CHAPTER 21 – INFECTIONS OF THE RESPIRATORY SYSTEM

WHY IS THIS IMPORTANT?

- The respiratory system is the most commonly infected system.
- Health care providers will see more respiratory infections than any other type.

OVERVIEW

- Infections of the Respiratory System
  - Anatomy of the Respiratory System
  - Pathogens of the Respiratory System
  - Bacterial Infections of the Upper Respiratory Tract
  - Bacterial Infections of the Lower Respiratory Tract
  - Fungal Infections of the Respiratory System
  - Viral Infections of the Upper Respiratory Tract
  - Viral Infections of the Lower Respiratory Tract
THE RESPIRATORY SYSTEM

- A major portal of entry for infectious organisms
- It is divided into two tracts – upper and lower.
  - The division is based on structures and functions in each part.
  - The two parts have different types of infection.

THE RESPIRATORY SYSTEM

- The upper respiratory tract:
  - Nasal cavity, sinuses, pharynx, and larynx
  - Infections are fairly common.
  - Usually nothing more than an irritation
- The lower respiratory tract:
  - Lungs and bronchi
  - Infections are more dangerous.
  - Can be very difficult to treat

ANATOMY OF THE RESPIRATORY SYSTEM

- The most accessible system in the body
  - Breathing brings in clouds of potentially infectious pathogens.
- The body has a variety of host defense mechanisms.
  - Innate immune response
  - Adaptive immune response
Upper respiratory tract is continuously exposed to potential pathogens.

Lower respiratory tract is essentially a sterile environment.

Many bacterial organisms infect the respiratory system.

Upper respiratory tract also portal of entry for viral pathogens.

Vaccination has eliminated many respiratory infections.

Some still seen in underdeveloped parts of the world.
Respiratory pathogens are easily transmitted from human to human.
- They circulate within a community.
- Infections spread easily.
- Some respiratory pathogens exist as part of the normal flora.
- Others are acquired from animal sources – zoonotic infections.
  - Q fever from farm animals
  - Psittacosis from parrots and other birds

Water can be a source of respiratory infections.
- Legionellosis
- Contaminated water can be aerosolized.
- Droplets can be inhaled and infection can result.
PATHOGENS OF THE RESPIRATORY SYSTEM

- Fungi are also a source of respiratory infection.
  - Usually in immunocompromised patients
  - Most dangerous are *Aspergillus* and *Pneumocystis*.

PATHOGENS OF THE RESPIRATORY SYSTEM

- Some pathogens are restricted to certain sites.
  - *Legionella* only infects the lung.
- Other pathogens cause infection in multiple sites.
  - *Streptococcus* can cause:
    - Middle ear infections.
    - Sinusitis.
    - Pneumonia.

SITES OF INFECTION

- Frequent sites of infection are:
  - Middle ear.
  - Mastoid cavity.
  - Nasal sinuses.
  - Nasopharynx.
DEFENSES OF THE RESPIRATORY SYSTEM

- The respiratory system has significant defenses.
- The upper respiratory tract has:
  - Mucociliary escalator.
  - Coughing.
- The lower respiratory tract has:
  - Alveolar macrophages.

Compromise of any of these defenses
  - Predisposition to respiratory-system infection
BACTERIA INFECTING THE RESPIRATORY SYSTEM

- Can be divided into groups depending on the infections they cause
  - Otitis media, sinusitis, and mastoiditis
  - Pharyngitis
  - Typical and atypical community-acquired pneumonia
  - Hospital-acquired (nosocomial) pneumonia
BACTERIAL INFECTIONS OF THE UPPER RESPIRATORY TRACT

- Otitis media, mastoiditis, and sinusitis
- Pharyngitis
- Scarlet fever
- Diphtheria

OTITIS MEDIA, MASTOIDITIS, AND SINUSITIS

- Middle ear, mastoid cavity, and sinuses are connected to the nasopharynx.
- Sinuses and eustachian tubes have ciliated epithelial cells.
  - A virus initially invades the ciliated epithelium.
  - This destroys the ciliated cells, allowing bacteria to invade.
- Mastoiditis is uncommon but very dangerous.
  - Mastoid cavity is close to the nervous system and large blood vessels.

PHARYNGITIS

- A variety of bacteria can cause infection in the pharynx.
- A classic infection is strep throat.
  - Caused by Streptococcus pyogenes
    - Contains M proteins which inhibits phagocytosis
    - Produces pyrogenic toxins which cause the symptoms seen with pharyngitis
  - Group A streptococci can cause abscesses on the tonsils.
  - S. pyogenes can cause scarlet fever and toxic shock syndrome.
PHARYNGITIS

PHARYNGITIS

SCARLET FEVER

- Caused by Group A streptococci
- Usually seen in children under age of 18 years
SCARLET FEVER:
Pathogenesis

- Symptoms usually begin with appearance of a rash.
  - Tiny bumps on the chest and abdomen
  - Can spread over the entire body
    - Appears redder in armpits and groin
  - Rash lasts 2-5 days

SCARLET FEVER:
Pathogenesis

- Symptoms can also include:
  - Very sore throat with yellow or white papules
  - Fever of 101˚F or higher
  - Lymphadenopathy in neck
  - Headache, body aches, and nausea

SCARLET FEVER:
Treatment

- A variety of antibiotic therapies is available
DIPHTHERIA

- Caused by the toxin produced by *Corynebacterium diphtheriae*
  - A potent inhibitor of protein synthesis
- It is a localized infection.
  - Presents as severe pharyngitis
  - Can be accompanied by plaque-like pseudomembrane in the throat

Toxemia can make diphtheria life threatening.
- Can involve multiple organ systems
- Can cause acute myocarditis
- Diphtheria is transmitted by:
  - Droplet aerosol.
  - Direct contact with skin.
  - Fomites (to a lesser degree).
DIPHTHERIA: Vaccination

- Vaccination against diphtheria is part of the DTaP protocol.
  - Infection is rare when vaccination is in place.
- Diphtheria still occurs frequently in some parts of the world.
  - Particularly where conditions do not permit vaccination.

DIPHTHERIA: Pathogenesis

- Corynebacterium diphtheriae is a small Gram-positive bacillus.
  - Has V and L forms
  - Forms are caused by a unique cell division process – snapping.
**DIPHTHERIA:**

**Pathogenesis**

- *Corynebacterium* is poorly invasive.
  - Effects of infection are due to the exotoxin.
- The exotoxin has two polypeptide chains.
  - B chain – entry into the target
  - A chain – inhibition of protein synthesis

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**DIPHTHERIA:**

**Pathogenesis**

- Local effects include epithelial cell necrosis and inflammation.
- Pseudomembrane is composed of a mixture of fibrin, leukocytes, cell debris.
  - Size varies from small and localized to extensive
  - An extensive membrane can cover the trachea.
- Diphtheria can also be systemic, causing acute myocarditis.
  - *Tox* genes that code for the toxin regulated by operons.

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**DIPHTHERIA:**

**Pathogenesis**

- Incubation takes two to four days.
- Disease usually presents as pharyngitis or tonsillitis with fever, sore throat, and malaise.
- Pseudomembrane can develop on tonsils, uvula, soft palate, or pharyngeal walls.
  - May extend downward toward larynx and trachea.
**DIPHTHERIA: Pathogenesis**

- Uncomplicated cases resolve spontaneously.
  - Membrane is coughed up in days.
- Complicated cases are due to respiratory obstruction.
  - Can result in suffocation
- Systemic infection can result in myocarditis.
- Diphtheria can also cause infections of the skin.
  - Simple pustules or chronic nonhealing ulcerations

**DIPHTHERIA: Treatment**

- Toxin neutralization is the most important.
  - Must be done as quickly as possible
  - Antitoxin can only neutralize free toxin.
- Pathogen elimination is also important.
  - *Corynebacterium diphtheriae* is sensitive to many antibiotics.

**VIRAL INFECTIONS OF THE UPPER RESPIRATORY TRACT**

- Rhinovirus infection (the common cold)
- Parainfluenza
RHINOVIRUS INFECTION

- There are several hundred serotypes of rhinovirus.
  - Fewer than half have been characterized.
  - 50% that have are all picornaviruses.
  - Extremely small, non-enveloped, single-stranded RNA viruses
- Optimum temperature for picornavirus growth is 33°C.
  - The temperature in the nasopharynx

RHINOVIRUS INFECTION: Pathogenesis

- The glycoprotein ICAM is the cellular receptor.
- Rhinovirus is the major cause of mild upper respiratory infections.
  - Known as the common cold virus
  - Affects people of all ages, especially older children and adults
- Infection is seen throughout the year.
  - Usually epidemic in spring and early fall
- Infection is rarely seen in the lower respiratory tract.

RHINOVIRUS INFECTION: Pathogenesis

- Incubation period is 2-3 days.
- Acute symptoms can last for 3-7 days.
- Infection is usually mild.
  - Little damage to the body
RHINOVIRUS INFECTION:
Treatment

- There is no specific therapy or treatment.

PARAINFLUENZA

- There are four types of parainfluenza virus.
  - All belong to the paramyxovirus group.
  - Single-stranded enveloped RNA viruses
  - Contain hemagglutinin and neuraminidase
- Transmission and pathology similar to influenza virus, but there are differences.
  - Parainfluenza virus replicates in the cytoplasm.
  - Influenza virus replicates in the nucleus.

PARAINFLUENZA

- Parainfluenza is genetically more stable than influenza.
  - Very little mutation
  - Little antigenic drift
  - No antigenic shift
- Parainfluenza is a serious problem in infants and small children.
  - Only a transitory immunity to reinfection
  - Infection becomes milder as the child ages.
PARAINFLUENZA INFECTION:
Pathogenesis

- Onset of infection may be abrupt.
  - Can appear as an acute spasmodic croup
- Progresses over 1-3 days to involve the lower respiratory tract.
- Duration of the illness between 4 and 21 days
  - Usually 7-10 days

PARAINFLUENZA INFECTION:
Pathogenesis

- Type 1 parainfluenza virus
  - Major cause of laryngotracheitis (acute croup) in infants and young children
  - Causes severe upper respiratory illness (pharyngitis, and tracheobronchitis) in all age groups
  - Outbreaks usually in the fall

PARAINFLUENZA INFECTION:
Pathogenesis

- Type 3 parainfluenza virus
  - Major cause of severe lower respiratory infection in infants and young children
  - Causes bronchitis and pneumonia in children less than one year of age
  - Infections can occur throughout the year.
  - 50% of all children are exposed to this virus during their first year of life.
PARAINFLUENZA INFECTION:
Treatment

- There is currently no method of treatment.

BACTERIAL INFECTIONS OF THE LOWER RESPIRATORY TRACT

- Bacterial pneumonia
- Chlamydial pneumonia
- *Mycoplasma* pneumonia
- Tuberculosis
- Pertussis
- Inhalation anthrax
- *Legionella* pneumonia (Legionnaire’s disease)
- Q fever
- Psittacosis (Ornithosis)

BACTERIAL PNEUMONIA

- One of the most serious lower respiratory tract infections.
- Can be divided into two types:
  - Community-acquired
  - Nosocomial
- Each type can be caused by a variety of organisms.
BACTERIAL PNEUMONIA

- Nosocomial pneumonia
  - Occurs approximately 48 hours after admission to hospital
  - Usually associated with *Staphylococcus aureus*
  - Also caused by Gram-negative bacteria
  - Particularly difficult to deal with if pathogen is resistant to antibiotics
- Community-acquired pneumonia
  - Usually presents as a lobar pneumonia
  - Accompanied by fever, chest pain, and production of purulent sputum

Atypical pneumonia

- Coughing without sputum
- Caused by a variety of bacteria
- Bacterial pneumonia can progress to the production of lung abscesses.

NOSOCOMIAL PNEUMONIA: Pathogenesis

- Hospital is clinically dangerous.
  - Large number of pathogens
  - Large number of debilitated patients
- Debilitation causes increased proteolytic enzyme activity in saliva.
  - Contributes to the rapid turnover of the fibronectin layer
  - This layer covers the epithelium of the pharynx.
  - Without fibronectin, it can become colonized with opportunistic pathogens.
  - These can be aspirated into the lungs and cause pneumonia.
COMMUNITY-ACQUIRED PNEUMONIA:
Pathogenesis

- Usually occurs after the aspiration of pathogens
  - Requires enough pathogens to overwhelm resident defenses
- Establishment of an infection in the lungs depends on:
  - The number of pathogens entering.
  - The competence of the mucociliary escalator.

COMMUNITY-ACQUIRED PNEUMONIA:
Pathogenesis

- Classical lobar pneumonia has four stages:
  - Acute congestion
    - Local capillaries become engorged with neutrophils.
  - Red hepatization
    - Red blood cells from the capillaries flow into the alveolar spaces.
  - Grey hepatization
    - Large numbers of dead neutrophils and degenerating red cells
  - Resolution
    - Adaptive immune response begins to produce antibodies.
    - These control the infection.
**BACTERIAL PNEUMONIA: Treatment**

- Course of treatment depends on:
  - Severity of the infection.
  - Type of organism causing the infection.
  - Most common pathogen is *Streptococcus pneumoniae*.
  - Treated with penicillin, amoxicillin-clavulanate, and erythromycin.
  - Other antibiotics used are: cefuroxime, ofloxacin, and trimethoprim-sulfamethoxazole.

**CHLAMYDIAL PNEUMONIA**

- Caused by *Chlamydia pneumoniae*:
  - Found throughout the world.
  - Responsible for 10% of pneumonia cases.
  - Infection occurs throughout the year.
  - Spread by person-to-person contact.
  - More infections in the elderly.
  - Can cause both community-acquired and nosocomial infections.

**CHLAMYDIAL PNEUMONIA: Pathogenesis**

- Disease can present as:
  - Pharyngitis.
  - Lower-respiratory-tract infection.
  - Both.
- It is clinically similar to *Mycoplasma pneumoniae*.
  - Initial pharyngitis lasts for 1-3 weeks.
  - Replaced by persistent cough lasting for weeks.
CHLAMYDIAL PNEUMONIA: Treatment

- Tetracycline or erythromycin is effective.

MYCOPLASMA PNEUMONIA

- Mild form of pneumonia
- Accounts for about 10% of all pneumonias
- Referred to as walking pneumonia
  - No need for hospitalization.
- Most common age for infections between 5 and 15 years.
  - Causes approximately 30% of all teenage pneumonias

MYCOPLASMA PNEUMONIA

- Caused by Mycoplasma pneumoniae
  - Lacks a cell wall
  - Acquired by droplet transmission
  - Infectious dose fewer than 100 pathogens
  - Found throughout the world, especially in temperate climates
### Mycoplasma Pneumonia: Pathogenesis

- Incubation period is between 2 and 15 days.
- Infection has an insidious onset.
  - Fever, headache, and malaise for 2 to 4 days
  - Then appearance of respiratory symptoms
- Infection affects the trachea, bronchi, and bronchioles.
  - May extend down to the alveoli

- Bacteria initially attach to the cilia and microvilli on cells lining the bronchial epithelium.
- Attachment interferes with ciliary action causing:
  - Detachment of the mucosal layer.
  - Inflammation and appearance of exudates.
- Inflammatory response is initially composed of lymphocytes, plasma, macrophages.

- Organism can be shed in upper respiratory secretions for:
  - 2 to 8 days before symptoms appear.
  - Up to 14 weeks after symptoms subside.
**MYCOPLASMA PNEUMONIA:**

**Pathogenesis**

- Infection causes:
  - Mild tracheobronchitis.
  - Fever, cough, headache, and malaise.
- Infection sometimes causes:
  - Sore throat.
  - Otitis media.

**Treatment**

- Usual treatment is erythromycin or tetracycline
  - Can shorten the clinical symptoms
  - Organism remains in the nasopharynx for long periods after the symptoms have subsided.

**TUBERCULOSIS**

- An estimated 1.7 billion people are infected.
  - 3 million die each year
- AIDS and HIV infection have had a significant role in the increase of tuberculosis.
  - They increase the efficiency of the tuberculosis transmission cycle.
- Poverty and poor socioeconomic conditions are breeding grounds for tuberculosis.
TUBERCULOSIS

- Drug resistance is becoming increasingly dangerous.
- A major reason for resistance is noncompliance.
  - Many patients stop taking the drugs early.
- Early detection is vital.
- Initial symptoms are similar to those seen in other respiratory infections – it is important to look for:
  - Fever
  - Fatigue
  - Weight loss
  - Chest pain
  - Shortness of breath
  - Congestion with coughing

TUBERCULOSIS

- Caused by *Mycobacterium tuberculosis*
  - Rod-shaped bacillus
  - Acid-fast
  - Nonspore forming
  - Produces mycolic acid
    - Makes it difficult to Gram stain
    - Protects the pathogen from antibiotic therapy and host defenses

TUBERCULOSIS

- [Image of Mycobacterium tuberculosis]
**TUBERCULOSIS:**

**Pathogenesis**

- For healthy people, tuberculosis is a self-liming disease.
  - Host defenses deal with it effectively.
- Tuberculosis can be serious if cell-mediated immunity is compromised or inefficient.

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**M. tuberculosis** cell wall interferes with macrophage function and T-cell activation.
- Inhibits the formation of the phagolysosome
- This allows it to escape into the cytoplasm where it:
  - Increases in number.
  - Eventually spreads to the lymph nodes.
- From here it enters the blood and is distributed throughout the body.

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**Cell wall components attract T cells and macrophages.**
- Uncontrollable release of enzymes that destroy tissues
- Necrosis results
- Necrosis in the lung liquefies.
  - Spreads to adjacent areas
  - Causes the cycle to continue
Two basic types of tuberculosis
  ❘ Primary
    ❘ Follows initial exposure to the pathogen
  ❘ Secondary
    ❘ Can occur years later

Primary Tuberculosis: Pathogenesis

◆ Occurs when a host encounters pathogen for the first time.
◆ Organisms find their way to the alveoli.
  ◆ A localized inflammatory response develops.
  ◆ Phagocytosis of the bacilli by macrophages and neutrophils
PRIMARY TUBERCULOSIS: Pathogenesis

- Pathogens are not killed, they:
  - Are transported by white cells to the regional lymph nodes.
  - Continue to divide intracellularly.
  - Cell mediated immune response begins.
  - If the primary lesion is not contained, tubercles form.

- Tubercles are aggregates of enlarged macrophages filled with bacteria.
  - Can be surrounded by fibroblasts and lymphocytes
  - Center of the tubercle can undergo caseous necrosis
    - May calcify – Ghon complexes
    - Readily seen on X-rays

- Most primary infections become quiescent and asymptomatic.
- About 10% evolve into clinical disease.
  - Bacilli spread through the lymphatic channels, bloodstream, and gastrointestinal system and cause:
    - Tuberculous meningitis
    - Miliary (disseminated) tuberculosis
    - Both.
  - Localized tubercles discharge their contents.
    - Can be aspirated and distributed to other parts of the lungs
SECONDARY TUBERCULOSIS: Pathogenesis

- Secondary tuberculosis can be due to:
  - Reactivation of old lesions.
  - Gradual progression of primary tuberculosis into chronic disease.
  - Recurrence of disease occurs in a small percentage of patients.
    - Usually manifests itself in the apices of the lungs
    - Usually occurs within two years of the primary infection
    - It can evolve decades later when innate resistance is diminished.

TUBERCULOSIS: Treatment

- Usually a triple therapy containing:
  - Isoniazid (INH)
  - Pyrazinamide (PZA)
  - Rifampicin (RFP)
- All three are taken once a day for two months.
- INH and RFP are taken for nine more months.
- If the strain is drug-resistant, initial treatment includes ethambutol.

- Compliance with the drug therapy is very important.
- Compliance can be difficult because of side effects.
  - The drugs are very toxic.
  - Most serious is liver toxicity.
**TUBERCULOSIS: Treatment**

- Directly observed therapy (DOT) is used to prevent multi-drug-resistant tuberculosis.
- DOT involves delivery of scheduled doses of medication by a health care worker.
  - Patient’s ingestion or injection of drugs is directly administered, observed, and documented.
  - Ensures that patients receive medication.
- DOT helps prevent:
  - Spread of tuberculosis.
  - Occurrence of multi-drug-resistant tuberculosis.

**PERTUSSIS (WHOOPING COUGH)**

- Spread by airborne droplets from patients in the early stages.
- Highly contagious
  - Infects 80-100% of exposed susceptible individuals.
  - Spreads rapidly in schools, hospitals, offices, and homes – just about anywhere.

**PERTUSSIS**

- Caused by *Bordetella pertussis*
  - Gram-negative coccobacillus
  - Does not survive in the environment
  - Reservoir is humans.
- Symptoms can be similar to those of a cold.
  - Infected adults often spread the infection to schools and nurseries.
PERTUSSIS

- Mortality is highest in infants and children under 1 year old.
- Immunization against pertussis started in the 1940s.
  - Continues today as part of DTaP vaccination
- Pertussis appears to be making a comeback.
  - Epidemics are occurring every 3-5 years.
  - Greatest numbers of infections are among 10-20 year-olds.
    - People who were not immunized
  - Shows a relationship between lack of vaccination and infection

PERTUSSIS: Pathogenesis

- *Bordetella pertussis* has an affinity for ciliated bronchial epithelium.
- After attaching, it produces a tracheal toxin.
  - Immobilizes and progressively destroys the ciliated cells.
  - Causes persistent coughing
    - Caused by the inability to move the mucus that builds up
- Pertussis does not invade cells of the respiratory tract or deeper tissues.
- Incubation period is 7 to 10 days.

PERTUSSIS: Pathogenesis

- Infection has three stages:
  - Catarrhal stage – 1-2 weeks
    - Persistent perfuse and mucoid rhinorrhea (runny nose)
    - May have sneezing, malaise, and anorexia
    - Most communicable during this stage
PERTUSSIS: Pathogenesis

- Infection has three stages:
  - Paroxysmal stage
    - Persistent coughing
      - Up to 50 times a day for 2 to 4 weeks
    - Characteristic whooping sound is heard.
      - Patient’s trying to catch his/her breath
    - Apnea may follow the coughing, especially in infants.
    - Significant increase in lymphocytes.

- Convalescent stage
  - Frequency and severity of coughing and other symptoms gradually decrease.

- Most common complications of pertussis are:
  - Superinfection with Streptococcus pneumonia.
  - Convulsions.
  - Subconjunctival and cerebral bleeding and anoxia.
PERTUSSIS: Treatment

- Antibiotics can be used in the early stages.
  - Limits the spread of infection.
- Once the paroxysmal stage is reached, therapy is only supportive.
- Vaccination is the best option.

INHALATION ANTHRAX

- Produces a fulminate pneumonia
  - Comes on suddenly with great severity
  - Leads to respiratory failure and death
- Anthrax primarily a disease of herbivores
  - Acquired from spores found in pastures
  - If spores are inhaled, anthrax can occur in the respiratory tract.

INHALATION ANTHRAX

- Infection is infrequently seen in healthy individuals.
  - Usually presents as localized lesions where it occurs.
- Has been recent interest in inhalation anthrax as a biological weapon
  - In October 2001, letters contaminated with powdered anthrax spores were mailed to various locations in the US.
  - Several deaths resulted.
INHALATION ANTHRAX:
Pathogenesis

- The causative agent is *Bacillus anthracis*.
  - Gram-positive rod
  - Spore-forming
  - Spores germinate in human tissues.
  - Antiphagocytic properties of the capsule aid its survival and growth in large numbers.

INHALATION ANTHRAX:
Pathogenesis

- Pathogenesis results from the powerful exotoxin produced.
- Symptoms of pulmonary anthrax are:
  - 1-5 days of nonspecific malaise, mild fever, nonproductive cough.
  - Progressive respiratory distress and cyanosis.
- Rapid and massive spread to the central nervous system and bloodstream is followed by death.

INHALATION ANTHRAX:
Treatment

- Antibiotic therapy can be successful.
  - *B. anthracis* is susceptible to penicillin.
  - Doxycycline and ciprofloxacin are alternative prophylactics.
**LEGIONELLA PNEUMONIA (LEGIONNAIRES’ DISEASE)**

- Caused by *Legionella pneumophila*
  - Gram-negative rod
  - Cannot be stained or grown using normal techniques

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**LEGIONELLA PNEUMONIA**

- Unrecognized as a disease before 1976.
- *Legionella* is ubiquitous in fresh water.
  - Lives within *Acanthamoeba* organisms
  - These are infectious reservoirs.
- Transmitted to humans as a humidified aerosol
  - Person-to-person transmission has never been seen.
LEGIONELLA PNEUMONIA

- Healthy people not affected very often.
  - Many cases go undetected.
  - Legionella has low virulence for humans.
- Infection is seen in less than 5% of population.
  - Usually in the immunocompromised

LEGIONELLA PNEUMONIA:
Pathogenesis

- Legionella is a facultative intracellular parasite.
  - Aggressively attacks the lungs
  - Produces a necrotizing multifocal pneumonia
    - Involves alveoli and terminal bronchioles
- The inflammatory response produces an exudate containing:
  - Fibrin, polymorphonuclear leukocytes, and red blood cells.

LEGIONELLA PNEUMONIA):
Pathogenesis

- Organisms inhaled enter the alveoli.
  - Infect alveolar macrophages
  - Produce an endocytic vesicle
    - Continue replication
    - Prevent fusion of the vesicle with lysosomes
  - Infected macrophages show a coiled morphology.
LEGIONELLA PNEUMONIA: Pathogenesis

Disease causes severe toxic pneumonia.
- Begins with myalgia and headache
- Followed by rapidly rising fever
  - Chills, pleuritic chest pain, vomiting, and diarrhea
  - Occasional confusion and delirium
- Interstitial infiltrates in lung are seen on X-ray
- Can also cause hepatic dysfunction

Serious cases show progressive illness over 3 to 6 days.
- Ends in shock or respiratory failure
- Mortality rate is about 15%
- Can be as high as 50% in hospital outbreaks
  - High population of the immunocompromised or immunosuppressed
**LEGIONELLA PNEUMONIA:**

**Treatment**

- Erythromycin is better than penicillin.
  - *Legionella* produces a β-lactamase.
- Tetracycline, rifampin, and quinolones are effective.
- Azithromycin and clarithromycin are the agents of choice.

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**Q FEVER**

- A zoonotic infection seen worldwide
  - Cattle, sheep, and goats are the primary reservoirs for humans.
- Caused by *Coxiella burnetii*
  - Gram-negative
  - Spore-forming
  - Grows well in placenta of animals
    - Large numbers of *Coxiella* can be transmitted by inhalation during animal births.
    - Transmission can also be by ingestion of unpasteurized milk.

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**Q FEVER: Pathogenesis**

- Not clearly understood
  - Begins 9 to 20 days after inhalation
  - Abrupt onset of chills, fever, and headache
  - Can also be a mild hacking cough and patchy interstitial pneumonia
  - Some cases show abnormal liver function
Q FEVER: Treatment

- Most cases resolve spontaneously.
- Tetracycline can be given to shorten fever.
  - Reduces risk of rare chronic infection

PSITTACOSIS (ORNITHOSIS)

- Zoonotic pneumonia
- Contracted by inhalation of bird droppings infected with *Chlamydia psittaci*.
  - Found in many birds, including turkeys
  - Some strains of *C. psittaci* are extremely contagious.

PSITTACOSIS: Pathogenesis

- Presents as an acute infection of the lower respiratory tract.
  - Acute onset of fever, headache, malaise, muscle aches, dry hacking cough, and bilateral pneumonia
  - Occasional systemic complications include:
    - Myocarditis, endocarditis, and hepatitis.
    - Splenomegaly and hepatomegaly can also occur.
**PSITTACOSIS: Treatment**

- Tetracycline and erythromycin are effective if given early.

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**VIRAL INFECTIONS OF THE LOWER RESPIRATORY TRACT**

- 75-80% of all acute respiratory tract infections in the US are of viral origin.
  - Everyone has 3 or 4 per year
  - Incidence varies inversely with age.
  - Greatest in young children

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**VIRAL INFECTIONS OF THE LOWER RESPIRATORY TRACT**

- Majority of acute viral infections are in the lower respiratory tract and caused by:
  - Influenza virus.
  - Respiratory syncytial virus.
- Common characteristics of infection are:
  - Short incubation period of 1 to 4 days.
  - Transmission from person to person.
- Transmission can be direct or indirect.
  - Direct – through droplets
  - Indirect – through hand transfer of contaminated secretions
**INFLUENZA**

- Influenza virus is an orthomyxovirus.
  - Virions are surrounded by an envelope.
- Genome is single-stranded RNA in eight segments.
  - Allows a high rate of mutation
- Three major serotypes of virus: A, B, and C.
  - Differences are based on antigens associated with the nucleoprotein.

**INFLUENZA**

- Influenza is a significant health concern.
  - Human virus can combine with an avian virus to produce a highly pathogenic virus.
- Humans are the hosts for influenza.
  - Aquatic birds are the reservoir.

**INFLUENZA**

- As seen in panels (a) and (b), the influenza virus possesses a lipid bilayer surrounding a segmented RNA core. Key viral enzymes such as neuraminidase (N) and hemagglutinin (H) are also depicted. Matrix protein helps in viral budding and release.
INFLUENZA

- Primary manifestation of infection is severe respiratory problems.
- Outbreaks have been described since the sixteenth century.
  - Differ in severity nearly every year
  - Occur more frequently in the winter
- Direct droplet transmission most common method of spreading.

INFLUENZA

- A major outbreak occurs every 2 to 3 years.
  - Typical epidemic lasts 3 to 6 weeks.
  - Up to 10% of the general population is affected.
  - Illness rates exceed 30% in certain groups.
    - In school-aged children
    - Residents of closed institutions

INFLUENZA: Pathogenesis

- Influenza virus prefers the respiratory epithelium.
  - Viremia is rare.
- Virus multiplies in the ciliated cells of lower respiratory tract.
  - Results in functional and structural abnormalities
- Cellular synthesis of nucleic acids and proteins is shut down.
- Ciliated and mucus-producing epithelial cells are shed.
  - Substantial interference with clearance mechanisms
  - Localized inflammation
INFLUENZA: Pathogenesis

- Respiratory epithelium may not be restored for 2 to 10 weeks.
- Viral destruction of tissues causes inflammation.
- Impaired phagocytic and chemotactic responses can result in superinfection by bacteria.

INFLUENZA: Pathogenesis

- Recovery from influenza starts with interferon.
  - Limits the spread of infection
- Next step is rapid generation of natural killer cells.
  - Reverses the infection
- Finally, cytotoxic T cells and specific antibodies appear in large numbers.
  - Control the infection

INFLUENZA: Pathogenesis

- Acute influenzal syndrome can develop.
  - Short incubation time – about 2 days
  - Symptoms appear in a few hours.
  - Fever, myalgia, headache, and occasional shaking chills
  - Maximum severity appears in 6 to 12 hours.
  - Nonproductive cough develops
INFLUENZA: Pathogenesis

- Acute influenza syndrome can develop.
  - Acute symptoms can last 3 to 5 days.
  - Usually followed by improvement but a progressive infection can develop.
    - Affects the tracheobronchial tree and lungs
    - Lethal pneumonia can occur.

INFLUENZA: Pathogenesis

- Bacterial superinfections are a serious complication of influenza.
  - Usually involves the lungs
  - Can develop during the convalescent stage
    - Patient is debilitated.
  - Superinfection is identified by an abrupt worsening of the patient’s condition after initial stability.

INFLUENZA: Pathogenesis

- Three bacteria are common causes of superinfection.
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*
INFLUENZA: Pathogenesis

- Influenza can cause death in three ways:
  - Underlying disease
    - People with limited cardiovascular activity or pulmonary function
  - Superinfection
    - Bacterial pneumonia and disseminated bacterial disease
  - Direct rapid progression
    - Overwhelming viral pneumonia and asphyxia

INFLUENZA: Treatment

- Two basic approaches
  - Symptomatic care
  - Anticipation of potential complications
- The best treatments are:
  - Rest and fluid intake
  - Conservative use of analgesics for myalgia and headache
  - Cough suppressants.
  - Amantidine and rimantadine are useful only if the infection is diagnosed within 12-24 hours.

RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION

- Named because of the syncytia associated with it
- Community outbreaks of RSV occur annually in late fall to early spring.
  - Outbreaks last about 8-12 weeks.
  - Can involve 50% of families with small children
    - An older sibling usually brings the virus home.
    - Young children or infants are infected most often.
RSV INFECTION

- Virus is shed for 5-7 days.
  - Up to 20 days in infants
- Major cause of nosocomial infections
  - Control of these infections in a hospital is difficult but helped by:
    - Attention to hand washing.
    - Exclusion of staff and visitors with respiratory symptoms.

RSV INFECTION:
Pathogenesis

- Spreads to upper respiratory tract by contact with infectious secretions.
- Infection is usually confined to respiratory epithelium.
  - Progresses to the middle and lower airways
  - Viremia is rare.
- Effect on respiratory epithelium is similar to influenza.
- Cytotoxic T cells have a significant role in controlling disease.

RSV INFECTION:
Pathogenesis

- Has major pathological consequences in the bronchi, bronchioles, and alveoli.
  - Necrosis, interstitial mononuclear cell infiltration, and inflammation
  - Can result in the plugging of the small airways with mucus, necrotic cells, and fibrin
- Incubation period is 2 to 4 days.
  - Followed by onset of rhinitis
  - Severity peaks within 3 days
RSV INFECTION:
Pathogenesis

- Clinical signs include:
  - Hyperexpansion
  - Hypoxia
  - Hypercapnia
  - Pulmonary collapse
- Acute signs normally last 10-14 days.
- Infection is mild in adults and older children.
- Can be fatal in infants
  - Fatality rate in hospitalized infants is 1%.
  - Can be as high as 15% in compromised children

RSV INFECTION:
Treatment

- Treatment is directed at the underlying clinical pathology.
  - Oxygenation and ventilation
  - Close observation to deal with potential bacterial superinfections
- There is no vaccine.

HANTAVIRUS PULMONARY SYNDROME (HPS)

- No recognized hantavirus infection in humans until 1993.
- Virus causes a fulminant respiratory infection.
  - High mortality rate (50-70%)
- Three types of hantavirus
  - Sin Nombre is the most common.
- Infections are associated with increases in the rodent population.
HPS:
Pathogenesis

- Transmission is via dried rodent excreta.
  - By inhalation
  - Through the conjunctival route
  - By direct contact through breaks in the skin

Fungal Infections of the Respiratory System

- Two major factors govern the incidence and spread of fungal infection.
  - Ubiquity of the infectious organisms
    - Found in soil
    - Resident flora
  - The adaptive immune response
    - Usually keeps these infections under control
    - Immunocompromised patients at much greater risk

Pneumocystis Pneumonia (PCP)

- A lethal pneumonia
  - Common in AIDS patients
  - Caused by the fungus *Pneumocystis (carinii) jiroveci*
    - Never been grown in culture
    - Most information comes from clinical information from patients.
PCP

- *P. (carinii) jiroveci* has atypical features.
  - Shape, nucleus, and spores resemble structures seen in protozoans.
  - Plasma membrane has cholesterol – most fungi have ergosterol.
  - Showed to be a fungus by RNA typing
  - Infection occurs in humans and animals.
  - Antibodies against it are found in almost all children by the age of 4 years.

- Reservoirs and modes of transmission are yet to be defined.
  - Transmitted by aerosol in models
  - AIDS is the most common predisposing factor for PCP.
    - Most patients with AIDS develop it.
  - *P. (carinii) jiroveci* has a low level of virulence.
    - Rarely affects immunocompetent hosts

- Little is known about early stages of infection.
- A glycoprotein is thought to be involved in attachment to host cells.
  - Seems to undergo antigenic variation
- *Pneumocystis* pneumonia characterized by alveoli filled with sloughed-off alveolar cells, monocytes, and fluid.
  - Produces distinct foamy honeycombed appearance
  - Presents as progressive diffuse pneumonitis in compromised hosts.
PCP: Pathogenesis

- Onset is insidious in patients with AIDS.
  - Can be present for 3 to 4 weeks before discovered.
- Principal manifestations of infection are:
  - Progressive dyspnea
  - Tracheal pneumonia
  - Eventual cyanosis and hypoxia
  - Nonproductive cough in 50% of patients

PCP: Pathogenesis

- X-rays show alveolar infiltrates spreading out from the hila.
  - Eventually affects the entire lung
- Causes decreased O\(_2\) capability
  - Decreased saturation of arterial blood
  - Decreased lung vital capacity
  - Death occurs through progressive asphyxiation
- In some cases lesions occur in other parts of the body.

PCP: Treatment

- Non AIDS patients
  - Combination of trimethoprim and sulfamethoxazole for 14 - 21 days.
- Patients with AIDS
  - Pentamidine and trimetrexate for more than 21 days
    - Present with more advanced infection
    - Respond more slowly
    - Relapse more often
BLASTOMYCOSIS

- Caused by *Blastomyces dermatitidis*.
- Spores of the fungi enter through the respiratory system.
- Primarily affect the lungs
  - Can spread through bloodstream and affect other parts.
- Men between ages of 20 and 40 years are the most commonly infected.
- Blastomycosis is not increased in AIDS.

BLASTOMYCOSIS: Pathogenesis

- Infection of the lungs is gradual.
  - Fever, chills, and drenching sweats develop.
  - Chest pain, difficulty breathing, and cough may also develop.
  - Can sometimes heal without treatment.

- When infection spreads it can affect many areas.
  - Skin – warty patches develop surrounded by tiny painless abscesses
  - Bones – painful swellings
  - Genitourinary tract – prostatitis or painful swelling of epididymis
BLASTOMYCOSIS: Treatment

- Intravenous amphotericin B or oral itraconazole
  - Patients feel better quickly.
  - Therapy must be continued for months.
- Without treatment blastomycosis can be fatal.

HISTOPLASMOSIS

- Caused by *Histoplasma capsulatum*
  - Occurs in soil contaminated with bat or bird droppings
  - Commonly found in temperate, subtropical, and tropical zones
  - 50% - 90% of residents in these areas test positive for exposure.
  - People who live and work in the vicinity of bat or bird droppings are at increased risk of infection.

HISTOPLASMOSIS: Pathogenesis

- Transmission is through inhalation of conidia.
  - Small enough to reach bronchioles and alveoli
  - Because of minute size, usually referred to as microconidia.
- Most cases are asymptomatic.
  - Some present with fever and mild cough.
HISTOPLASMOSIS: Pathogenesis

- Initial infection pulmonary
  - Elements of the mononuclear phagocytic system (lymph nodes, spleen, and bone marrow) can also be affected.
- After inhalation:
  - Microconidia convert to yeast form.
  - These are phagocytosed.
  - Yeast form survives formation of the phagolysosome.
    - Capture iron which lowers pH of the phagolysosome
  - Continue to divide in the cytoplasm of the phagocytic cell.
  - Tubercles form.

HISTOPLASMOSIS: Pathogenesis

- Majority of cases never go further than tubercle formation.
- Some patients develop fever and cough.
  - Lasts a few days or even weeks
- Severe cases may develop chills, malaise, chest pain, and extensive pulmonary infiltration.
  - These usually resolve spontaneously.

HISTOPLASMOSIS: Treatment

- Usually resolves spontaneously and there is no need for treatment.
- Amphotericin B is the treatment of choice if necessary.
  - It is toxic.
  - Used only for short times and only in severe cases.
- Itraconazole and ketoconazole are used in patients with AIDS.
COCCIDIOIDOMYCOSIS

- Caused by *Coccidioides immitis*
- Infection can be symptomatic or asymptomatic.
  - Symptomatic form known as Valley Fever.
- Restricted to certain geographical areas.

COCCIDIOIDOMYCOSIS: Pathogenesis

- Arthroconidia of the fungus are inhaled.
  - Small enough to bypass defenses of the upper tract.
  - Lodge directly in bronchioles.

- Fungal outer wall has antiphagocytic properties.
  - Prevents elimination
- Arthroconidia convert to spherules which grow slowly.
  - Completely inhibit phagocytosis
**COCCIDIOIDOMYCOSIS:**

**Pathogenesis**

- More than half of infected individuals show no signs of infection.
- Remainder progress to valley fever
  - Present with malaise, cough, chest pain, fever, and arthralgia.
  - All signs occur 1 to 3 weeks after infection begins.
  - Signs can last for up to 6 weeks.
- Most patients spontaneously resolve.
- Only 10% ever experience pulmonary symptoms.
- Disseminated coccidioidomycosis is seen in patients with AIDS and on immunosuppressive therapy.
- Can also cause a form of coccidioidal meningitis
  - Can be fatal if not treated aggressively

**Treatment**

- Usually self-limiting and no treatment is required.
- Progressive pulmonary infection or infection of central nervous system is treated with amphotericin B.
ASPERGILLOSIS

- Invasive aspergillosis shows a rapid progression to death.
- Typically seen in the immunocompromised.
  - Particularly patients with leukemia or AIDS.
  - Patients undergoing bone marrow transplantation.
- Also seen in individuals with preexisting pulmonary disease
  - Chronic bronchitis, asthma, and tuberculosis

ASPERGILLOSIS

- Caused by the fungus Aspergillus
  - Widely distributed and found throughout the world
  - Dispersal is through inhalation of resistant conidia.
  - Seen more and more in nosocomial infections associated with air-conditioning systems.

ASPERGILLOSIS: Pathogenesis

- Conidia of Aspergillus are small enough to reach alveoli when inhaled.
- Infection is rare if the immune system is working properly.
- Fungus produces extracellular proteases, phospholipases, and toxic metabolites.
  - Their involvement in infection is unknown.
**ASPERGILLOSIS: Pathogenesis**

- Colonization with *Aspergillus* leads to invasion of tissues.
  - Invasion of lung tissue causes penetration of blood vessels.
  - This causes hemoptysis and/or acute pneumonia.

**ASPERGILLOSIS: Pathogenesis**

- Pneumonia is accompanied by multifocal pulmonary infiltrates and high fever.
  - Prognosis is grave.
  - Mortality for invasive aspergillosis is 100%.

**ASPERGILLOSIS: Treatment**

- Amphotericin B and itraconazole can be used but are usually ineffective.