infection (5% mortality).

Pregnant women should be screened for colonization in the third trimester and if found positive are treated with a course of IV antibiotics during labor (and before labor). A GBS vaccine is currently being developed. See the CDC for more information at: [http://www.cdc.gov/groupbstrep/](http://www.cdc.gov/groupbstrep/)

**Group D Enterococci and Groups C and G Streptococci**

---

5. *Vibrio vulnificus* is another type of bacteria capable of causing severe necrotizing fasciitis.

6. Other agents which cause inflammation of the pharynx similar to "strep throat": *Staphylococcus aureus*, *Haemophilus influenzae*, and *Corynebacterium diphtheriae*. 
Group D Enterococcus faecalis, E. faecium and E. durans are the “enterococci”, normally inhabit the human large intestine. Enterococci are emerging as a serious nosocomial infection that is becoming highly drug resistant to vancomycin (VRE).

Groups C and G found in domestic animals, seen in severely compromised patients.

Formerly known as Streptococcus faecalis, Enterococcus faecalis was assigned its own genus based on DNA hybridization tests. It shares many of the cellular characteristics of Streptococcus (i.e. Gram-positive, non-spore forming, non-motile, etc.). Lancefield Group D, hemolysis type α, β, and N. Habitat = human and animal intestine. Causative agent of endocarditis and UTI (urinary tract infection).

Infections common in elderly patients having undergone surgery. These are an emerging nosocomial opportunists whose multi-drug resistance is becoming more prevalent. Vancomycin- resistant strains (VRE) are of particular concern.

Laboratory Identification Techniques

It is important to recognize group A streptococcal infections. A rapid identification test is used to identify Group A strep from throat samples. The test is based on monoclonal antibodies that react with the C carbohydrate (fig. 18.14). Other tests include the CAMP test (fig. 18.15). Table 18.4 summarizes the scheme for differentiating Beta-hemolytic streptococci.

Treatment and Prevention of Group A, B, and D Streptococcal Infections

Treatment:
Penicillin remains the drug of choice since streptococci have not developed extensive resistance to the drug. However, there are now strains of S. pneumoniae that are penicillin resistant (PRSP). Lincomycin, erythromycin, clindamycin and third-generation cephalosporins are also effective.

Alpha-Hemolytic Streptococci: The Viridans Group

Viridans strep are of human origin but do not fall into a Lancefield serology. They are mostly in the oral cavity. They produce an alpha hemolysis. Usually enter via dental or surgical work. The most important complication is subacute endocarditis (fig. 18.16).

Streptococcus pneumoniae: The Pneumococcus

Bacteria in the mouth and pharynx can sometimes gain access (via the eustachian tube) to the middle ear chamber and cause infections called otitis media (fig. 18.19 & fig. 18.20). In young children Streptococcus pneumoniae is the most common cause of otitis media. Inflammation of this sensitive area of the ear results in very painful earaches and even temporary deafness.

Pneumonia is an inflammation of the lungs accompanied by fluid buildup in the alveolar sacs (fig. 18.18). It can result from infectious and non-infectious processes. Bacterial pneumonia is often caused by pneumococci, pyogenic cocci, and bacilli. It is characterized by high fever, chest pains, chills, and a purulent cough (purulent = pus-containing). Worldwide, pneumonia is the highest ranking of infectious disease and among top ten causes of death.

Pneumococcal pneumonia is caused by Streptococcus pneumoniae. Characterized by acute onset of fever, chills, dyspnea (difficulty in breathing), pleurisy (inflammation of the pleura\(^7\)), and productive cough. Sputum has purulent discharge tinged with blood. Streptococcus pneumoniae is a Gram-positive coccus arranged in lancet-shaped pairs (fig. 18.17). Various strains can be differentiated by Quellung test, a serological test which differentiates the strains based on surface antigens. Virulent strains are encapsulated (antiphagocytosis), demonstrate alpha-hemolysis on blood agar, and form small mucoid colonies with a central depression. The organism can be found as part of the normal flora in up to 50% of adults.

\(^7\) pleura are the membranes that cover the outside of the lungs.
18.3 The Family Neisseriaceae: Gram-Negative Cocci

Two species within the *Neisseria* genus are of most relevance to human health: *N. gonorrhoeae* and *N. meningitidis*. Both are Gram negative, so caution must be taken if the infection spreads systemically as septicemia. Their morphology is diplococcus (fig. 18.20). Most in the genus *Neisseria* are strict parasites, so they do not survive long outside the human body. Endotoxic shock can result from improper antibiotic administration (especially for *N. meningitidis*).

*Neisseria gonorrhoeae*: The Gonococcus

*Neisseria gonorrhoeae* is a Gram negative, nonmotile “bean-shaped” coccus: (fig. 18.20). Strict parasites, they do not survive long outside the body, i.e. you cannot catch it from inanimate objects. Etiologic agent of gonorrhea. Also, see notes below on *Neisseria meningitidis*. Gonorrhea is second only to chlamydia infections in the number of cases reported to the Centers for Disease Control and Prevention (CDC); 332,511 cases were reported to CDC in 2007.

Factors Contributing to Gonococcal Pathogenicity

Gonorrhea is characterized by acute inflammation of the genital mucosal epithelium and a purulent discharge. Only piliated strains are pathogenic, and attach to mucosal epithelium by pili. Apparently, pili alone do not make *N. gonorrhoeae* virulent, they also contain a cell wall component that destroys anti-gonococcal IgA antibodies (secretory antibodies).

Epidemiology and Pathology of Gonorrhea

Fig. 18.21 shows the comparative graph of two reportable infectious sexually transmitted diseases (STDs): gonorrhea and syphilis. Gonorrhea is normally acquired through sexual intercourse. Gonococcal pharyngitis and anorectal gonorrhea are also communicable via intimate contact. The incubation period for gonorrhea is 2-4 days.

Females: Approximately 50% of cases are asymptomatic. Signs and symptoms include purulent exudates from the vagina and painful urination. *Salpingitis*, also known as PID (pelvic inflammatory disease) results when the infection spreads to the fallopian tubes where inflammation and scarring can result in the blockage of the oviducts which can result in infertility or ectopic pregnancy (fig. 18.23 & 18.3 MAKING CONNECTIONS).

Males: anterior urethritis (inflammation of the urethra) (fig. 18.23) together with painful urination and characteristic purulent exudates (containing leukocytes – often with gonococci located intracellularly, cellular debris, and gonococci) (fig. 18.25). With antibiotics, epididymitis (inflammation of epididymis) and prostatitis (inflammation of prostate glands) have all but disappeared as complications.

Preadolescent children: Symptoms same as adults. Results from sexual molestation. Appropriate authorities should be notified if gonorrhea is diagnosed in a child.

Newborns can acquire infection as they pass through the birth canal. *Ophthalmia neonatorum* is a common result and can lead to blindness. The newborn’s eyes are treated with drops of erythromycin to kill bacteria (fig. 18.24).

Treatment: Penicillin is the preferred drug of choice, but some strains have begun to produce penicillinase and new drug resistant strains have appeared over the past two decades. Alternative drugs: Tetracycline, spectinomycin, and the quinolones. There is no vaccine and no permanent immunity after an active case.
History of *Neisseria* Antibiotic Resistance Development:
Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) showed up in 1976.
  Shifted to spectinomycin.
  Shifted to tetracycline.
Tetracycline resistance was observed in 1986.
  Shifted to fluoroquinolones.
On September 21, 2000, the CDC announced gonorrhea showing increased resistance to fluoroquinolones.

*Neisseria meningitides*: The Meningoccus

*Neisseria meningitidis*, which causes *meningococcal meningitis*, is the only one to cause small epidemics (e.g. crowded army barracks, crowded slum areas, daycare centers, refugee camps). It is transmitted by droplets. Meningococcemia is when the organism spreads to the bloodstream, where toxins can overwhelm the body in as little as 2 hours; this is associated with the appearance of subcutaneous hemorrhages called *petechiae* (fig. 18.27). Drug of choice: Penicillin G.

**Epidemiology and Pathogenesis of Meningococcal Disease**

Sporadic or epidemic incidence in late winter or early spring. The reservoir is humans who harbor it in the nasopharynx. Easily transmitted to people who live in close quarters, like the military or college dorms. It can cross the blood-brain barrier and grow in the CSF (fig. 18.26).

**Clinical Diagnosis of Meningococcal Disease**

Bacterial meningitis is an emergency. CSF and blood samples are stained. Cultures may be used to help in the identification. Specific rapid tests are also available.

**Immunity, Treatment, and Prevention of Meningococcal Infection**

Most people have a natural immunity. Drug treatment for those infected are given a third generation cephalosporin called ceftriaxone. Vaccination is recommended for those 11-18 who may come into contact with the infectious agent. Two vaccines are available – Menactra and Menomune.

**Differentiating Pathogenic from Nonpathogenic**

Lab tests include gram stain, growth on enriched media, growth at high CO₂ levels, and oxidase testing. Also PCR is used.

**Other Genera of Gram-Negative Cocci and Coccobacilli**

*Brachmella catarrhalis* is normal flora of the human nasopharynx. It can cause purulent disease, associated with meningitis, endocarditis, and other infections. It is important to differentiate it from the meningococcus.

*Acinetobacter baumannii* lives in water and soil and can survive harsh environments. It can survive on fomites. It can cause nosocomial infections.

---

8 [http://www.cdc.gov/meningitis/bacterial/faqs.htm](http://www.cdc.gov/meningitis/bacterial/faqs.htm)
*Moraxella* species are found on mucous membranes of domestic animals and humans. Rarely causes infections in humans.

V. Pneumonia & Meningitis: Cocci and other etiologic agents – ADDITIONAL NOTES FYI!!!!!

A. Pneumonia

Pneumonia is an inflammation of the lungs accompanied by fluid buildup in the alveolar sacs (fig. 18.18). It can result from infectious and non-infectious processes. Bacterial pneumonia is often caused by pneumococci, pyogenic cocci, and bacilli. It is characterized by high fever, chest pains, chills, and a purulent cough (purulent = pus-containing). Worldwide, pneumonia is the highest ranking of infectious disease and among top ten causes of death.

1. Pneumococcal pneumonia is caused by *Streptococcus pneumoniae*. Characterized by acute onset of fever, chills, dyspnea (difficulty in breathing), pleurisy (inflammation of the pleura⁹), and productive cough. Sputum has purulent discharge tinged with blood. *Streptococcus pneumoniae* is a Gram-positive coccus arranged in lancet-shaped pairs (fig. 18.17). Various strains can be differentiated by Quellung test, a serological test which differentiates the strains based on surface antigens. Virulent strains are encapsulated (antiphagocytosis), demonstrate alpha-hemolysis on blood agar, and form small mucoid colonies with a central depression. The organism can be found as part of the normal flora in up to 50% of adults.

2. *Haemophilus influenzae* pneumonia is more common in children. Gram-negative bacilli, non-motile, oxidase positive. Hib vaccine now provides protection and has dramatically reduced incidence.

3. *Klebsiella pneumoniae* is Gram-negative bacillus. It is an opportunistic pathogen found in the upper respiratory tract and in feces. Often shows up in persons with compromised immune systems (e.g. nosocomial infection), the very young, very old, and alcoholics. In general, the symptoms of pneumonia caused by Klebsiella are indistinguishable from pneumococcal pneumonia.

4. *Mycoplasma pneumoniae* causes a mild form of pneumonia (Primary Atypical Pneumonia - PAP) commonly called “walking pneumonia.” Mycoplasmas as a group lack a cell wall (and are therefore neither Gram + or Gram -). This makes the cells pleomorphic, forming sphere, filaments and irregular shapes (fig. 21.24). Resistant to antibiotics that act on cell walls!

5. *Legionnaire’s disease* or *Legionellosis*¹⁰ is a pneumonia characterized by high fever, chills, pleuritic pain, a nonproductive cough and accelerated breathing. Begins with headache, achy muscles and malaise. It is caused *Legionella pneumophila*, a Gram-negative, aerobic, aquatic, fastidious (nutritionally demanding) organism. Culturing media requires L-cysteine, iron salts and activated powered charcoal (fig. 20.8).

Note on Pneumonia Treatment:
As for “fever of unknown origin”, the identification of the organism causing pneumonia is absolutely necessary for treatment with the proper antibiotic! For example: Mycoplasma pneumoniae (which lacks a cell wall) will not respond to cell-wall synthesis inhibitors such as penicillins or cephalosporins.

B. Meningitis

⁹ pleura are the membranes that cover the outside of the lungs.
Acute pyogenic meningitis is a severe inflammation of the meninges with pus formation (fig. 18.27). The meninges are the 3 layers of tissue around the brain and spinal cord.

Several species of bacteria (and many viruses\textsuperscript{11}) can cause meningitis, with the following being the primary agents. There is a correlation between the age of the patient and the incidence of individual infectious agent.

Meningitis caused by \textit{N. meningitidis}, \textit{Streptococcus pneumoniae}, and \textit{Haemophilus influenzae} are preceded by an upper respiratory tract infection, ear infection, or lung infection. Symptoms include headache, stiff neck, muscle and back pain, and vomiting early on. Later symptoms include muscle ache, backache, stiff neck, fever, drowsiness, confusion, and unconsciousness. Blood clots and pus accumulate in the brain and block the flow of cerebrospinal fluid. This causes the subarachnoid space to swell leading to seizures, paralysis, and coma.

1. \textit{Neisseria meningitidis}, which causes \textit{meningococcal meningitis}\textsuperscript{12}, is the only one to cause small epidemics (e.g. crowded army barracks, crowded slum areas, daycare centers, refugee camps). It is transmitted by droplets. Meningococcemia is when the organism spreads to the bloodstream, where toxins can overwhelm the body in as little as 2 hours; this is associated with the appearance of subcutaneous hemorrhages called \textit{petechiae} (fig. 18.28). Drug of choice: Penicillin G.

2. \textit{Streptococcus pneumoniae} causes \textit{pneumococcal meningitis} and occurs in persons with ear infections or mastoid infections (30%), pneumonia (30%), alcoholism or cirrhosis of the liver (20%), and severe non-penetrating head injuries (10%). Drug of choice: Penicillin.

3. \textit{Haemophilus influenzae} is a Gram negative rod. Before the 1990s, \textit{Haemophilus influenzae} type b (Hib) was the leading cause of bacterial meningitis, but the new vaccines being given to all children as part of their routine immunizations have reduced the occurrence of invasive disease due to \textit{H. influenzae} (fig. 20.23) Drug of choice: Cephalosporin.

\textbf{Note on Treatment:} Antibiotics are used to treat, but when Gram negative bacterial cells (Neisseria & Haemophilus) lyse, they can release an endotoxin (lipopolysaccharide) that can result in endotoxic shock – a severe anaphylactic reaction – a likely cause for fatal outcomes of meningitis. (See comments on endotoxins in chapters 4, 13, and 20).

\textsuperscript{11} Meningitis can also be caused by viral infections. As a matter of fact, viral meningitis is much more common than bacterial meningitis. Etiologic agents include: enteroviruses, such as coxsackieviruses and echoviruses. Herpesviruses and the mumps virus can also cause viral meningitis, \url{http://www.cdc.gov/meningitis/viral/viral-faqs.htm}
\textsuperscript{12} \url{http://www.cdc.gov/meningitis/bacterial/faqs.htm}