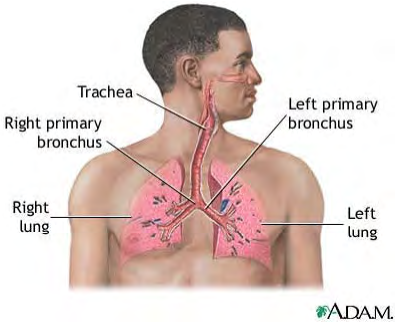
Respiratory infections

Community acquired pneumonia: a review of common pathogens

Natalie Neu, MD

MID 2009

Respiratory tract anatomy



CAP: general principles

- Pathogenesis
- Clinical presentation
- Diagnostic work up
- Specific organisms:
  - Bacteria (e.g. *S. pneumoniae*)
  - Viral (e.g. Influenza)
  - Fungi (e.g. Histoplasma)
  - Other (e.g. Mycobacterium tuberculosis)

Community acquired pneumonia: CAP

- 5.6 million cases annually = 8-15 per 1000 persons per year
- Very young and very old usually have highest rates of disease
- Seasonal and geographic variation: WINTER!
- 3 groups for patient management
  - Outpatient, inpatient (non- intensive care unit (ICU), and ICU
- Etiology:
  - *Streptococcus pneumoniae (#1)*
  - "Atypical organisms"
  - Viral (e.g. RSV, influenza, adenovirus)
  - Gram negative
  - Other

Pathogenesis

- Lungs Defenses:
  - Innate (mucocilary escalator/phagocytes and acquired host defenses lungs-antibodies from vaccines)
- Why do you get CAP?
  - Alteration in host defenses, virulent organism or large innoculum
- How do you get CAP?
  - Micro-aspiration, hematogenous, contiguous spread, or macro-aspiration

Predisposing host conditions

- Environmental: smoking, alcohalism (altered conscienciousness), toxic inhalations, travel/geographic
- Altered lung architecture/function: cystic fibrosis, chronic obstructive lung disease (COPD), immotile cilia syndrome, Kartagener's syndrome (ciliary dysfunction, situs inversus, sinusitis, bronchiectasis)
- Altered immune system: chemotherapy, transplant, HIV, malnutrition, uremia, etc

Microbiology of CAP bacteria

- "Typical" organisms
  - S. pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Group A streptococci, Moraxella catarrhalis, anaerobes, and aerobic gram-negative bacteria.
- "Atypical" refers to pneumonia caused by Legionella spp, Mycoplasma pneumoniae, Chlamydophila (formerly Chlamydia) pneumoniae, and C. psittaci

Microbial causes of CAP in childhood

Age	Organisms
Birth to 3 weeks	Group B Strepotococcal, Gram negative enteric bacilli, Cytomegalovirus, *Listeria monocytogenes*, HSV
3 weeks- 3 months	*Chlamydia trachomatis*, Respiratory syncycial virus (RSV), Parainfluenza virus type 3 (PIV), *Streptococcus pneumoniae*, *Bordetella pertussis*, *Staphylococcus aureus*
3 months - 5 years	RSV, PIV, influenza, adenovirus, rhinovirus, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*
5-15 years	*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*

IDSA/ATS Guidelines for CAP in Adults. CID 2007; 44 (suppl 2)

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

Patient type	Etiology
Outpatient	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* Respiratory viruses[a]
Inpatient (non-ICU)	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella* species Aspiration Respiratory viruses[a]
Inpatient (ICU)	*S. pneumoniae* *Staphylococcus aureus* *Legionella* species Gram-negative bacilli *H. influenzae*

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

[a] Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

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

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

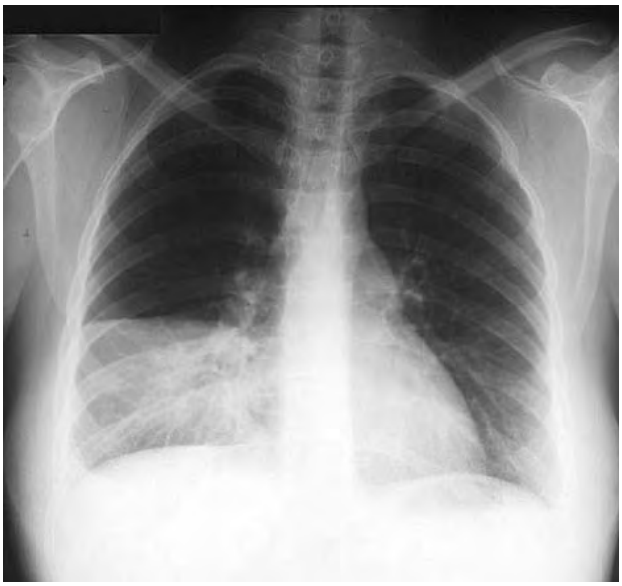
NOTE. CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.

Pneumonia: presentation and working up the etiology

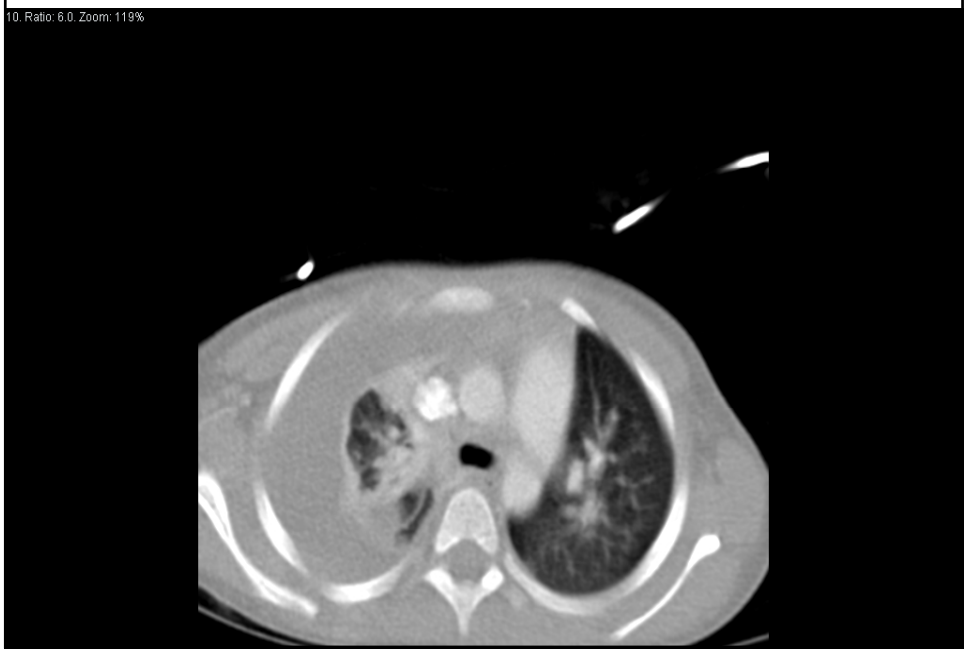
- Common complaints
  - Dyspnea, fever, cough (productive or not), chills, chest pain, myalgia, headache
- History
  - Age, co-morbidities, sick contacts, unusual exposures, social situation/support
- Physical exam findings
  - Oxygen saturation
  - Rales, tactile fremitus, decreased breath sounds, rhonchi
- Radiology
  - Confirming the diagnosis; may or may not help narrow the diagnosis e.g. *S. pneumonia:* lobar; *S. aureus:* multilobar/abscess; Mycoplasma- diffuse interstitial

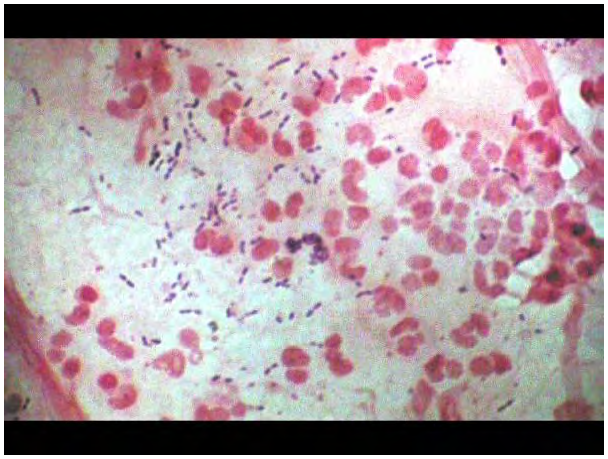
Clinical scenario 1

- Francisco is a 2 year old, 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



Complicated pneumonia with empyema





Streptococcus pneumoniae

- Gram-positive; oval or lancet-shaped, occur in pairs or short chains (diplococci)
- Capsular polysaccharide is most important virulence factor; approximately 90 capsular types
  - Most common serotypes are 6, 14, 18, 19, and 23
- Organism causes pneumonia, meningitis, otitis media, sinusitis, bacteremia, pericarditis, arthritis

From colonization to disease

- Adherence- cell wall proteins (phosphorylcholine) allow for adherence to receptor for platelet activating factor. Other binding sites include sialic acid and N-acetylgalactosamine b1-4 galactose
  - Faciliated by viral infections
- Secretory **IgA protease** - inhibits function of secretory IgA which normally binds bacteria to mucin to facilitate clearance from the respiratory tract
- Capsule- antiphagocytic
- Invasion-cell wall, adhesins, and the cytotoxin pneumolysin- promotes intra-alveolar replication, penetration of pneumococci from the alveoli into the interstitium, and dissemination of the organisms into the bloodstream and cell death
- Host inflammatory response- cell wall (lipoteichoic acid) initiates alternative complement pathway, induce production of cytokines, nitric oxide (tissue damage), and PAF and initiate influx of neutrophils

Risk factors for pneumococcal pneumonia

- Alcohol, smoking, and asthma
- Hyposplenism or splenectomy
- Immunocompromised (HIV, chemotherapy, etc)
- Others

Risk factors resistance to β-lactam antibiotics

- Age >65
- Recently taking antibiotics within 3 months
- Alcoholism
- Immune suppression
- Multiple medical co-morbidities
- Exposure to child in daycare

S. pneumoniae

- Diagnosis
  - Blood culture
    - (6-10% CAPs are bacteremia and 60% of these are S. pneumoniae)
  - Urine antigen test
  - Sputum culture
- Antimicrobial susceptibility testing is key especially
  - Penicillin: 60% susceptible, 20% intermediate, 20% resistant

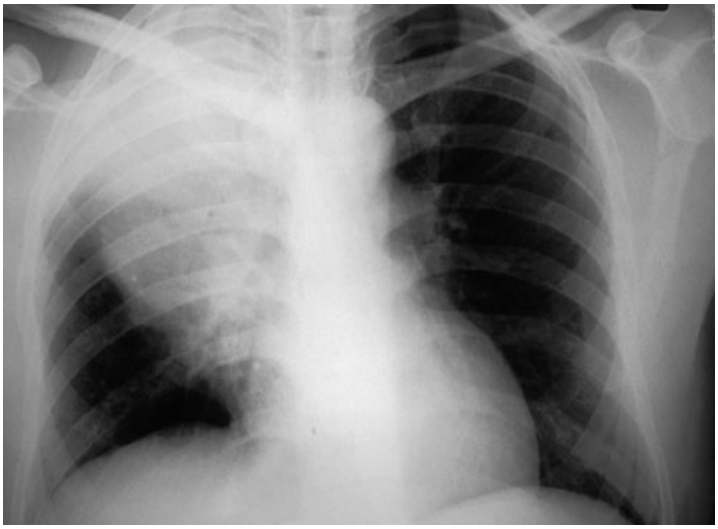
S. Pneumoniae treatment and prevention

- Treatment: Beta-lactam antibiotics
  - PCN Resistance classified by breakpoints
    - Meningitis (only a fraction of plasma concentration gets in to CSF):
      - Sensitive MIC $\leq$ 0.6
      - Intermediate MIC 0.1-1 mcg/ml
      - Resistant MIC $\geq$ 2 mcg/ml
    - Non-meningitis pneumococcal disease
      - Susceptible — MIC $\leq$2 mcg/mL
      - Intermediate — MIC =4 mcg/mL
      - Resistant — MIC $\geq$8 mcg/mL
  - Cephalosporins, vancomycin, macrolides, linezolid
- Prevention: Vaccines
  - Conjugated pneumococcal vaccine (Prevnar®)
  - 23 valent pneumococcal vaccine (Pneumovax®)

Clinical scenario 2

- 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- nothing impressive
- The Dr sends her for an xray that reveals bilateral infiltrates

Mycoplasma pneumonia



Mycoplasma

- Does not have a cell wall
- Cell membrane contains sterols not present in other bacteria
- Special enriched media needed for growth
- Laboratory cultures rarely done- diagnosis usually by serology (IgG)
- PCR testing not routinely available
- Bedside test- cold agglutinins

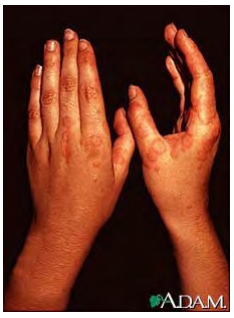
Mycoplasma- pathogenesis and immunity

- Toll-like receptor 2 important for binding to respiratory epithelium
- P1- protein attachment factor- facilitates attachment to sialic acid receptors of respiratory epithelium and RBC surface
- Remains extracellular
- Causes local destruction of cilia, interferes with normal airway clearance which leads to mechanical irritation and persistent cough
- Acts as a super antigen stimulating PMS's and macrophages to release cytokines (TNFα, IL1, and IL 6)

A common atypical pneumoia "Walking pneumonia"

- Lacks seasonal pattern, spread by droplet secretions
- Common in children and young adults
  - 7-20% of CAP especially for non-hospitalized cases
- Mild respiratory symptoms
- Complications: otitis media, erythema multiforme, hemolytic anemia, myocarditis, pericarditis, neurologic abnormalities
- Treatment: macrolides (erythromycin, azithromycin, clarithromycin) or fluoroquinolones (levofloxacin)

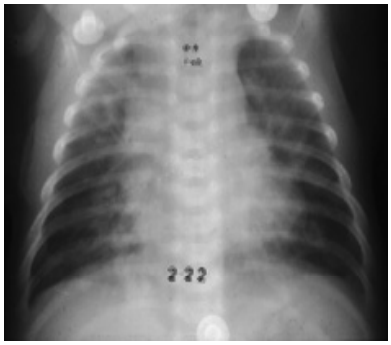
Erythema multiforme



Clinical scenario 3

- 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
- Seen by pediatrician at 2 weeks old with eye discharge was given eye drops
- Returned to ER: RR 60, cough but no fever
- Xray done and bloods drawn

C. trachomatis xray



Chlamydophila (Chlamydial) pneumonias: *trachomatis, pneumoniae, psittaci*

- Intracellular parasites- use host high energy phosphate compounds
- Trilaminar outer membrane which contains LPS
- Two phase life cycle- Elementary body (infectious) and reticulate body (divides by binary fission in the host)

Chlamydophila pneumonias

- Infect non-ciliated columnar cells
- Multiply in alveolar macrophages
- Perivascular and peribronchiolar infiltrates
- Clinical symptoms due to host immune response
- Immunity not long-lasting
- Diagnosis by serology- four fold rise in titer

C. trachomatis pneumonia

- Neonatal infection presents at 1-3 months of age
- Staccato-like cough, rapid respiratory rate
- NO FEVER
- Evaluation: minimal chest findings, xray hyperinflation and diffuse infiltrates, peripheral eosinophilia
- Treatment: erythromycin
- Prevention: maternal screening

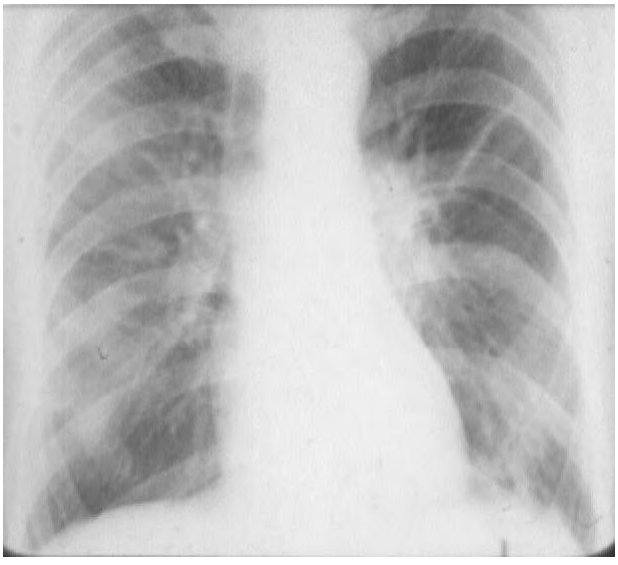
C. pneumoniae

- Single strain- TWAR
- Prolong incubation period
- Common in school age children and elderly (over 65)
- Indolent course-sore throat, chronic cough, no fever
- Chest xray variable (lobar, diffuse, bilateral)
- Diagnosis: PCR and serology
- Treatment: macrolide, doxycycline, levofloxacin

C. psittaci

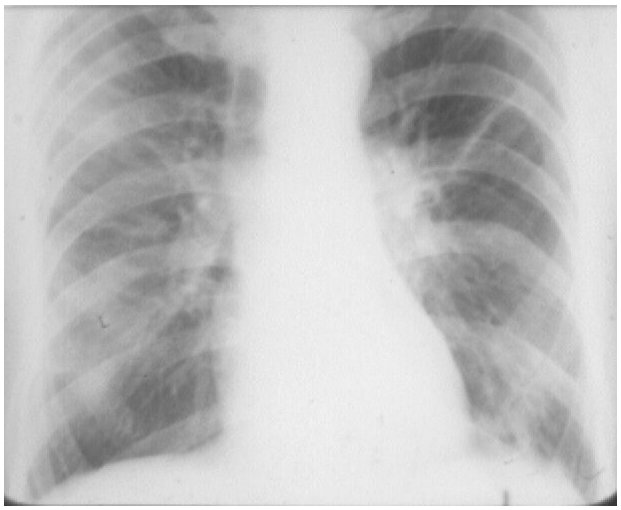
- History: Parrot exposure
- Mild clinical respiratory symptoms, fever, rash
- Concomitant symptoms: cns- headache, confusion, cranial nerve palsy, seizures; hepatitis; pericarditis
- Xray-consolidation, reticular nodular pattern, adenopathy
- Titers: > 1:64 diagnostic
- Treatment: doxy, tetracycline, erythromycin

Psittacosis

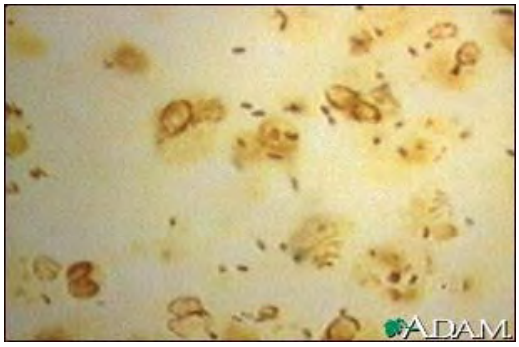


Clinical scenario 4

- 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
- Chest xray reveals multilobar process



Legionella species



The 1976 Legionnaire's Convention, Philadelphia, PA

- 29/180 patients died due to pneumonia
- Identification of a gram negative bacilli
- Epidemiologic link to being in the lobby of Hotel A; historical link to 1966 outbreak in a psychiatric hospital
- National panic- worries about biologic and chemical warfare- media frenzy
- 6 months to identify the organism

Legionella pneumophila and micdadei

- 2-6% community acquired pneumonias
- Risk: immunocompromised, hospitalized, and outbreak situations
- Gram negative bacilli- don't stain with common reagents
- 50 species and 70 serogroups- most common *L. pneumophila* and most common serogroups 1,4, 6
- Fastidious and grow on supplemented media
- Organisms contaminate water sources: air conditioning systems and water tanks

Legionella: pathogenesis and immunity

- Aspiration or inhalation of organism
- Flagellae and pili allow attachment to respiratory epithelium and macrophages
- Trafficking within cell due to dot (defective organelle trafficking) and icm (intracellular multiplication) genes which allow the organism to evade phagosome-lysosome fusion
- Intracellular replication facilitated by intracellular multiplication locus (Lgn-1) and by Mip
- Virulence factors: exotoxins, including a hemolysin, cytotoxin, deoxyribonuclease, ribonuclease, and various proteases cause destruction by killing the infected respiratory cells leading to formation of microabscesses
- Immunity primarily cell mediated immunity (T cells) (inhibited by gluocorticoids and immune suppressive agents e.g. transplant medications

Legionnaires disease

- Incubation period up to 10 days
- Clinical- influenza like illness or severe manifestation= pneumonia
- Fever (105), rigors, cough, headache
- Multilobular infiltrates and microabscesses
- Extrapulmonary manifestations: CNS, diarrhea, abdominal pain, nausea
- High white counts, abnormal liver, renal panel
- High mortality-15-20% depending on host

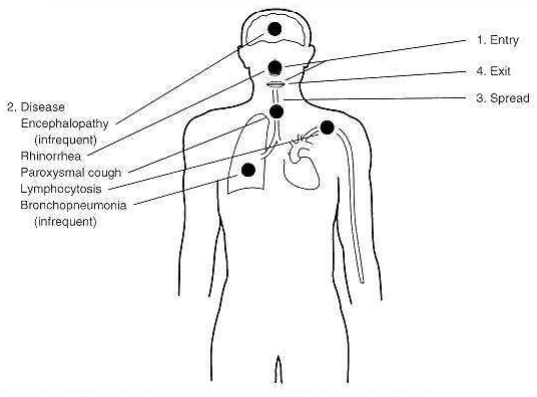
Legionella: Diagnosis, prevention and treatment

- Urine antigen detection assays- EIA for *L. pneumophila* only
- Serology >1:128 positive however late development of antibodies
- Culture on special media
- Treatment: macrolide or levofloxacin
- Prevention: hyperclorination, super heating, continuous copper-silver ionization

Clinical scenario 5 (Loyola Univ Medical Center)

- Jerry, a 7 month old child, comes to clinic with a running 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 leucocytosis with lymphocytosis

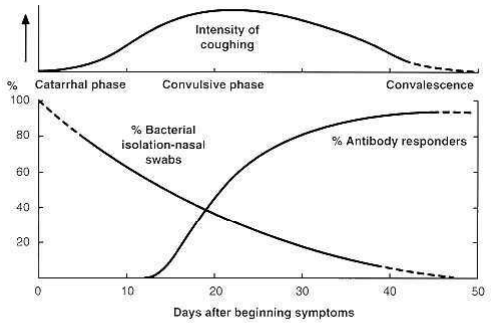
Bordetella pertussis



Pertussis

- Affects children under 1 and adults with waning immunity
- Three stages of disease:
  - Catarrhal
  - Paroxysmal
  - Convalescent

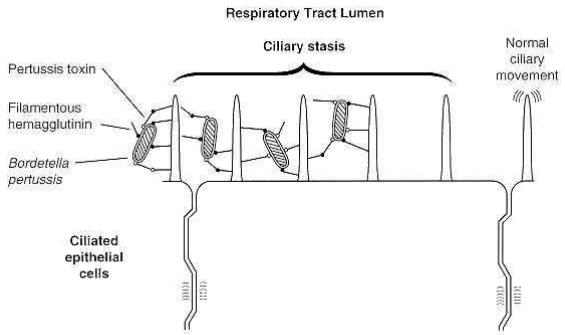
Pertussis clinical symptoms



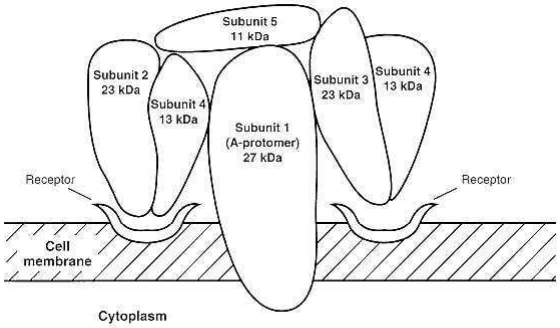
Bordetella pertussis "Whooping cough"

- Fastidious, gram negative coccobacilii
- *Pertussis, parapertussis, and bronchiseptica*
- Spread by respiratory droplets
- Rapid multiplication in mucus membrane
- No bacteremia
- Toxins cause local tissue damage

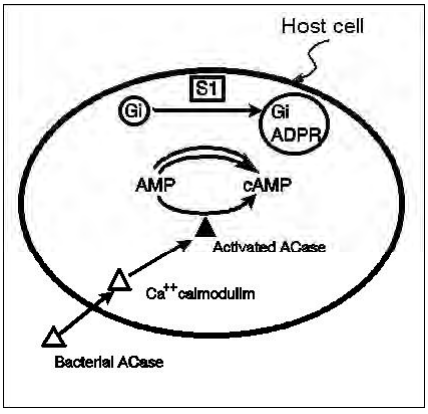
Binding and uptake by phagocytic cells



Pertussis toxin

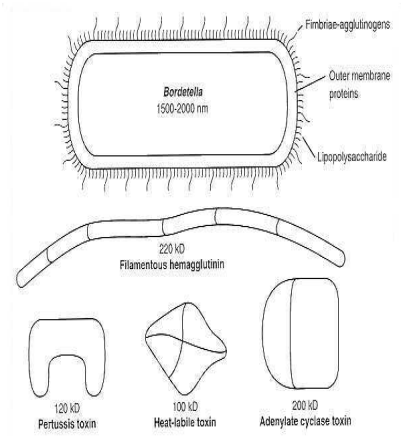


G protein and ADP riboyslation



Toxin production and pathophysiology

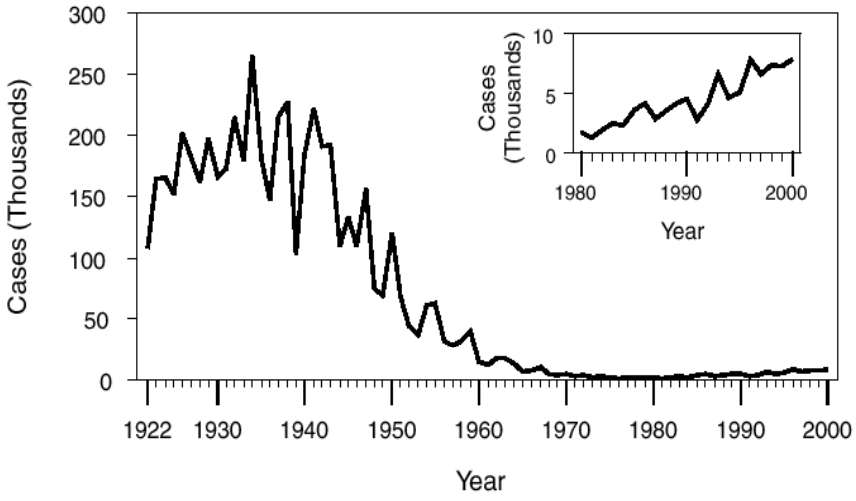
Pertussis toxin- ↑ CAMP	↑ secretions (paroxysmal stage)
Adenylate cyclase and hemolysin toxin	Inhibit WBC chemotaxis, phagocytosis, and killing
Heat-labile toxin	Local tissue destruction
Tracheal cytotoxin	Destroys ciliated cells, IL-1 (fever), NO (kills epithelial cells)
Lipid A and Lipid X	Activate alternative complement, cytokine release



Pertussis: diagnosis, Rx and prevention

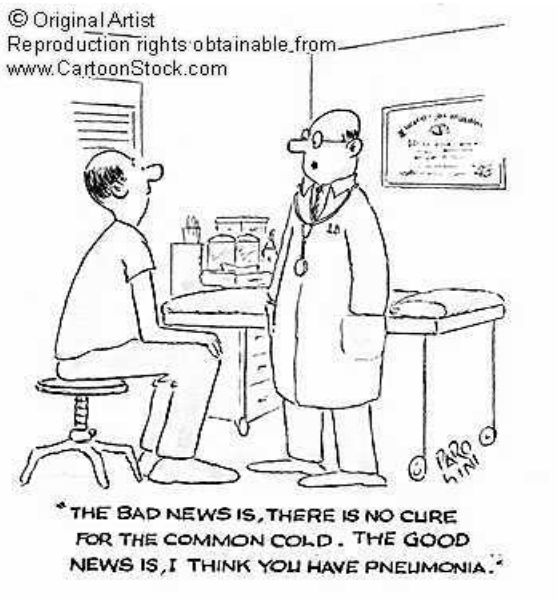
- Diagnosis:
  - Special media- Bordet-Gengou- blood, charcoal, and starch. Nasopharyngeal culture
  - Serologic testing: acute and convalescent titers
  - PCR testing
- Treatment- decrease symptoms and transmission- best if early in disease
  - Erythromycin or Macrolide (better tolerated, shorter course)
  - Alternative for some: trimethoprim-sulfamethoxazole
- Prevention
  - Antimicrobial prophylaxis- close contacts and high risk individuals
  - Vaccination- during childhood and booster vaccine for those over 18 (Tdap)

FIGURE 1. Number of reported pertussis cases, by year — United States, 1922–2000



Summary: Community acquired pneumonia CAP

- Understand historical elements, physical examination finding and exposures relative for CAP
- Inpatient or outpatient management
  - Perform diagnostic tests
- Empirical antimicrobial therapy
- Prevention: smoking cessation, vaccination, etc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"THE BAD NEWS IS, THERE IS NO CURE FOR THE COMMON COLD. THE GOOD NEWS IS, I THINK YOU HAVE PNEUMONIA."