Respiratory infections

Community acquired pneumonia: a review of common pathogens

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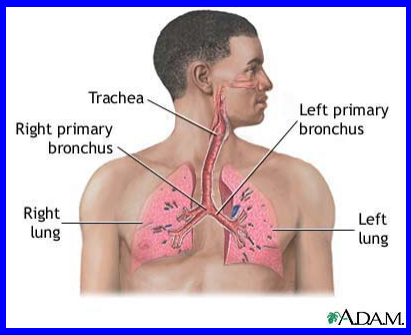
MID 2008

Respiratory tract anatomy



Community acquired pneumonia: CAP

- 5.6 million cases annually
- #1 cause of death due to infectious diseases in the U.S.
- $9.7 billion dollars annually
- 3 groups for patient management
  - Outpatient, inpatient (non- ICU), ICU
- Etiology:
  - *Streptococcus pneumoniae (#1)*
  - "Atypical organisms"
  - Viral (e.g. RSV, influenza, adenovirus)
  - Gram negative
  - Other

CAP: general principles

- Presentation
- Etiology
- Specific organisms and pneumonia
  - *Streptococcus pneumoniae*
  - Mycoplasma
  - Chlamydia
  - Legionella
  - Pertussis

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

Bartlett, J. G. et al. N Engl J Med 1995;333:1618-1624

Table 2. Microbiologic Pathogens in Community-Acquired Pneumonia.

Microbial Agent or Cause	Prevalence (%)	
	North American studies*	British Thoracic Society†
Bacteria		
Streptococcus pneumoniae	20–60	60–75
Haemophilus influenzae	3–10	4–5
Staphylococcus aureus	3–5	1–5
Gram-negative bacilli	3–10	Rare
Miscellaneous‡	3–5	—
Atypical agents	10–20	—
Legionella	2–8	2–5
Mycoplasma pneumoniae	1–6	5–18
Chlamydia pneumoniae	4–6	—
Viruses	2–15	8–16
Aspiration	6–10	—

*Based on 15 published reports from North America.[7-21] None of these studies used techniques adequate to detect anaerobes in respiratory secretions; these organisms account for 20 to 30 percent of cases in some reports.[3,6,7] *P. carinii* is excluded but may account for up to 15 percent in recent reports from urban centers.[20]

†Based on an analysis of 453 adults in a prospective study of community-acquired pneumonia in 25 British hospitals.[3,9,10] Dashes indicate that the pathogen was not included in the study.

‡Includes *Moraxella catarrhalis*; group A streptococcus, and *Neisseria meningitidis* (each accounting for 1 to 2 percent of cases).

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 carar-rhalis*, *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 *Pneumocys-tis 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.

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*

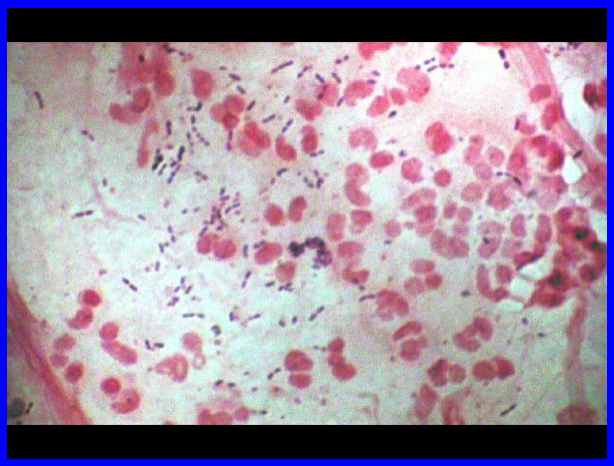
Clinical scenario 1

- 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 85 capsular types
- Decreasing incidence but remains the **most commonly isolated pathogen** in patients with pneumonia
- Organism causes pneumonia, meningitis, otitis media, sinusitis, bacteremia, pericarditis, arthritis



Structure, Virulence Factors and Pathogenesis

- Capsular polysaccharide is most important virulence factor; approximately 85 capsular types
- Protein adhesins: 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
- Hydrogen peroxide - reactive 02 intermediate causes tissue damage
- Teichoic acid, peptidoglycan and pneumolysin activate complement

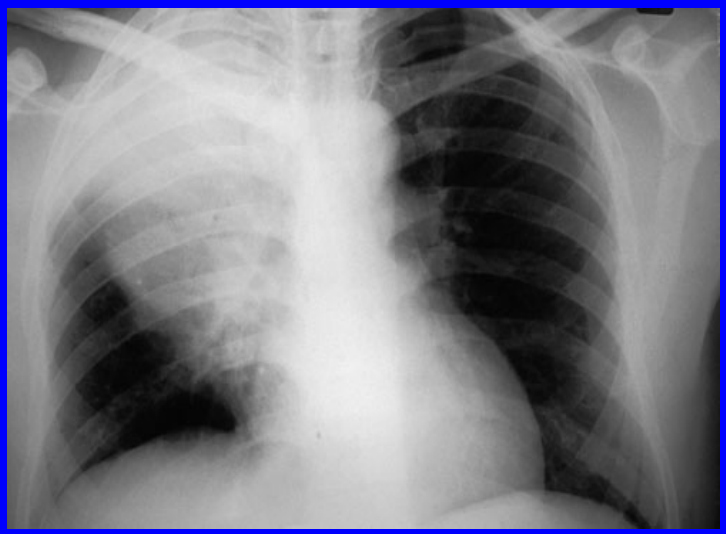
S. Pneumoniae Diagnosis, treatment and prevention

- Diagnosis:
  - Blood culture, urine antigen test, sputum culture
- Treatment: Beta-lactam antibiotics
  - Risk factors resistance in *Streptococcus pneumoniae*
    - Age >65, receipt of β-lactam therapy within 3 months, alcoholism, immune suppression, multiple medical co-morbidities, exposure to child in daycare
  - PCN Resistance classified by breakpoints
    - Sensitive MIC ≤ 0.6
    - Intermediate MIC 0.1-1 mcg/ml
    - Resistant MIC ≥ 2 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)
- Bedside test- cold agglutinins

Mycoplasma- pathogenesis and immunity

- 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)

Walking pneumonia

- Lacks seasonal pattern, spread by droplet secretions
- Common in children and young adults
- Mild respiratory symptoms
- Complications: otitis media, erythema multiforme, hemolytic anemia, myocarditis, pericarditis, neurologic abnormalities
- Treatment: erythromycin

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

Chlamydia trachomatis xray

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)

Chlamydial 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
- Associations: atherosclerotic heart disease
- Treatment: erythromycin
- Prevention: maternal screening

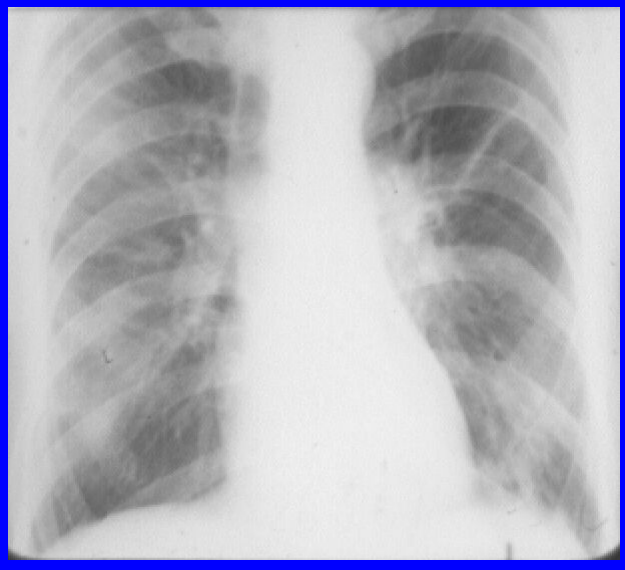
C. pneumoniae

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

C. psittaci

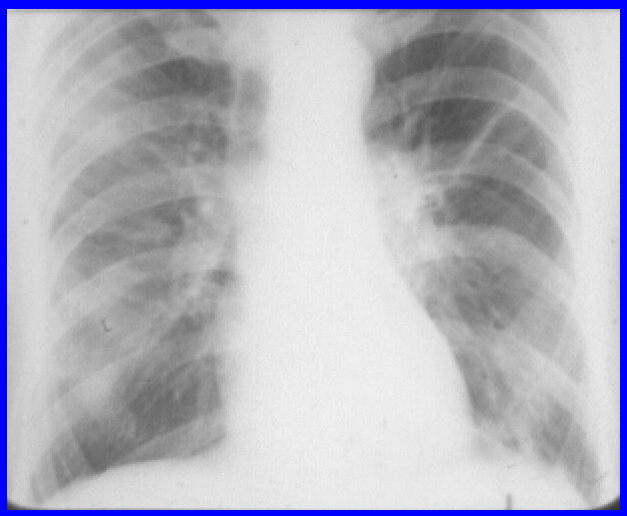
- History: Parrot exposure
- Mild clinical respiratory symptoms, fever, rash
- Concomitant symptoms: cns- headache, confusion, cranial nerve palsy, seizures; hepatitis; pericarditis
- Xray-consolidation, reticular nodular pattern, adenopathy
- Titers: > 1:64 diagnostic
- Treatment: doxy, tetracycline,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

Psittacosis

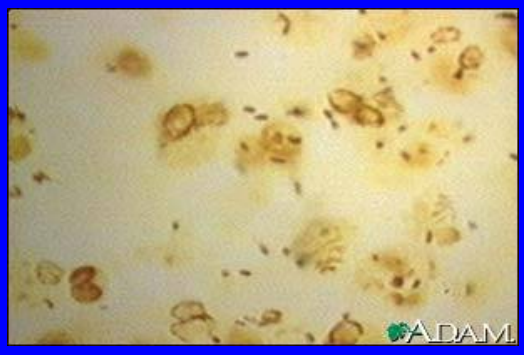


Clinical scenario 4

- 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
- Fastidious and grow on supplemented media
- Organisms contaminate water sources: air conditioning systems and water tanks

Legionella: pathogenesis and immunity

- Intracellular pathogen- multiply in macrophages and monocytes
- Proteolytic enzymes kill the infected respiratory cells leading to formation of microabscesses
- Immunity- Cell mediated immunity (T cells) needed for immune response

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

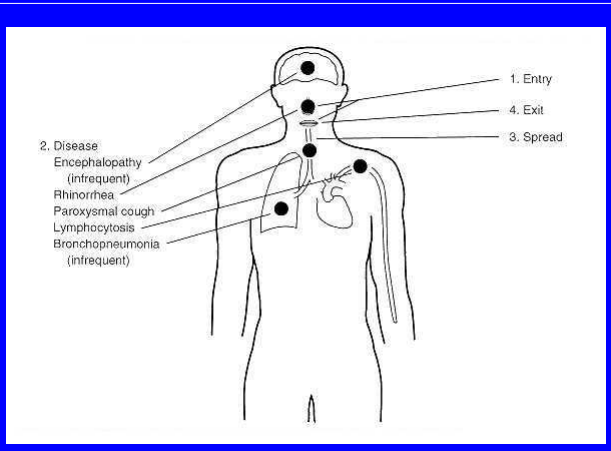
Legionella: Diagnosis, prevention and treatment

- 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

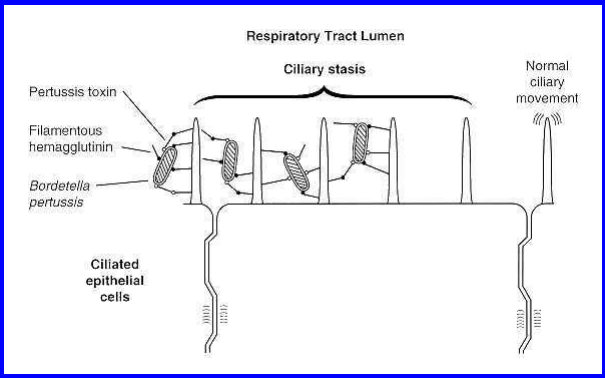
Bordetella pertussis



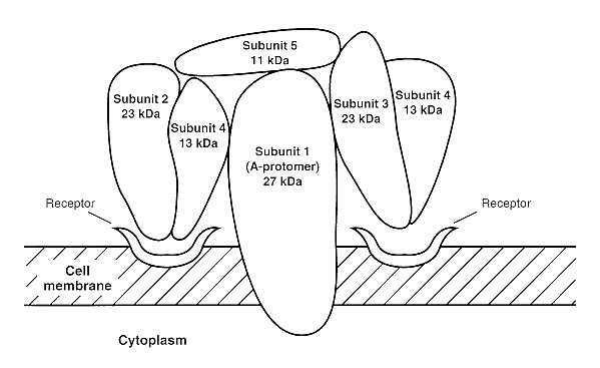
Bordetella pertussis "Whooping cough"

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

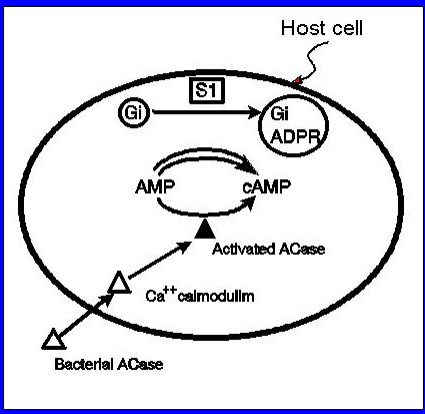
Binding and uptake by phagocytic cells



Pertussis toxin

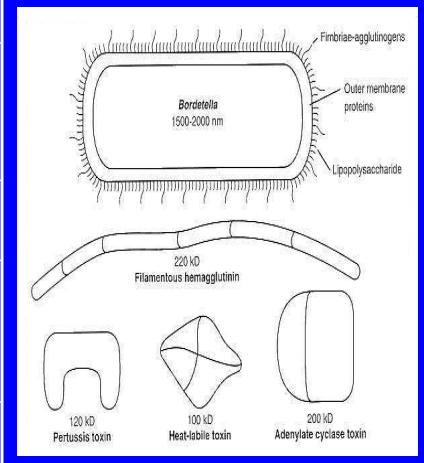


G protein and ADP riboyslation



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 clinical symptoms

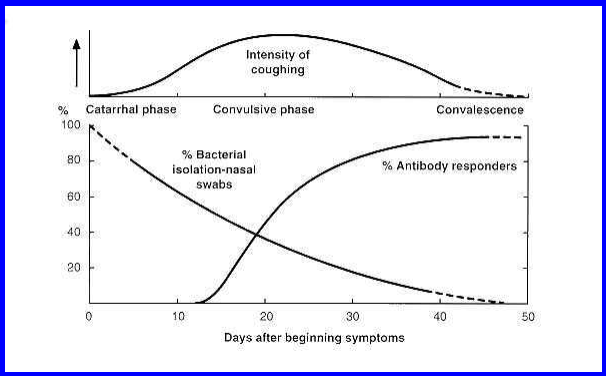
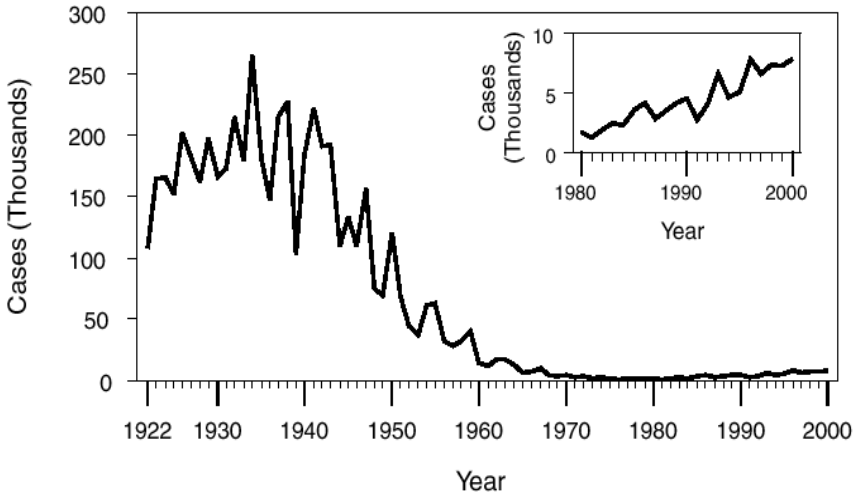


FIGURE 1. Number of reported pertussis cases, by year — United States, 1922–2000



Pertussis

- Incidence declined due to vaccine
- Affects children under 1 and adults with waning immunity
- New recommendations for booster vaccine for children 11-18 years of age
- Incubation period 7-10 days
- Three stages of disease: catarrhal, paroxysmal, convalescent
- Diagnosis: special media- Bordet-Gengou- blood, charcoal, and starch. Nasopharyngeal culture
- Serologic testing: acute and convalescent titers

CDC 2003 National Hospital Discharge Survey: July 8, 2005

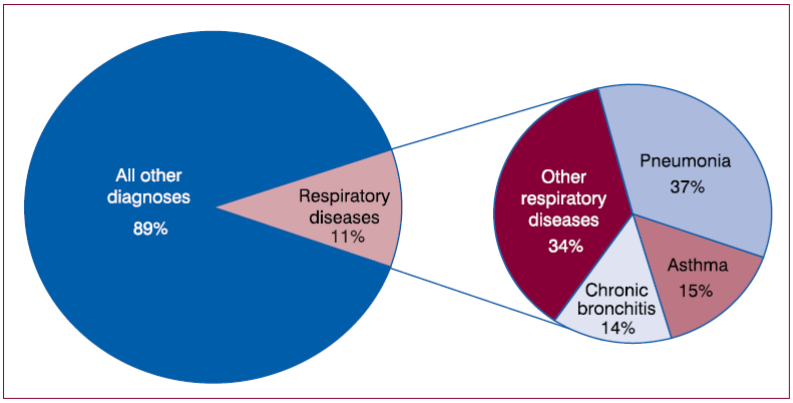


Figure 2. Percent distribution of patients hospitalized for respiratory diseases: United States, 2003

CAP guidelines: Implementing CAP guidelines locally

Table 2. Elements important for local community-acquired pneumonia guidelines.

- All patients
  - Initiation of antibiotic therapy at site of diagnosis for hospitalized patients
  - Antibiotic selection
    - Empirical
    - Specific
  - Admission decision support
  - Assessment of oxygenation
  - Intensive care unit admission support
  - Smoking cessation
  - Influenza and pneumococcal vaccine administration
  - Follow-up evaluation
- Inpatients only
  - Diagnostic studies
    - Timing
    - Types of studies
  - Prophylaxis against thromboembolic disease
  - Early mobilization
  - Thoracentesis for patients with significant parapneumonic effusions
  - Discharge decision support
  - Patient education

CID 2007::44

Treatment recommendations for CAP

Outpatient treatment

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

   A macrolide (strong recommendation; level I evidence)

   Doxycyline (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 β-lactam **plus** a macrolide (strong recommendation; level I evidence)

3. In regions with a high rate (>25%) of infection with high-level (MIC ≥16 μg/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 β-lactam **plus** a macrolide (strong recommendation; level I evidence)

Inpatients, ICU treatment

A β-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 β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)

or

The above β-lactam plus an aminoglycoside and azithromycin

or

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

(moderate recommendation; level III evidence)

If CA-MRSA is a consideration, add vancomycin or linezolid (moderate recommendation; level III evidence)