

## Respiratory Infections

Respiratory infections are a common cause of acute illnesses, especially in pediatrics. Infections are frequently divided into infections that cause problems in the upper respiratory tract (above the epiglottis; for example pharyngitis, croup, otitis media and sinusitis) or infections of the lower respiratory tract (below the epiglottis) such as bronchitis, bronchiolitis, bronchopneumonia (including community acquired, aspiration, hospital acquired (nosocomial) pneumonias).

Pneumonia is the #1 cause of death due to infectious diseases in the U.S. There are over 5.6 million cases annually and over \$9.7 billion dollars are spent annually for its management. Management of the patient is based on the patient acuity (e.g need for oxygen, work of breathing, degree of hypoxia etc); patients may be managed as an outpatient, admitted to the hospital, or admitted to the intensive care unit.

Pneumonia occurs because of inflammation in the lung parenchyma caused by bacteria, viruses or fungi that evade our normal host defenses. Particles in the upper airway can be aspirated or inhaled bypassing the normal mechanical protective mechanisms e.g. closure of the vocal cords, beating mucociliary cells- the “escalator”, and/or immune mechanisms such as alveolar macrophages, neutrophils (IL-8 produced by respiratory epithelium which stimulates migration of PMNs), antibody and complement. All of these cause inflammation but help also with the clearance of bacteria from the airway.

There are many pathogens that can cause community acquired pneumonia (CAP) and these will be detailed in this lecture. In general, in over 50% of the cases of pneumonia, the cause or etiology cannot be identified. Often blood cultures or sputum cultures are not revealing. The microbiologic cause of pneumonia is based on the patients risk factors e.g. age, sick contacts, underlying illnesses, epidemiologic exposures e.g. occupation (e.g farm worker), lifestyle (e.g. alcoholism or smoking) or place of residence (e.g. nursing home, day care, etc).

Bacterial causes of CAP include but are not limited to: *Streptococcus pneumoniae*, non-typeable *H. influenzae*, *S. aureus*, *Streptococcus pyogenes*, *N. meningitidis*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* (and other gram negative rods). Previously, pneumonias that caused a “classic picture” of acute illness (acute onset of fever, cough) with a focal, lobular infiltrate on chest xray were attributed to the bacterial etiologies above, specifically Streptococcal pneumonia. Other clinical presentations that were more indolent in nature and that presented with a diffuse interstitial pattern on chest xray were called “atypical”. However, recent studies have shown that this clinical differentiation does not help narrow the etiology of the pneumonia.

Other pathogens that cause CAP include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* species, influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, etc. The tables below nicely outline the epidemiologic conditions related to specific pathogens in patients with CAP.

**Table 6. Most common etiologies of community-acquired pneumonia.**

Patient type	Etiology
Outpatient	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Haemophilus influenzae</i> <i>Chlamydia pneumoniae</i> Respiratory viruses <sup>a</sup>
Inpatient (non-ICU)	<i>S. pneumoniae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i> <i>H. influenzae</i> <i>Legionella</i> species Aspiration Respiratory viruses <sup>a</sup>
Inpatient (ICU)	<i>S. pneumoniae</i> <i>Staphylococcus aureus</i> <i>Legionella</i> species Gram-negative bacilli <i>H. influenzae</i>

**NOTE.** Based on collective data from recent studies [171]. ICU, intensive care unit.

<sup>a</sup> Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

**Table 5.** Diagnostic studies for evaluation of community-acquired pneumonia.

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Baseline assessment
Chest radiography to substantiate diagnosis of pneumonia, to detect associated lung diseases, to gain insight into causative agent (in some cases), to assess severity, and as baseline to assess response
Outpatients
Sputum Gram stain and culture for conventional bacteria are optional
Inpatients
Determination of complete blood cell and differential counts
Serum creatinine, urea nitrogen, glucose, electrolyte, bilirubin, and liver enzyme values
HIV serological status for persons aged 15–54 years
O <sub>2</sub> saturation arterial blood gas values for selected patients
Blood cultures (×2; before treatment)
Gram stain and culture of sputum <sup>a</sup>
Test for <i>Mycobacterium tuberculosis</i> , with acid-fast bacilli staining and culture for selected patients, especially those with cough for >1 mo, other common symptoms, or suggestive radiographic changes
Test for <i>Legionella</i> in selected patients, including all seriously ill patients without an alternative diagnosis, especially if aged >40 years, immunocompromised, or nonresponsive to β-lactam antibiotics, if clinical features are suggestive of this diagnosis, or in outbreak settings
Thoracentesis with stain, culture, and determination of pH and leukocyte count differential (pleural fluid)
Alternative specimens to expectorated sputum
Aspirates of intubated patients, tracheostomy aspirates, and nasotracheal aspirates: manage as with expectorated sputum
Induced sputum: recommended for detection of <i>M. tuberculosis</i> or <i>Pneumocystis carinii</i>
Bronchoscopy (see text under Special Considerations: Pneumococcal Pneumonia)
Transtracheal aspiration: recommended only in cases of enigmatic pneumonia, to be done by persons skilled in the technique, preferably before antibiotic treatment
Optional
Additional cytological or microbiological tests, as listed in table 8, depending on clinical features, available resources, underlying conditions, and/or epidemiological associations of the patient
Serum: to be frozen and saved for serological analysis, if needed <sup>b</sup>

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<sup>a</sup> Should be deep-cough specimen obtained before antibiotic therapy. Gram stain should be interpreted by trained personnel and culture done only if specimen is adequate by cytological criteria, except for *Legionella* and mycobacteria. Consider diagnostic studies for endemic fungi and mycobacteria when clinical features suggest infection with these. For hospitalized patients with severe pneumonia or clinical features that suggest legionnaires' disease, perform culture and urinary antigen testing for *Legionella*. Inability to obtain specimens for diagnostic studies should not delay antibiotic treatment of acutely ill patients.

<sup>b</sup> Serological tests would include those for *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, or others (i.e., viruses, *Chlamydia psittaci*, or *Coxiella burnetii*), depending on the circumstances.

**Table 8. Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia.**

Condition	Commonly encountered pathogen(s)
Alcoholism	<i>Streptococcus pneumoniae</i> , oral anaerobes, <i>Klebsiella pneumoniae</i> , <i>Acinetobacter</i> species, <i>Mycobacterium tuberculosis</i>
COPD and/or smoking	<i>Haemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i> , <i>Legionella</i> species, <i>S. pneumoniae</i> , <i>Moraxella cararrhialis</i> , <i>Chlamydophila pneumoniae</i>
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, <i>M. tuberculosis</i> , atypical mycobacteria
Exposure to bat or bird droppings	<i>Histoplasma capsulatum</i>
Exposure to birds	<i>Chlamydophila psittaci</i> (if poultry: avian influenza)
Exposure to rabbits	<i>Francisella tularensis</i>
Exposure to farm animals or parturient cats	<i>Coxiella burnetti</i> (Q fever)
HIV infection (early)	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. tuberculosis</i>
HIV infection (late)	The pathogens listed for early infection plus <i>Pneumocystis jirovecii</i> , <i>Cryptococcus</i> , <i>Histoplasma</i> , <i>Aspergillus</i> , atypical mycobacteria (especially <i>Mycobacterium kansasii</i> ), <i>P. aeruginosa</i> , <i>H. influenzae</i>
Hotel or cruise ship stay in previous 2 weeks	<i>Legionella</i> species
Travel to or residence in southwestern United States	<i>Coccidioides</i> species, <i>Hantavirus</i>
Travel to or residence in Southeast and East Asia	<i>Burkholderia pseudomallei</i> , avian influenza, SARS
Influenza active in community	Influenza, <i>S. pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>H. influenzae</i>
Cough >2 weeks with whoop or posttussive vomiting	<i>Bordetella pertussis</i>
Structural lung disease (e.g., bronchiectasis)	<i>Pseudomonas aeruginosa</i> , <i>Burkholderia cepacia</i> , <i>S. aureus</i>
Injection drug use	<i>S. aureus</i> , anaerobes, <i>M. tuberculosis</i> , <i>S. pneumoniae</i>
Endobronchial obstruction	Anaerobes, <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i>
In context of bioterrorism	<i>Bacillus anthracis</i> (anthrax), <i>Yersinia pestis</i> (plague), <i>Francisella tularensis</i> (tularemia)

**NOTE.** CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.

### Microbial causes of community acquired pneumonia in childhood

Age	Etiologic agent	Clinical features
<b>Birth – 3 weeks</b>	Group B streptococci	Part of early onset sepsis; usually severe
	Gram negative enteric bacilli	Often nosocomial, usually after 1 week of age
	Cytomegalovirus (CMV)	Part of systemic infection with CMV
	<i>Listeria monocytogenes</i>	Part of early onset sepsis
	Herpes simplex virus	Part of disseminated infection
<b>3 weeks- 3 months</b>	<i>Chlamydia trachomatis</i>	Due to maternal genital infection; afebrile, interstitial pneumonia
	Respiratory syncycial virus (RSV)	Peak incidence 2-7 months of age; wheezing illness; rhinorrhea; mid-winter to early spring
	Parainfluenza virus type 3 (PIV)	Similar to RSV; affects slightly older infants, not epidemic in winter
	<i>Streptococcus pneumoniae</i>	Most likely cause of bacterial lobar pneumonia, may cause other presentation as well
	<i>Bordetella pertussis</i>	Primarily bronchitis; severe cases can have pneumonia
	<i>Staphylococcus aureus</i>	Severe disease; often with abscesses and effusions
<b>3 months - 5 years</b>	RSV, PIV, influenza, adenovirus, rhinovirus	Most common cause of pneumonia in younger children
	<i>Streptococcus pneumoniae</i>	Most likely causes of lobar pneumonia
	<i>Haemophilus influenzae</i>	Type b uncommon with vaccine use; non-typeable in developing world
	<i>Mycoplasma pneumoniae</i>	Pneumonia in older children in this age group
	<i>Mycobacterium tuberculosis</i> (Mtb)	Important cause of pneumonia in areas where Mtb is highly prevalent
<b>5-15 years</b>	<i>Mycoplasma pneumoniae</i>	Major cause of pneumonia in this age child; xray variable
	<i>Chlamydia pneumoniae</i>	Controversial, probably important cause of pneumonia in older children in this age group
	<i>Streptococcus pneumoniae</i>	Most likely cause of lobar pneumonia, may cause other presentations
	<i>Mycobacterium tuberculosis</i> (Mtb)	Common in high prevalence area, may be exacerbated by onset of puberty and pregnancy

## **Clinical Scenario #1 (Streptococcal pneumoniae)**

- Francisco is a 2 year old boy, previously well
- Presented with URI symptoms and fever to PMD in July
- Respiratory symptoms worsened, cxr revealed right sided pneumonia, WBC 24K with 80% PMN and 3% bands
- Initially treated with IV therapy without resolution in 4 days
- CT scan showed large right sided effusion

This is a typical patient that we see in pediatrics with pneumococcal pneumonia. Often the disease is complicated with effusions requiring either prolonged antibiotics or even a procedure to drain the effusion.

### Physiology and structure

As you learned previously, *Streptococcus pneumoniae* is a Gram positive diplococci which occurs in pairs or short chains. Its virulence is primarily due to the capsular polysaccharide of which there are approximately 85 capsular types.

### Pathogenesis and immunity

The **capsular polysaccharide** is the most important virulence factor. In addition, there are protein adhesins that allow binding to epithelial cells in the oropharynx. Secretory **IgA protease** inhibits function of secretory IgA (which normally binds bacteria to mucin to facilitate clearance from the respiratory tract). **Pneumolysin** - creates pores in and destroys ciliated epithelial cells and **hydrogen peroxide**, a reactive O<sub>2</sub> intermediate, causes tissue damage. *Streptococcus pneumoniae* also has **teichoic acid, peptidoglycan and pneumolysin** which activate complement.

### Epidemiology and clinical presentation

*Streptococcal pneumoniae* is a common cause of pneumonia, especially in the pediatric and elderly populations. However, the incidence is decreasing due to the recommendations for universal pneumococcal vaccination for all children starting at 2 months of age. This organism causes many clinical problems including pneumonia, meningitis, otitis media, sinusitis, bacteremia, pericarditis, and arthritis. The diagnosis may be confirmed by blood culture (positive in approximately 25% of cases), urine antigen test (this may result in false + tests if the patient was recently vaccinated), and sputum culture (difficult to obtain in pediatric patients).

### Treatment and prevention

Treatment: of streptococcal infections is usually with Beta-lactam antibiotics including penicillin, amoxicillin, etc. However, the incidence of resistant *Streptococcus pneumoniae* has significantly increased over the last 10 years. One must be aware of the rates of pneumococcal resistance in your hospital and outpatient setting before prescribing antibiotics for presumed pneumococcal pneumonia infection. Other antibacterials have activity against the pneumococcus however resistance is increasing to those antibiotics as well e.g.

cephalosporins, macrolides, quinolones. As previously mentioned, the incidence of disease has significantly decreased with the universal use of the pneumococcal vaccine, specifically the conjugated vaccine which has efficacy in children less than 2 years of age (in contrast to the 23 valent vaccine). Special populations at risk for pneumococcal disease (e.g. asplenic, sickle cell patients, HIV infected patients) should also receive pneumococcal vaccination.

### **Clinical Scenario #2 (*Mycoplasma pneumoniae*)**

- Myra is a 21 year old medical student living in the dorm room studying for exams
- She goes to student health complaining of low grade fever, headache, non-productive cough, sore throat and general malaise
- Her exam reveals mild fine inspiratory rales
- The doctor sends her for an x-ray that reveals bilateral infiltrates

This is the classic scenario for *Mycoplasma pneumoniae*, the so-called walking pneumonia. The x-ray appears worse than the patient looks clinically. *M. pneumoniae* symptoms (atypical pneumonia or tracheobronchitis) were first described in 1938 by Ryeman but the organism was not identified at the time. Infections with Mycoplasma usually occur in children 5-9 years of age and young adults.

### **Mycoplasma pneumoniae**

#### **Physiology and structure**

Mycoplasma is the smallest free-living bacteria. It does not have a cell wall, and the cell membrane contains sterols not present in other bacteria. Because it does not have a cell wall, this organism is resistant to “cell wall” antibiotics such as penicillins, cephalosporins, vancomycin, and others. *M. pneumoniae* is a strict aerobe and grows only on special enriched media. Mycoplasma grows slowly e.g. 1-6 hours generation time and most labs do not culture for this organism. Laboratory confirmation is usually by serology or PCR-research based. Bedside tests that suggest the diagnosis of mycoplasma include cold agglutinins (IgM antibodies that bind to the I antigen of the red cells). When the blood is put on ice, the I antigens appear on RBCs and the antibodies cause a snowflaky precipitate to form.

#### **Pathogenesis and immunity**

Mycoplasma has a unique protein, the P1 protein, that acts as an attachment factor and facilitates the attachment to the sialic receptors of the respiratory epithelium and to red cells. Mycoplasma is interesting because it remains extracellular and interacts with the cilia in the respiratory tract causing both the cilia and the epithelial cells to be destroyed which leads to loss of these cells and then interference of normal airway clearance which leads to contamination of the airway with microbes which cause mechanical irritation and then chronic cough.

*M. pneumoniae* also acts as a super antigen stimulating PMNs and macrophages to the site with subsequent release of cytokines including TNF  $\alpha$ , IL-1 and IL-6.

Immunity to Mycoplasma is local and systemic. IgA appears early and disappears by 4 weeks, IgG appears at 3-4 weeks. Testing using complement fixation techniques is difficult and lacks specificity. Antibody-directed tests such as enzyme-linked immunosorbent assays and immunofluorescence, are used more often. The production of cold-agglutinins, a non-specific reaction to the outer membrane of the glycolipids of the *M. pneumoniae* (e.g. IgM antibodies that bind to the I antigen on the surface of RBC's when cold) are a useful but nonspecific test. Cold agglutinins are positive in ~65% of symptomatic cases.

#### Epidemiology and clinical presentation

Unlike other respiratory infections, illness due to *M. pneumoniae* does not follow a seasonal pattern. Infections more commonly occur in children, young adults (e.g. it is the cause of 50% of the pneumonias for college age students). Infection is spread by droplets (hence outbreaks occur in close quarters e.g. college, military) and the incubation period is 2-3 weeks with infectious droplets being shed 2-8 days prior to developing symptoms.

Typically, *M. pneumoniae* produces a mild upper respiratory tract illness- a cold- especially in young children. Patients develop low-grade temperatures (100-102), malaise, headache, dry, non-productive cough that is worse at night and persists for weeks. Lower tract disease may occur in the form of tracheobronchitis and "atypical pneumonia" or walking pneumonia (since the xray (a diffuse interstitial infiltrate) appears worse than the clinical or laboratory exam of the patient e.g. normal WBC). These lower tract infections occur more often in adolescents suggesting a cellular immune response to this infection rather than antibody mediated. Some of the complications that have been noted with Mycoplasma infections and pneumonia include otitis media, erythema multiforme (red and white patchy rash often on hands), hemolytic anemia, myocarditis, pericarditis, neurologic abnormalities.

#### Treatment and prevention

Treatment is with erythromycin or tetracycline (or doxycycline- children over 9 years old). Prevention is difficult since disease is spread by droplets and close contact and organisms are shed for weeks. Isolation is not feasible. No vaccines are available.

### **Chlamydial pneumonias: trachomatis, pneumonia, and psittaci**

#### **Clinical scenario 3 (Chlamydial pneumonia)**

- JM 10 week old infant born to a 16 year old mom
- Pregnancy history limited due to lack of prenatal care but baby born full term, no complications, left hospital 2 days after birth

- Seen by pediatrician at 2 weeks old with eye discharge was given eye drops
- Returned to ER (2-4 weeks later): RR 60, cough but no fever
- CXR done and bloods drawn and child was admitted

This is an example of *Chlamydia trachomatis* pneumonia in an infant. You typically see diffuse infiltrates bilaterally with some perivascular cuffing. The baby's risk factor for acquiring this infection was his mother's history of a lack of prenatal care and the possibility that she carried the chlamydia due to an untreated genital infection. The baby received eyedrops which clear the infection locally without eradicating the organism systemically so the baby went on to develop pneumonia. There will be more information on Chlamydia to follow in the STD lecture.

### Microbiology

Chlamydia is an intracellular parasite because it uses the host energy, ATP, unlike other organisms. It resembles a Gram negative bacteria in that chlamydia has a trilaminar outer membrane that contains LPS even though it is not Gram(-).

Chlamydia species are unique for their two phase life cycle. The elementary body (EB) is the infectious yet metabolically inactive spore-like particle that enters the cell through various mechanisms including endocytosis via clathrin-coated pits. It is converted to the reticulate body (RB) that divides by binary fission in the host cell and is then converted back into elementary bodies for extrusion from the cell and infection of new cells.

Two genera in this family cause respiratory tract diseases, chlamydia (*trachomatis*) and chlamydophila (consisting of *pneumoniae* and *psittaci*). A single strain of *C. pneumoniae* is responsible for the clinical disease with this organism. The strain is called TWAR, named for the first two laboratory isolates of this chlamydial species (TW-183 and AR-39).

### Pathogenesis and immunity

Chlamydial species infect non-ciliated columnar, cuboidal, or transitional epithelial cells found in the respiratory tract. Organisms multiply in alveolar macrophages and perivascular and peribronchiolar infiltrates develop. Clinical manifestations are due to destruction of cells during replication and host inflammatory responses. Immunity is not long lasting. Organisms are not readily cultured and thus detection relies on serology or antigen tests (ELISA, DFA) or the more sensitive amplification tests now available (PCR).

### Epidemiology, clinical syndromes, prevention and treatment

#### *C. trachomatis*

Neonatal pneumonia due to *C. trachomatis* usually presents between 1-3 months of life (usually 6 weeks). Infants present with a staccato-like cough, rapid respiratory rate, and often do not have fever. On physical examination, wheezing

is rarely heard. Diagnostic evaluation reveals hyperinflation and diffuse infiltrates on chest radiograph and a peripheral eosinophilia.

Diagnosis may be made by culture or non-culture tests of the nasopharynx. Non-culture tests of the nasopharynx have a lower sensitivity rate and may yield negative results. An IgM antibody test for *C. trachomatis* with a titer of > 1:32 is strongly suggestive of disease. Children with disease consistent with *C. trachomatis* pneumonia should be started on therapy (erythromycin) while waiting for diagnostic test results. Infection in newborns may be prevented by screening and treating pregnant women.

### *C. pneumoniae*

Risk for infection increases with age such that by young adulthood, 50% of the population is seropositive for infection with *C. pneumoniae*. TWAR may cause pneumonia (up to 28% of school age pneumonias and <10% of adult cases of outpatient pneumonias), bronchitis and sinusitis (5% of cases) and infrequently pharyngitis (<1%). Asymptomatic carriage of *C. pneumoniae* has been documented. Disease may result after a prolonged incubation period of up to 21 days.

Respiratory disease due to *C. pneumoniae* often has an indolent course beginning with non-specific upper respiratory symptoms such as rhinorrhea or sore throat and progressing to chronic cough that may persist for weeks despite appropriate antibiotic therapy. Patients are usually afebrile. Chest radiographs often show a lobar consolidation but disease may also present as a diffuse interstitial pattern, or with bilateral involvement with pleural effusions and lymphadenopathy. Patients usually have a normal peripheral white blood cell count.

*C. pneumoniae* has been associated with “atypical pneumonias” as well as atherosclerotic disease. It is interesting to note the association of this pathogen with atherosclerotic heart disease. This was first discovered in 1993 by a pathologist (Dr. Store) in South Africa who was looking at atheromas of patients who had coronary artery disease and he discovered some structures that were later confirmed as elementary bodies of the TWAR strain. Other studies have linked *C.pneumoniae* to atherosclerotic heart disease in that they have shown chlamydia PCR tests positive from the atheromatous plaques. These same studies were not able to grow chlamydia in culture, the gold standard for making a chlamydia diagnosis. The other problem with the association is that studies have tried to use antibiotics to treat atherosclerotic heart disease to see whether it has any effect on cardiac outcome and, thus far, no significant change in cardiac events while on antibiotics has been shown. Future studies are planned as atherosclerotic heart disease is a major cause of death in the U.S.

Diagnosis of *C. pneumoniae* is usually made with serologic testing using microimmunofluorescence tests to detect *C. pneumoniae* specific antibody. IgM antibody develops within 4 weeks and IgG by 6 weeks. PCR testing of sputum, the pharynx or a pathologic specimen is very sensitive and provides a more prompt result. Treatment with standard courses of azithromycin or clarithromycin is often preferred to erythromycin (500 mg four times per day for up to 21 days) or doxycycline (100 mg twice a day for up to 21 days) due to ease of administration and fewer side effects. Either treatment has a clinical efficacy of > 90%. In clinical trials, the efficacy rate of levofloxacin (a quinolone) was 98%. Failures do occur and re-treatment may be necessary after a 10-14 day course.

### *C. psittaci*

Psittacosis, a Greek term meaning parrot, is the disease state associated with this species of chlamydia. It is so named because the initial cases of this type of pneumonia were first associated with sick parrots. Many types of birds may carry and transmit this disease through respiratory droplets. Clinical presentation is usually that of an atypical pneumonia in that the patient has mild clinical symptoms such as cough, fever, malaise and the chest radiograph appears worse than expected. Non-specific central nervous system findings may also be present such as headache, confusion, cranial nerve palsy (including sensorineural hearing loss), meningitis, and seizures. Hepatitis and pericarditis may be complications of this infection. On physical examination, many patients will have fever, pharyngeal erythema and rales on examination of the lungs. Horder's spots may appear on the skin. These spots are pink blanching maculopapular lesions. Chest radiographs may show consolidation, a reticular nodular pattern, and/or hilar lymphadenopathy.

Diagnosis of *C. psittaci* may be made by blood culture (within the first 4 days) or sputum culture within the first 2 weeks. However as this is hazardous to laboratory personnel, serologic testing is preferred. Titers of > 1:64 are diagnostic of infection. Treatment strategies include tetracycline 500 mg four times a day or doxycycline 100 mg twice a day for 10-21 days. Erythromycin is an alternative but is less efficacious. Most patients respond to therapy within 24 hours of starting medications.

### **Clinical scenario 4 (Legionnaires' disease)**

- Charlie is a 68 year old retired plumber who recently underwent a renal transplantation
- Felt great and was tinkering around his house updating his bathroom fixtures
- Came for follow up visit complaining of high fever, cough, chills and his wife said that he was acting confused at times
- Laboratory studies reveal WBC 35,000 with left shift, LDH >1000(Lactic dehydrogenase, very high here, indicates that there is probably some pulmonary process going on).

- Chest x-ray reveals multilobar process

### Legionella

*Legionella* is the cause of 2-6% of community acquired pneumonias. *Legionella* is uncommon among the pediatric population but is an important consideration in immunocompromised, hospitalized patients, and outbreak situations. Historically it was first recognized as an important pathogen during the 1976 outbreak of severe pneumonias and deaths among members of the American Legion convention in Philadelphia.

### Microbiology

There are 39 species and 60 serogroups however the bulk of the human disease is caused by *L. pneumophila* and *L. micdadei*. *Legionella* are pleomorphic gram negative bacilli and don't stain with common reagents and thus need Dieterle's silver stain. They are fastidious organisms and grow in supplemented media (iron salts, L-cysteine).

*Legionella* is a facultative intracellular ubiquitous aquatic saprophyte (live inside amoeba). Thus it is found contaminating sources of water e.g. air conditioning systems and water tanks.

### Pathogenesis and Immunity

*Legionella* is inhaled and multiplies within macrophages and monocytes in the alveoli (intracellular). It binds to the complement receptor on alveolar macrophages and gets into the cell by endocytosis. Phagolysosome fusion is prevented and thus the organisms survive within the cells. The bacilli proliferate in the lungs and produce proteolytic enzymes, phosphatase, lipase, and nuclease which kill the cell when the vacuole is lysed. This causes multifocal microabscess formation. Activated/sensitized T cells are needed to kill these organisms (cell mediated immunity). Humoral immunity also plays a limited role.

### Epidemiology

Disease due to legionella occurs sporadically and epidemically. Incidence peaks late summer to fall. People with greatest risk for disease are those with impaired cellular immunity and/or those with compromised pulmonary function e.g. elderly, transplants, neutropenic patients, smokers, alcoholics, etc and those at risk due to occupational exposure e.g. construction- working with moist environments and water systems (cooling towers, hot tubs, showers etc).

### Clinical Syndromes

Legionnaires' disease- Symptomatic infection due to *legionella* may present as two different syndromes -- pneumonia or influenza like illness. Legionnaires' disease is severe pneumonia due to *legionella*. Incubation period is up to 10 days and then symptoms manifest themselves abruptly with high fevers (105),

rigors, cough (non-productive), headache etc. The pneumonia is usually multilobar with areas of microabscesses. As the disease progresses it spreads from lobe to lobe. Extrapulmonary manifestations include diarrhea, abdominal pain, nausea, mental confusion or delirium. Laboratory evaluation reveals high white cell counts (10-20,000) with a left shift in the majority of cases. Liver and renal functions may also be affected. The overall mortality is 15-20% depending on the immune function of the host. Death is usually due to respiratory or renal failure and/or shock.

Pontiac Fever- due to *L. pneumophila* causes a self-limited febrile illness like the flu (fevers, chills, myalgia, headaches etc.). Symptoms last 2-5 days and resolve spontaneously. It is called Pontiac fever after the town, Pontiac, Michigan, in which workers developed these symptoms in 1968 and the Department of Health did a large investigation into the cause.

### Diagnosis

The rapid and moderately sensitive (70%) method of diagnosing *Legionella* is by using a direct fluorescent antibody test (DFA), in which fluorescein-labeled monoclonal or polyclonal antibodies are directed against *Legionella* species. *Legionella* can be cultured on special media, buffered charcoal-yeast extract agar. Commercially available antigen detection assays (urine test) using EIA or radioimmunoassays are available for detection of *L. pneumophila serogroup 1* only.

However, Legionellosis is usually diagnosed by serology with a fourfold or greater increase in antibody titer (1: 128 or greater) considered positive. However, as with other illnesses, antibody titers usually are not seen until 3 weeks into the illness. Titers may persist over prolonged periods (>1 year).

### Prevention and Treatment

Treatment of legionellosis is usually with a macrolide antibiotic (azithromycin, erythromycin) or levofloxacin (a quinolone).  $\beta$ -lactam antibiotics usually are not effective due to the production of  $\beta$ -lactamases.

Hyperchlorination and super-heating have been used to eliminate legionella bacilli from water supplies. Low levels of organisms can persist and usually don't cause disease. However, if complete elimination is necessary, continuous copper-silver ionization can be used.

### **Clinical scenario 5 (*Bordetella pertussis*)**

- Jerry, a 7 month old child, comes to clinic with a runny nose, sneezing and slightly irritable
- Diagnosed with URI
- Returns 2 weeks later because he is turning blue with coughing spells. Spells are worse at night, seems to have spasms and then he "whoops" for air.
- Examination reveals mildly dehydrated, not distressed, clear lung exam

- WBC reveals leukocytosis with lymphocytosis

## **Bordetella pertussis- Whooping cough**

### Introduction

*Bordetella pertussis* is the organism responsible for pertussis or whooping cough -- an acute respiratory infection marked by episodic spasmodic coughing in the paroxysmal phase. It causes significant clinical disease such as bronchopneumonia especially in young children (<6 months). A milder form of the disease is caused by *B. parapertussis*.

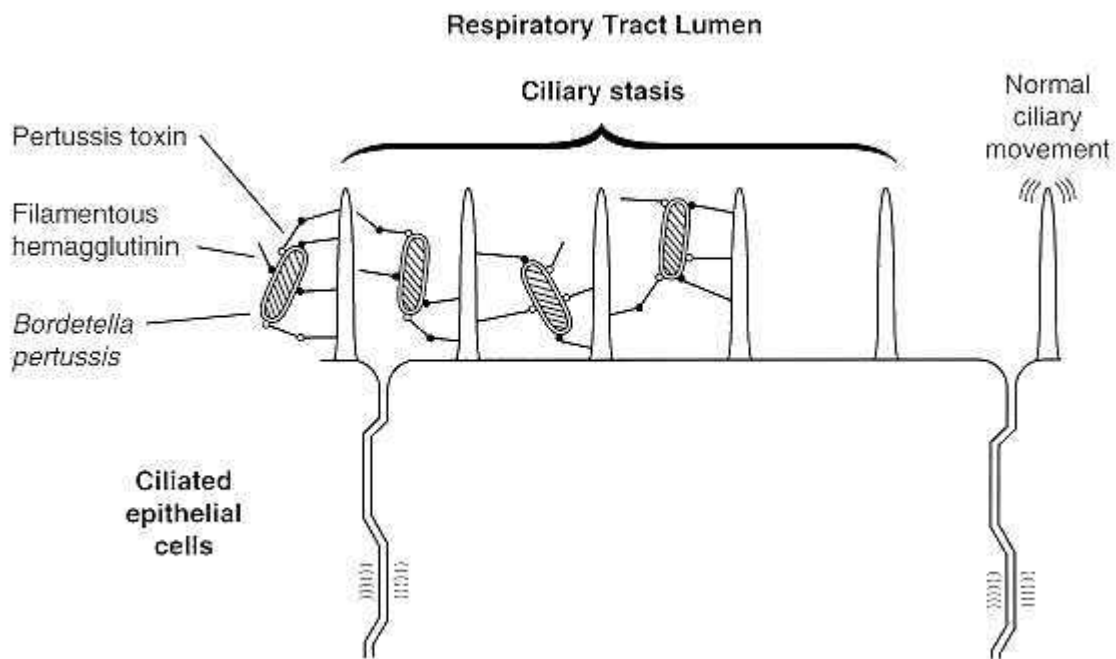
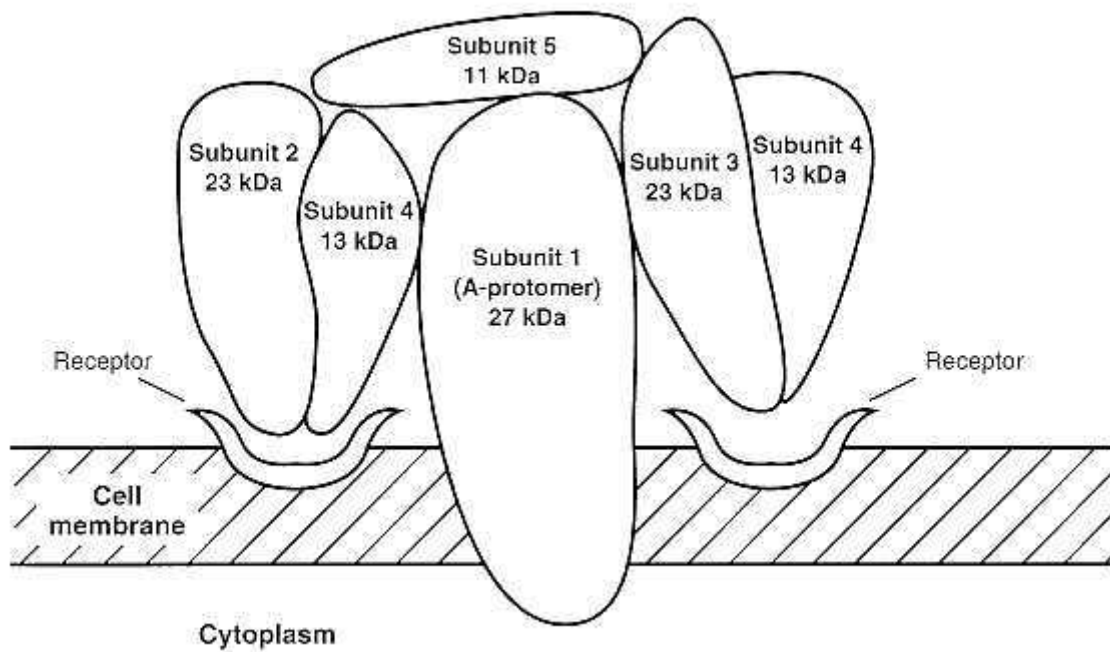
### Microbiology

*Bordetella* organisms are small, aerobic, fastidious, gram negative coccobacilli. Of the 7 species identified, 3 cause disease in man: *pertussis*, *parapertussis* and *bronchiseptica* (which usually causes disease in animals but can occasionally infect man). It requires special media (including blood, charcoal and starch- also called Bordet-Gengou agar after the investigators who first isolated the organism in culture in 1906) to grow and prolonged incubation periods. Culture can be used for diagnosis but care must be taken in obtaining a specimen (nasopharyngeal culture preferred), and immediately plating it on appropriate media. Serologic tests can be used following acute and convalescent titers.

### Pathogenesis and Immunity

Pertussis is spread primarily by respiratory droplets. The organism colonizes and rapidly multiplies in the mucus membrane of the respiratory tract. Bacteremia does not occur. Disease is caused by the toxins that cause local tissue damage.

1. *B. Pertussis* attaches to the ciliated epithelial cells in the respiratory tract. This is facilitated by the action of the pertussis toxin and filamentous hemagglutinin. **(See graphic)** Pertussis toxin functions in the adhesion process with its classic A-B subunit. The A unit has the toxic subunit (S1) and the B unit has 5 binding subunits (S2-5) which help with binding. S2 binds to the respiratory epithelium and S3 binds to phagocyte cells. The filamentous hemagglutinin binds to the respiratory epithelial cells and polymorphonuclear cells and facilitates uptake into those cells. Other adhesins (pili and pertactin) help bind the organism to cells.



## 2. Toxin production and disease manifestations

Pertussis contains many toxins: pertussis toxin, adenylate cyclase toxin, heat labile toxin. These will be described below.

a. Pertussis toxin

The S1 portion of the pertussis toxin has adenosine diphosphate (ADP)-riboylating activity for the surface G protein (whose function is to regulate adenylate cyclase activity). This causes the cyclic adenosine monophosphate (cAMP) levels to be unregulated resulting in increased respiratory secretions and mucus production characteristic of the paroxysmal state of pertussis.

b. Adenylate cyclase/hemolysin toxin and others

This toxin is activated by intracellular calmodulin and catalyzes the conversion of ATP to CAMP. Adenylate cyclase toxin also inhibits leukocyte chemotaxis, phagocytosis and killing.

c. Heat-labile toxin (dermonecrotic toxin)- causes local tissue destruction.

d. Tracheal cytotoxin destroys ciliated epithelial cells by inhibition of cilia movement and by causing extrusion of the cells. It also stimulates the release of IL-1 which causes fever and the release of nitric oxide from the respiratory cells which in turn kills the epithelial cells.

e. Lipid A and Lipid X are two lipopolysaccharides produced by pertussis. They can activate the alternative complement pathway and stimulate cytokine release.

Epidemiology

The incidence of pertussis has declined significantly since the introduction of an effective vaccine in 1949. Pertussis is still endemic around the world and although it primarily affects children under 1 year of age, there have been an increasing number of cases in older children and adults due to waning immunity.

Clinical Syndromes

Unvaccinated persons and young children are at highest risk for disease. Aerosolized droplets infect the host and after a 7-10 day incubation period, the patient develops symptomatic disease in three stages.

First Stage: Catarrhal stage

This stage resembles the common cold with rhinorrhea (runny nose), sneezing, malaise, anorexia, and low-grade fever.

Second Stage: Paroxysmal Stage

This stage occurs 1-2 weeks after symptoms have begun. During this stage, the patient characteristically coughs and “whoops” – that is a series of coughs followed by an inspiratory whoop. Vomiting after these coughing spasms is a common occurrence. Lymphocytosis is noted at this time. These symptoms are thought to be due to the intense inflammatory response (discussed above) in the airway which causes local obstruction and mucous plugging.

Third Stage: Convalescent Stage

After 2-4 weeks, the cough is subsiding however other complications occur such as pneumonia (often due to other organisms that colonize the airway e.g. *Streptococcus pneumoniae*), seizures, and encephalopathy.

### Prevention and treatment

Although *B. pertussis* is susceptible to erythromycin, antibiotics do not alter the course of the infection but may decrease the communicability. Thus treatment is usually supportive. Chemoprophylaxis is recommended for household contacts without regard to immune status or age.

Whole-cell inactivated vaccines and multivalent acellular vaccines combining diphtheria, pertussis, and tetanus (DPT) are commonly administered to most children in the U.S. and are considered between 80-85% effective. Acellular vaccines are preferred due to a lower incidence of side effects such as pain, erythema at the site, and fever. In January 2006, the Advisory Committee on Immunization Practices (ACIP) recommended that children 11-12 years of age receive a Tdap booster (Tetanus, diphtheria, and acellular pertussis vaccine). In adolescents 13-18 years of age who have missed their Td/Tdap booster dose, should receive a single dose of Tdap if they have completed the recommended childhood DTP/DTap vaccination series.

### Summary

Respiratory infections are a significant cause of morbidity in the U. S. as reflected in the number of hospital discharges and the amount of money spent on antibiotics and caring for patients with pneumonia.

Knowledge of the basic pathogens that cause pneumonia, the pathogenesis and immunity, clinical presentation and epidemiology as well as treatment and prevention are critical for the care of these patients.

Below find a table from IDSA/ ATS guidelines for management of CAP in 2007.

**Table 7. Recommended empirical antibiotics for community-acquired pneumonia.**

**Outpatient treatment**

1. **Previously healthy** and no use of antimicrobials within the previous 3 months

A macrolide (strong recommendation; level I evidence)

Doxycycline (weak recommendation; level III evidence)

2. **Presence of comorbidities** such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)

A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)

A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence)

3. In regions with a high rate (>25%) of infection with high-level (MIC  $\geq 16$   $\mu\text{g/mL}$ ) macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed above in (2) for patients without comorbidities (moderate recommendation; level III evidence)

**Inpatients, non-ICU treatment**

A respiratory fluoroquinolone (strong recommendation; level I evidence)

A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence)

**Inpatients, ICU treatment**

A  $\beta$ -lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) or a respiratory fluoroquinolone (level I evidence) (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

**Special concerns**

If *Pseudomonas* is a consideration

An antipneumococcal, antipseudomonal  $\beta$ -lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)

**or**

The above  $\beta$ -lactam plus an aminoglycoside and azithromycin

**or**

The above  $\beta$ -lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above  $\beta$ -lactam)

(moderate recommendation; level III evidence)

**If CA-MRSA is a consideration, add vancomycin or linezolid**

(moderate recommendation; level III evidence)