UPPER RESPIRATORY TRACT INFECTION
OVERVIEW

• To learn the epidemiology and various clinical presentation of URT
• To identify the common etiological agents causing these syndromes
• To study the laboratory diagnosis of these syndromes
• To determine the antibiotic of choice for treatment
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.
• Doctors will prescribe more antibiotics for these infections than for any other type.
Five Things Physicians and Patients Should Question

1. **Don’t treat asymptomatic bacteruria with antibiotics.**

Inappropriate use of antibiotics to treat asymptomatic bacteruria (ASB), or a significant number of bacteria in the urine that occurs without symptoms such as burning or frequent urination, is a major contributor to antibiotic overuse in patients. With the exception of pregnant patients, patients undergoing prostate surgery or other invasive urological surgery, and kidney or kidney pancreas organ transplant patients within the first year of receiving the transplant, use of antibiotics to treat ASB is not clinically beneficial and does not improve morbidity or mortality. The presence of a urinary catheter increases the risk of bacteruria, however, antibiotic use does not decrease the incidence of symptomatic catheter-associated urinary tract infection (CAUTI), and unless there are symptoms referable to the urinary tract or symptoms with no identifiable cause, catheter-associated asymptomatic bacteruria (CA-ASB) does not require screening and antibiotic therapy. The overtreatment of ASB with antibiotics is not only costly, but can lead to C. difficile infection and the emergence of resistant pathogens, raising issues of patient safety and quality.

Avoid prescribing antibiotics for upper respiratory infections.

The majority of acute upper respiratory infections (URIs) are viral in etiology and the use of antibiotic treatment is ineffective, inappropriate and potentially harmful. However, proven infection by Group A Streptococcal disease (Strep throat) and pertussis (whooping cough) should be treated with antibiotic therapy. Symptomatic treatment for URIs should be directed to maximize relief of the most prominent symptom[s]. It is important that health care providers have a dialogue with their patients and provide education about the consequences of misusing antibiotics in viral infections, which may lead to increased costs, antimicrobial resistance and adverse effects.
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
DEFENSES OF THE RESPIRATORY SYSTEM

• The body has a variety of host defense mechanisms.
  – Innate immune response - the cells and mechanisms that defend the host from infection by other organisms, in a non-specific manner
  – Adaptive immunity - the body's immune system prepares itself for future challenges

• The respiratory system has significant defenses.
  – The upper respiratory tract has:
    • Mucociliary escalator.
    • Coughing.
  – The lower respiratory tract has:
    • Alveolar macrophages.
PATHOGENS OF THE RESPIRATORY SYSTEM

- 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 source, water, air, etc.
- 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.
INFECTIONS OF THE UPPER RESPIRATORY TRACT

• Laryngitis & Epiglottitis
• Otitis media, mastoiditis, and sinusitis
• Pharyngitis
• Scarlet fever
• Diphtheria
• Pertussis
Laryngitis is swelling and irritation (inflammation) of the voice box (larynx) that is usually associated with hoarseness or loss of voice.

- Rhinoviruses
- Parainfluenza viruses
- Respiratory syncytial virus
- Adenoviruses
- Influenza viruses
- Measles virus
- Mumps virus
- *Bordetella pertussis*
- Varicella-zoster virus.
EPIGLOTTITIS

• Usually young unimmunized children presented with dysphagia, and respiratory distress
• *H. influenzae* (++)
• *H. parainfluenzae*
• *S. pneumoniae*
• *Streptococcus* group A
• Viral

Antibiotic Treatment:
- Ceftriaxone/Cefotaxime
- Amoxi/clav
Otitis media - general term for infection or inflammation of the ear - fluid/exudates/pus in the middle ear
ACUTE OTITIS MEDIA

- *S. pneumoniae*
- *H. influenzae*
- *Streptococcus pyogenes*
- *S. aureus*
- *Moraxella catarrhalis*
- Viral and fungal
- Tympanocentesis in certain circumstances:
  - Neonates <6 weeks
  - Failure of Tx
  - Immunosuppressed
ACUTE OTITIS MEDIA
Antibiotic treatment

• Antibiotic is not always necessary (symptomatic treatment).

• **Amoxicillin** is the first choice of antibiotic therapy; if amoxicillin is contraindicated, **azithromycin** is the appropriate first-line therapy.

• For AOM that is unresponsive to amoxicillin after 72 hours of therapy, administer **amoxicillin-clavulanate** or azithromycin.

• Patients with significant, persistent symptoms on high-dose amoxicillin-clavulanate or azithromycin may respond to intramuscular **ceftriaxone**.
SINUSITIS
<table>
<thead>
<tr>
<th>SINUSITIS</th>
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<tbody>
<tr>
<td><strong>Acute sinusitis</strong></td>
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<tr>
<td>- Viral (+++)</td>
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<tr>
<td>- <em>S. pneumoniae</em></td>
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<tr>
<td>- <em>H. influenzae</em></td>
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<tr>
<td>- <em>M. catarrhalis</em></td>
</tr>
<tr>
<td>- <em>S. aureus</em> (sphenoid)</td>
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</table>

| **Chronic sinusitis** |
| - *S. pneumoniae* |
| - *H. influenzae* |
| - *M. catarrhalis* |
| - Oral anaerobes |
| - Fungus |
Acute bacterial sinusitis. Axial CT scan (A) shows an air-fluid level in the right antrum. The attenuation of this fluid is less than that of muscle and typically is watery sinus secretions. This could represent an acutely obstructed sinus, a sinus with poor drainage in a chronically supine (unconscious) patient, or a patient who had a recent antral washing for sinusitis. Coronal CT scan (B) shows a typical air-fluid level in the left antrum with minimal mucosal thickening and obstruction of the ostiomeatal unit. Some mucosal disease is also present in the left ethmoid and right maxillary sinuses. Clinically, this patient had acute sinusitis. (From Som PM, Curtin HD: Head and neck imaging, ed 5, Philadelphia, 2011, Elsevier, 2011, p 174, Fig. 3-10.)
Acute bacterial sinusitis. Axial contrast-enhanced CT scans of three different patients. A, Enhancement of the inflamed mucosa within the left maxillary sinus. There is a zone of water attenuation separating this mucosa from the bony wall of the sinus. This zone is submucosal edema. There are also water attenuation secretions within the sinus cavity that represent increased surface secretions from the inflamed mucosa. This is the typical picture of sinus inflammation. (From Som PM, Curtin HD: Head and neck imaging, ed 5, Philadelphia, 2011, Elsevier, 2011, p 168, Fig. 3-2.)
SINUSITIS

• Acute sinusitis (duration range, 1–33 days) usually is caused by a viral infection associated with the common cold; symptoms include nasal congestion, purulent nasal discharge, maxillary tooth pain, facial pain, fever, and ear pain.

• Acute bacterial sinusitis can develop secondary to a viral upper respiratory infection (URI); however, fewer than 2% of viral URIs are complicated by bacterial rhinosinusitis.
SINUSITIS

- Given the similar radiographic appearance of viral sinusitis and bacterial sinusitis, imaging is not helpful.
- Antibiotics should be reserved for patients whose symptoms persist for >10 days, are severe (i.e., fever >39°C, purulent nasal discharge, facial pain for >3 consecutive days), or deteriorate after initial improvement.
- **Amoxicillin-clavulanate** is the preferred agent if antibiotics are necessary
PHARYNGITIS

- Late fall, winter, early spring
- 5 to 15 years (++)
- Erythema, edema, and/or exudates
- Tender, enlarged >1 cm lymph nodes
- Fever > 38.4º C
PHARYNGITIS

- Etiology
- Viral is the most common
  - Enterovirus, HSV, EBV, HIV, Respiratory viruses
- Bacterial
  - Group A *Streptococcus*
  - *Neisseria gonorrhoeae*
  - Anaerobic bacteria (e.g. Lemierre's syndrome)
  - *Corynebacterium diphtheriae*
PHARYNGITIS

• Pharyngitis most often is viral; a viral etiology is more likely in patients with associated cough, nasal congestion, conjunctivitis, or oral ulcers or vesicles.

• Patients with fewer than three Centor criteria (i.e., fever by history, tonsillar exudates, tender anterior cervical adenopathy, absence of cough) have a low probability of group A streptococcal infection and do not require further testing.

• Antibiotics (e.g., penicillin, amoxicillin) should be prescribed only if group A streptococcal pharyngitis is confirmed.
PHARYNGITIS

- Treatment
  - First line
    - Penicillin G Benzathine
      - 1.2 million units IM x1 (adults)
    - Amoxicillin
  - Alternatives
    - First generation oral cephalosporin
    - Macrolide (?)
  - 10 days of treatment (?)
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

• 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

- Mortality is highest in infants and children under 1 year old.
- Immunization against pertussis started in the 1940s, and in the 60s in Portugal
  - 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
  – Paroxysmal Stage 1-6 weeks
  – Convalescent Stage 3-6 weeks
• Complication of pertussis can lead to superinfection with
  *Streptococcus* pneumonia.
PERTUSSIS: Diagnosis

• A confirmed case is defined as one of the following:
  – Any cough illness in which *B. pertussis* is isolated and cultured
  – A case consistent with the clinical case definition confirmed by polymerase chain reaction (PCR) assay findings
  – Serologic antibody titer testing is available, but often needs to be compared with results 1-2 weeks later and thus is not commonly helpful
PERTUSSIS: Treatment

• Antibiotics can be used in the early stages.
  – Limits the spread of infection
  – *Azithromycin* is the choice for all ages

• Once the paroxysmal stage is reached, therapy is only supportive.

• Vaccination is the best option.
• **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
VIRAL INFECTIONS OF THE UPPER RESPIRATORY TRACT

• 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.
VIRAL INFECTIONS OF THE UPPER RESPIRATORY TRACT

- 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.
Epstein-Barr Virus
Infectious mononucleosis and Epstein-Barr virus

- EBV is a gamma herpes virus
  - Two distinct types of EBV:
    - type 1 (type A): more prevalent worldwide
    - type 2 (type B): more common in Africa
- In developing countries, subclinical infection in childhood is virtually universal.
- In developed countries, primary infection may be delayed until early adult life.
- The virus is acquired from asymptomatic excreters via saliva, by droplet infection, or by kissing.
- EBV is not highly contagious, isolation is unnecessary.
DISEASE ASSOCIATION

1. Infectious Mononucleosis
2. Burkitt's lymphoma
3. Nasopharyngeal carcinoma
4. Lymphoproliferative disease and lymphoma in the immunosuppressed.
5. X-linked lymphoproliferative syndrome
6. Chronic infectious mononucleosis
7. Oral leukoplakia in AIDS patients
8. Chronic interstitial pneumonitis in AIDS patients.
INFECTIOUS MONONUCLEOSIS

• Primary EBV infection is usually subclinical in childhood. However in adolescents and adults, there is a 50% chance that the syndrome of infectious mononucleosis (IM) will develop.

• IM is usually a self-limited disease which consists of fever, lymphadenopathy and splenomegaly. In some patients jaundice may be seen which is due to hepatitis. Atypical lymphocytes are present in the blood.

• Complications occur rarely but may be serious e.g. splenic rupture, meningoencephalitis, and pharyngeal obstruction.

• In some patients, chronic IM may occur where eventually the patient dies of lymphoproliferative disease or lymphoma.
INFECTIOUS MONONUCLEOSIS

Exudative pharyngotonsillitis
INFECTIONOUS MONONUCLEOSIS

• Whereas ~90% of cases of IM are due to EBV, 5–10% of cases are due to Cytomegalovirus (CMV).
• CMV is the most common cause of heterophile-negative mononucleosis.
• Less common causes: rubella, Toxoplasma, HIV, herpesvirus 6, hepatitis viruses and drug reactions.
# Complications of Epstein–Barr Virus Infection

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
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<tbody>
<tr>
<td>• Severe pharyngeal oedema</td>
<td>• Prolonged post-viral fatigue (10%)</td>
</tr>
<tr>
<td>• Antibiotic-induced rash (80–90% with ampicillin)</td>
<td>• Jaundice (&lt; 10%)</td>
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<tr>
<td>• Hepatitis (80%)</td>
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<tr>
<td><strong>Uncommon</strong></td>
<td></td>
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<tr>
<td><strong>Neurological</strong></td>
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<tr>
<td>• Cranial nerve palsies</td>
<td>• Transverse myelitis</td>
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<tr>
<td>• Polyneuritis</td>
<td>• Meningoencephalitis</td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
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<tr>
<td>• Haemolytic anaemia</td>
<td>• Thrombocytopenia</td>
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<tr>
<td><strong>Renal</strong></td>
<td></td>
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<tr>
<td>• Abnormalities on urinalysis</td>
<td>• Interstitial nephritis</td>
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<tr>
<td><strong>Cardiac</strong></td>
<td></td>
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<tr>
<td>• Myocarditis</td>
<td>• Pericarditis</td>
</tr>
<tr>
<td>• ECG abnormalities</td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td></td>
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<tr>
<td>• Ruptured spleen</td>
<td>• X-linked lymphoproliferative syndrome</td>
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<tr>
<td>• Respiratory obstruction</td>
<td></td>
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<tr>
<td>• Agranulocytosis</td>
<td></td>
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<tr>
<td><strong>EBV-associated malignancy</strong></td>
<td></td>
</tr>
<tr>
<td>• Nasopharyngeal carcinoma</td>
<td>• Primary CNS lymphoma</td>
</tr>
<tr>
<td>• Burkitt’s lymphoma</td>
<td>• Lymphoproliferative disease in immunocompromised</td>
</tr>
<tr>
<td>• Hodgkin’s disease (certain subtypes only)</td>
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</table>
INFECTIOUS MONONUCLEOSIS

Cervical lymphadenopathy

Hepatosplenomegaly
INFECTION MONONUCLEOSIS

IM with rash after treatment with amoxicillin or ampicillin
Epstein–Barr Virus (Mononucleosis and Lymphoproliferative Disorders)
Katz, Ben Z., Principles and Practice of Pediatric Infectious Diseases, 208, 1059-1065.e6
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MOLECULAR BIOLOGY: LATENCY

• Latently infected B cells are the primary reservoir of EBV in the body.
• >100 gene products may be expressed during active viral replication, only 11 are expressed during viral latency.
• In this way, the virus limits cytotoxic T-cell recognition of EBV-infected cells.
In children under 10 years the illness is mild and short-lived, but in adults over 30 years of age it can be severe and prolonged.

**Investigations**

**Atypical lymphocytes** are common in EBV infection but also occur in other causes of IM. The most commonly used diagnostic criteria is the presence of 50% lymphocytes (at least 10% atypical).

Acute EBV infection diagnosis is usually made by the heterophil antibody test and/or detection of anti-EBV VCA IgM.
INFECTIOUS MONONUCLEOSIS: LAB

• A 'heterophile' antibody is present during the acute illness and convalescence, agglutinates erythrocytes of other species, e.g. sheep and horse.

• Detected by the classical Paul-Bunnell titration or a more convenient slide test such as the 'Monotest'.
INFECTIOUS MONONUCLEOSIS: LAB

• Specific EBV serology (immunofluorescence) can be used to confirm the diagnosis if necessary.
  – Acute infection is characterized by IgM antibodies against the viral capsid, antibodies to EBV early antigen and the initial absence of antibodies to EBV nuclear antigen (anti-EBNA).
  – Seroconversion of anti-EBNA at approximately 1 month after the initial illness may confirm the diagnosis in retrospect.

• CNS infections may be diagnosed by detection of viral DNA in cerebrospinal fluid.
# Antibodies in EBV Infection

<table>
<thead>
<tr>
<th>Infection</th>
<th>VCA IgG</th>
<th>VCA IgM</th>
<th>EA</th>
<th>EBNA</th>
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<tbody>
<tr>
<td>No previous infection</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute infection</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Recent infection</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Past infection</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
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</table>
Specific EBV antibodies

response to viral capsid antigen (VCA) is divided because of the significant differences noted according to age of the patient.
I.M. - TREATMENT

• Largely symptomatic
• If a throat culture yields a β-haemolytic *Streptococcus*, a course of penicillin should **NOT** be prescribed (colonization, not infection).
  – ampicillin or amoxicillin in this condition commonly causes an itchy macular rash, and should also be avoided.
• When pharyngeal edema is severe, a short course of corticosteroids, e.g. prednisolone 30 mg daily for 5 days, may help.
  – Some advise using also metronidazole
• Antivirals are not sufficiently active against EBV.
I.M. - EVOLUTION

• Return to work or school is governed by the patient's physical fitness.

• Contact sports should be avoided until splenomegaly has completely resolved because of the danger of splenic rupture.

• 10% of patients with IM suffer a chronic relapsing syndrome.