Streptococcal pharyngitis
  
  Streptococcus pyogenes

Complications
  Scarlet fever, acute rheumatic fever, acute glomerulonephritis

Pathogenesis
  membrane damaging toxins, M proteins, ECM binding, super-antigen toxin
  immune-mediated complications
  
  Acute rheumatic fever – cross-reactive antibody
  Glomerulonephritis – antigen antibody complexes

Diagnosis
  rapid test, culture

Therapy
  antibiotics prevent acute rheumatic fever

Tuberculosis
  Mycobacterium tuberculosis

  cell wall structure

Disease chronic and progressive, usually pulmonary (in lung)

Pathogenesis
  Survival in alveolar macrophage
  Latency - granuloma – cavity

Diagnosis
  Previous or latent: tuberculin skin test or interferon gamma release assay (IGRA)
  Active: chest X-ray, sputum stain, sputum culture

Therapy
  antibiotics active on M. tb. cell wall, multiple antibiotics required in active
disease to prevent mutational acquisition of resistance

Epidemiology
  Highest incidence in Africa – significant mortality
Influenza

Influenza virus – enveloped, segmented – ssRNA
Replicated in nucleus
Spike proteins: hemagglutinin, neuraminidase

Disease
acquired by inhalation
complications – secondary viral and bacterial pneumonia, significant mortality

Pathogenesis
inhibition of cellular mRNA processing, inhibition of activation of interferon-induced antiviral proteins, esp. PKR
Local immunosuppression

Diagnosis
Rapid antigen detection, viral culture

Therapy
Antiviral – zanamivir: blocks viral neuraminidase, prevents release of progeny virus

Prevention
Killed and live-attenuated vaccine
must be reformulated annually

Epidemiology
Annual epidemics – significant mortality
Antigenic shift (reassortment) and drift (mutation)
Pandemics caused by antigenic shift

Highly virulent H5N1 avian influenza
Respiratory Tract Infections

• Upper respiratory tract infections (URI)
  • Sinusitus
  • Rhinitis (=coryza)
  • Pharyngitis
  • Otitis med

• Lower respiratory tract infections (LRI)
  • Bronchitis
  • Bronchiolitis
  • Pneumonitis
  • Pneumonia

Bacterial upper respiratory tract infections

• Streptococcus pyogenes: aka Group A Streptococcus
  • Gram-positive cocci in chains, colonies hemolytic on blood agar (beta hemolysis)
  • found among normal nasopharyngeal flora
  • Group A – serotype of cell wall carbohydrate
  • The disease: streptococcal pharyngitis (sore throat)
    • Pain, redness, fever, purulent pharyngeal exudate (neutrophils)
    • Self limiting after 1 week
  • Complications
    • Scarlet fever – rash occurring with pharyngitis (~10% of cases), resolution over weeks. Usually mild with appropriate antibiotic therapy.
    • Acute rheumatic fever: fever, joint pains, chest pains, rash
      • permanent heart valve damage can occur
    • Acute glomerulonephritis
      • kidney disease – fever, increased blood pressure, bloody urine

Streptococcal M protein

• 2 intertwined fibrillar molecules
• C-terminus attached in cell wall
• > 100 antigenic types

Bacterial upper respiratory tract infections

• Streptococcus pyogenes (continued)
  • Pathogenesis
    • Production of streptolysins: membrane damaging toxins that inhibit neutrophil function
    • Antiphagocytic surface properties: M proteins inhibit fixation of complement on surface of bacterial cell
    • Surface proteins mediate binding to extracellular matrix components (ECM)
    • Enzymes secreted which degrade ECM
    • Scarlet fever caused by superantigen toxin (more later)

Bacterial upper respiratory tract infections

• Streptococcus pyogenes
  • Pathogenesis (continued)
    • Surface proteins bind to connective tissue extracellular matrix proteins
      • Extracellular matrix
      • fibrous proteins
      • polysaccharides
      • proteoglycans
    • Fibroblasts
      • Cells that make ECM components

Bacterial upper respiratory tract infections

• Streptococcus pyogenes
  • Pathogenesis (continued)
    • Immune mediated complications (there are NO bacteria in affected tissue)
      • Acute rheumatic fever is caused by antibodies produced against streptococcal proteins that react with host tissue
      • Heart valves
    • Acute glomerulonephritis is caused by deposition of streptococcal antigen-antibody complexes in glomerular capilaries in the kidney
Bacterial upper respiratory tract infections

- *Streptococcus pyogenes* (continued)
  - Diagnosis of streptococcal pharyngitis
    - Rapid streptococcal antigen test
    - Throat culture
    - MOST PHARYNGITIS IS VIRAL!!
  - Therapy
    - Antibiotics
      - Purpose is to prevent acute rheumatic fever
  - Other *Streptococcus pyogenes* diseases
    - Scarlet fever: febrile rash illness involving superantigen toxin
    - Skin infections: usually mild
    - Wound infections, can be severe and destructive
    - Sepsis

- Viral pharyngitis
  - Rhinoviruses — picornavirus family
    - Small naked positive-sense ssRNA viruses
  - Other common cold viruses
  - Adenovirus
    - Naked DNA virus
    - Severe pharyngitis, fever, conjunctivitis (eye inflammation), diarrhea
  - Epstein Barr virus (EBV)
    - Herpes family virus — enveloped DNA virus
      - Mononucleosis: severe pharyngitis, fatigue and prolonged malaise, fever, lymphadenopathy, rash
  - Coxsackie A virus — picornavirus
    - Herpangina; hand, foot and mouth disease
    - Sore throat, fever, vesicular eruption of nasopharyngeal mucosa (herpangina) or oral mucosa and hands and feet (HFMD).

- The disease: tuberculosis
  - Acquired by inhalation of respiratory droplets from infected persons
  - Initial infection of lung is usually asymptomatic and usually becomes latent
  - Symptoms are cough, weight loss, fever, night sweats, chest pain
    - Active disease is chronic and progressive, sputum becomes bloody, disease can progress to death in 2-5 years
    - Active disease can progress continuously from primary lesion, or can reanimate from latent infection years after acquisition
  - Most disease is pulmonary, but infection can disseminate
    - granulomas in organs and bones
      - meningitis
  - HIV-infected persons at increased risk

- Other bacterial causes of pharyngitis
  - *Corynebacterium diphtheriae*
    - Gram-positive bacillus produces exotoxin that inhibits protein synthesis
  - Local (pharyngitis) and systemic (myocarditis) effects of toxin
  - Significant mortality
  - Eliminated from U.S. by vaccination
  - Epidemic in Russia 1990-93 demonstrates potential for re-emergence if vaccine coverage is reduced
  - *Mycoplasma pneumoniae*
    - Bacteria with no peptidoglycan
    - Pharyngitis may accompany pneumonia caused by this pathogen
  - *Neisseria gonorrhoeae*
    - Gram-negative diplococcus
    - Results from oral-genital contact

- Tuberculosis
  - One third of the world’s population is infected and 2 million die of the disease annually
  - *Mycobacterium tuberculosis*
    - Very slow growing aerobic bacillus
    - Does not stain with normal Gram stain, but can be stained with acid-fast staining
    - Cell wall has unusual carbohydrate (arabinogalactan) and complex glycolipids (mycolic acids) linked to the peptidoglycan
  - Capsule
  - Mycolic acids
  - Arabinogalactan
  - Peptidoglycan
  - Cytoplasmic membrane

- Pathogenesis of *M. tuberculosis*
  - Survival in alveolar macrophage
    - Prevention of phagosome lysosome fusion
  - Recruitment of additional macrophages to site forms granuloma
  - Activation of macrophages by cell mediated immunity controls infection, but viable bacteria can remain as LATENT INFECTION
  - Failure to control the infection results in expansion of the granuloma, necrosis in the center of the granuloma, and the formation of a cavity
  - Continued recruitment of macrophages and inflammatory mediators and failure to control the infection results in tissue damage.
  - Erosion of cavity into bronchi cause coughing and makes the patient highly infectious
Diagnosis of tuberculosis
- Diagnosis of present (latent or active) or prior infection
  - Tuberculin (PPD) skin test
  - Intradermal injection of M. tb. antigen
  - Positive test results in redness and swelling
  - Swelling (not redness) > 15 mm (in most persons) 48-72 hours later considered positive
  - Indicates present (latent or active) or prior infection
  - Reaction caused by Th and Tc recruitment to site of injection
  - IGRA (interferon-gamma release assay)
  - Laboratory blood test measures interferon gamma release from T lymphocytes exposed to M. tb. antigens

Diagnosis of active disease
- Chest X-ray
- Lung lesions characteristic of active pulmonary TB
- Sputum acid fast stain
- Sputum culture (more sensitive than stain)
  - requires very long incubation
- Nucleic acid amplification

Therapy
- Antibiotics
  - M. tb. is resistant to most common antibiotics
    - Most use antibiotics which target mycobacterial cell wall
      - Isoniazid, pyrazinamide – mycolic acid synthesis
      - Ethambutol – arabinogalactan synthesis
    - To treat latent infection
      - Isoniazid
    - To treat active disease
      - Multiple antibiotics necessary to prevent emergence of resistant mutants
    - Therapy takes months
    - Strains exist which are resistant to all useful antibiotics

Prevention
- Screening and treatment of latent infection
- Vaccine
  - BCG (bacille Calmette Guerin)
    - Live attenuated vaccine
    - Questionable efficacy, not used in U.S.

Other bacterial causes of lower respiratory tract infections
- Streptococcus pneumoniae – leading cause of pneumonia
  - Gram-positive diplococcus found in normal nasopharyngeal flora
  - Possesses antiphagocytic capsular polysaccharides
  - Acute onset pneumonia, severe in infants and elderly
  - Complications include meningitis and sepsis
- Mycoplasma pneumoniae – common cause of community-acquired pneumonia
  - Long incubation period, disease persists 2-3 weeks, chronic coughing, transmission in families
  - Adheres to ciliated epithelial cells, inhibits ciliary function
  - Pneumonia less severe than with other causes (walking pneumonia)

Epidemiology of Tuberculosis
Highest incidence in Africa
Over 50% of HIV-infected population also infected with TB

Other bacterial causes of lower respiratory tract infections
- Legionella pneumophila
  - Gram negative bacilli, natural pathogen of fresh water amoeba and ciliates
  - Acquired from aerosolized environmental fresh water sources (no person to person transmission)
  - Intracellular replication in vacuoles of alveolar macrophages
  - Acute onset, severe pneumonia with significant mortality in persons with pre-existing lung dysfunction (elderly with COPD, long history of smoking)
- Chlamydophillus pneumoniae
  - Another bacterial species with no peptidoglycan
  - Obligate intracellular parasite, replicates in intracellular vacuole in respiratory epithelium
  - Mild pneumonia in adolescents and young adults
  - Common cause of community-acquired pneumonia
  - Associations with asthma, atherosclerosis (causality not established yet)
- Bordetella pertussis
  - Gram negative coccobacillus
  - Toxin inhibit ciliary action and lung immune function
  - Prolonged severe coughing and secondary pneumonia
  - Severe disease in very young
  - Recent increase in incidence with local epidemics associated with reduction in vaccine coverage and possibly vaccine efficacy

Influenza
- Influenza virus – orthomyxovirus
  - Virion: enveloped
  - Genome: segmented negative-sense single stranded RNA
    - 8 segments encode 11 proteins
    - Replicates in the nucleus (unusual for an RNA virus)
    - Permits differential splicing of RNA
  - Surface proteins
    - HA: hemagglutinin – mediates binding of virus to receptor sialic acid, a component of host cell glycoproteins
    - NA: neuraminidase – cleaves sialic acid from host cell glycoprotein, allowing release of progeny virus
• Influenza: the disease
  • Acquired by inhalation of respiratory droplet from another person (or animal) or by contact with contaminated fomites
  • Symptoms
    • 2 day incubation period
    • Sore throat, coughing, fever, headache, muscle pain, eye pain, fatigue and weakness
    • 1 week duration, fatigue may persist
  • Complications
    • Viral and secondary bacterial pneumonia
    • Streptococcus pneumoniae, Staphylococcus aureus
    • Significant mortality in elderly, infants
    • Disease more severe in pregnancy
    • Exacerbation of asthma, chronic lung disease
    • Group in children (laryngotracheobronchitis) can be severe
    • Reye’s syndrome in children taking aspirin
    • Encephalopathy (change in mental status, respiratory arrest)
  • Overall influenza-associated mortality in U.S. may exceed 50,000 per year

• Viral pathogenesis
  • Inhibition of cellular mRNA processing
  • Sequestration of dsRNA suppresses activation of antiviral proteins
  • Direct and indirect inhibition of PKR activation
  • Local immunosuppression
    • Productive infection occurs in respiratory epithelium, but non-productive infection of lymphocytes, monocytes, and neutrophils has significant immunosuppressive effects
    • Viral nucleoprotein inhibits neutrophil chemotaxis and oxidative burst
  • Highly virulent strains (e.g. 1918 H1N1 epidemic strain, H5N1 avian flu) induce massive cytokine induction (cytokine storm), effective suppression of interferon response

• Diagnosis
  • Rapid antigen tests – specific but sensitivity is not great
  • Viral culture – takes 3-10 days but essential for disease surveillance
  • Nucleic acid detection
    • Not all patients need to be tested!
    • Disease severity
    • Surveillance

• Therapy
  • Oselamivir, zanamivir
    • Inhibits viral neuraminidase, prevents release of virions from host cell
    • Indicated in severe disease, or patients with specific risk factors
    • Resistant strains exist, and can arise by mutation

• Prevention
  • Vaccines
    • Killed vaccine viruses prepared in chicken eggs
    • Live attenuated vaccines administered by nasal mist
    • Vaccines must be reformulated annually to cover circulating strains

• Epidemiology of influenza
  • Annual epidemic of cases in winter months
  • Immunity to re-infection is limited
    • Multiple antigenic types and subtypes of virus
      • Type A: most severe disease
        • Subtypes based on antigenicity of HA and NA proteins
          • e.g. H1N1, H3N2, H5N1
        • Type B: less severe, less likely to produce epidemics
      • Antigenic drift
        • Antigenicity of HA and NA changes from season to season due to accumulation of mutations
      • Antigenic shift
        • Emergence of new viruses generated by genetic reassortment in animal host, swine and fowl most important for human disease

Influenza Pandemics

<table>
<thead>
<tr>
<th>Year</th>
<th>Deaths</th>
<th>Case Fatality Rate</th>
<th>Subtype</th>
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</thead>
<tbody>
<tr>
<td>Asiatic (Russian) Flu</td>
<td>1889-1890</td>
<td>1 million</td>
<td>0.15%</td>
</tr>
<tr>
<td>Spanish Flu</td>
<td>1918-1920</td>
<td>20 to 100 million</td>
<td>2%</td>
</tr>
<tr>
<td>Asian Flu</td>
<td>1957-1958</td>
<td>1 to 7.5 million</td>
<td>0.13%</td>
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<td>Hong Kong Flu</td>
<td>1968-1969</td>
<td>0.75 to 1 million</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>2009 flu pandemic</td>
<td>2009-2010</td>
<td>18,000</td>
<td>0.03%</td>
</tr>
</tbody>
</table>
The Next Influenza Pandemic?

“The world is teetering on the edge of a pandemic that could kill a large fraction of the human population.”

- Highly Pathogenic Avian Influenza H5N1 (HPAI H5N1)
  - Highly contagious among birds
  - High mortality in domestic poultry
  - Endemic in South and East Asia, sporadic in other countries in Eastern Hemisphere
  - Inefficiently transmitted to humans, but high mortality
  - 600 human cases since 2003, 60% case fatality rate
  - Very inefficiently transmitted from human to human
    - Majority of cases associated with direct exposure to infected poultry
    - Small number of probable human to human transmissions associated with prolonged close contact with infected person

Other viral causes of lower respiratory tract infections

- Respiratory syncitial virus
  - Severe bronchiolitis in infants
- Parainfluenza virus
  - Enveloped negative-sense ssRNA virus
  - Croup, bronchiolitis, pneumonia in children
- Hantavirus
  - Enveloped, negative-sense ssRNA virus
  - Natural pathogen of small wild rodents
  - Acquired by inhalation of aerosolized dried urine or feces from infected rodents
  - Hantavirus pulmonary syndrome
    - Initially vomiting, diarrhea, abdominal pain
    - Coughing, shortness of breath
    - Pulmonary edema and shock
    - Significant mortality
  - Recent outbreak associated with cabins in Yosemite National Park
    - (9 cases, 3 deaths)

- Preparations for potential H5N1 Pandemic
  - Vaccine production and stockpiling
  - Research
    - Identification of mutations enabling transmission of virus in mammals
    - Highly controversial
    - Research moratorium on H5N1 transmission involving gain-of-function mutations
  - Intensive surveillance and analysis of avian outbreaks and human cases