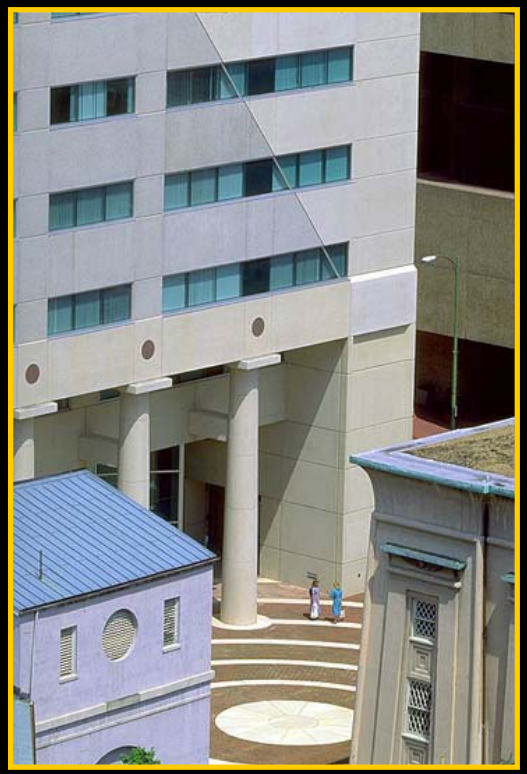
Community Acquired Pneumonia: for Medical Residents



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Outline

- Scope of the problem
  - Epidemiology
- Clinical Presentation
- Bacteriology and pathophysiology
  - Typical vs atypical pathogens
- Therapy
  - Inpatient vs Outpatient
    - Pneumonia Severity Index
  - Therapy
    - Outpatient, inpatient, ICU
- Selected diagnostic tests
- Conclusion

Scope of the problem

- **Epidemiology:**
- Sixth leading cause of death
  - number one cause of death from infectious disease
- Up to 5.6 million cases per year
  - >10 million physician visits
  - 1.1 million hospitalizations
- Average rate of mortality for hospitalized patients 12%

Niederman MS, et al. *Am J Respir Crit Care Med*. 2001;163:1730-1754.

Pathophysiology and Clinical Presentation

Case 1

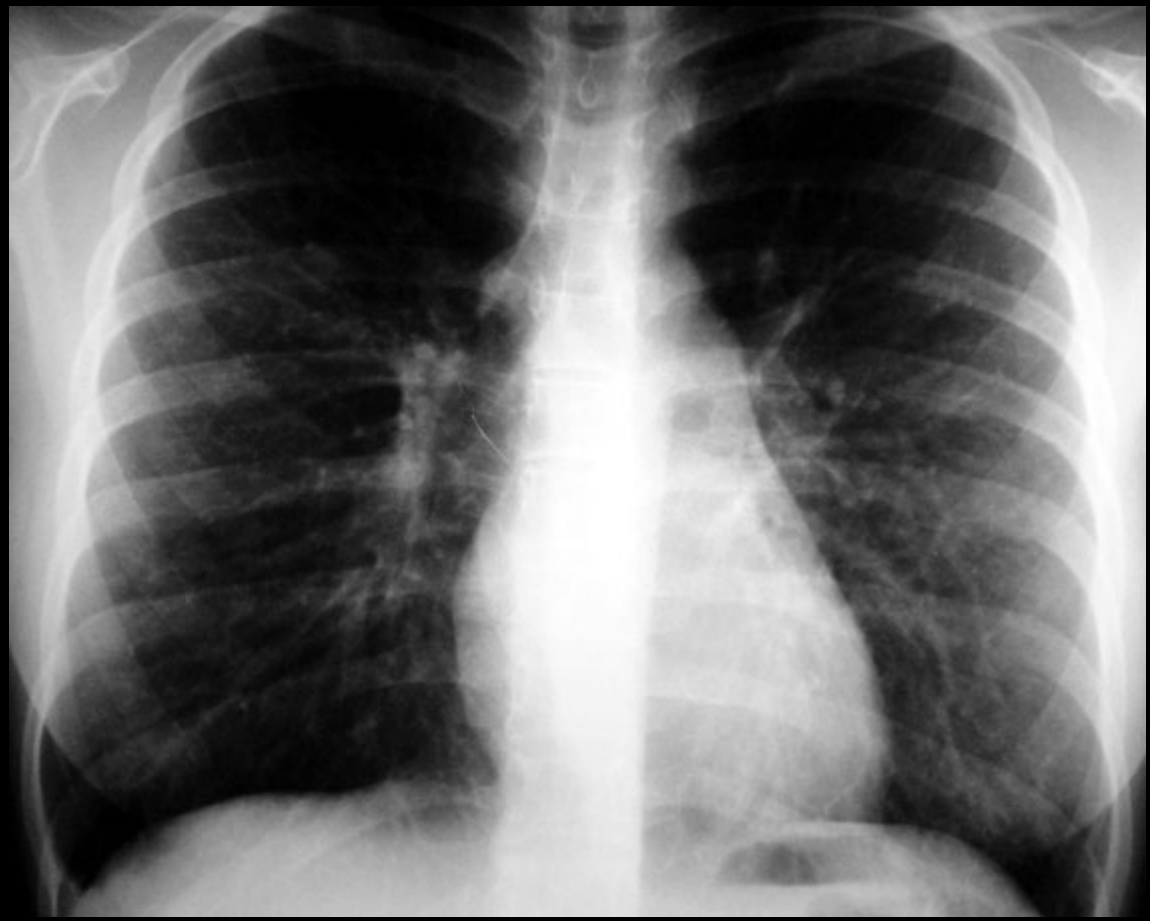
A 19-year-old college student presents with fever, cough, and sore throat of 4-week duration. The student health service prescribed erythromycin, and she took the antibiotic faithfully despite nausea and diarrhea, but the low-grade fevers and nonproductive cough persisted. One week after the onset of illness, persistent hoarseness developed. The patient denies headaches, abdominal pain, weight loss, and night sweats, and she has no known allergies. Her past medical history includes an appendectomy.

Cunha, B. ***Infectious Diseases Pearls.*** 1999

Physical Examination: Temperature 38.6°; pulse 78; respirations 22; blood pressure 120/60. General: well appearing, but coughing. HEENT: some pharyngeal edema, otherwise normal. Chest: minimal right lower lobe rales. Cardiac: normal. Abdomen: soft, nontender, no organomegaly.

Laboratory Findings: WBC 8900/µl; ESR 32 mm/hr. Liver function tests: normal. BUN and creatinine: unremarkable. Urinalysis: 1+protein. Cold aggultinin 1:4. Electrocardiogram: normal.

Chest X-ray



What is your presumptive diagnosis?

Case 2

A 70-year-old man presents to the emergency department complaining of right-sided pleuritic chest pain, cough productive of thick greenish-yellow sputum, increasing dyspnea, fevers, and shaking chills-all of 2-day duration. He denies nausea, vomiting, and diarrhea. His past medical history is significant for chronic obstructive pulmonary disease (COPD), tracheostomy for laryngeal cancer, and alcohol abuse.

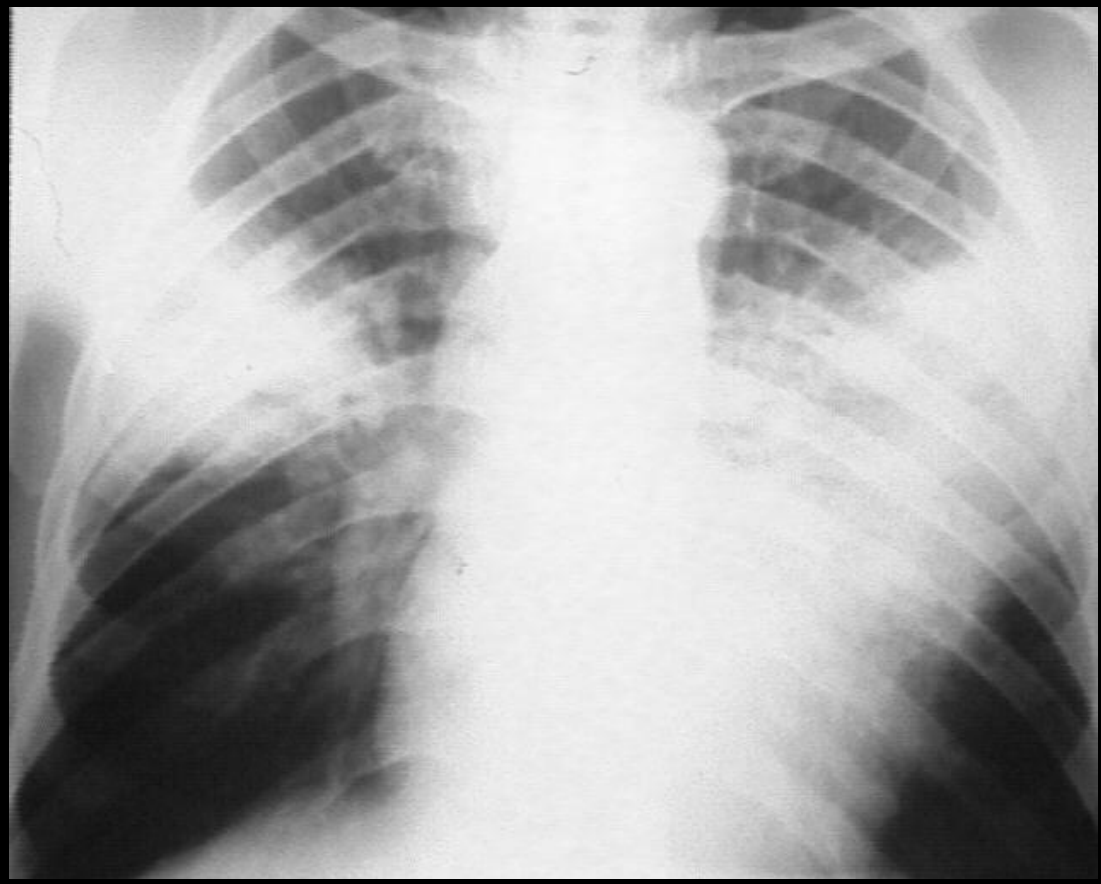
Cunha, B. ***Infectious Diseases Pearls***. 1999

Physical Examination: Temperature 38.6°; respirations 26; heart rate 110; blood pressure 140/84. General: ill appearing, but alert and orientated to person, place and time. HEENT: thick, greenish-yellow sputum from tracheostomy tube. Chest: bilateral scattered rhonchi and bronchial breath sounds, with dullness to percussion and egophony at the right base.

Laboratory Findings: Hct 3.7%; WBC 15,800/µl with 88% polymorphonuclear cells, 8% bands, 4% lymphocytes. Na^+ 137 mEq/L. BUN 32 mg/dl,creatinine 1.2 mg/dl. Arterial blood gas (room air): pH 7.38, PCO_2 78 mmHg.
Sputum Gram stain:abundant leukocytes and gram-positive diplococci. Blood cultures: pending.

Cunha, B. ***Infectious Diseases Pearls,*** 1999.

Chest X-ray



What is your presumptive diagnosis?

Pathophysiology

Pathogenetic Mechanisms in Pneumonia

Mechanism	Frequency
Inhalation of infectious particles	Common
Aspiration of oropharyngeal or gastric contents	Common
Hematogenous deposition	Uncommon
Invasion from infection in contiguous structures	Rare
Direct inoculation	Less common
Reactivation	More common in immunocompromised hosts

http://www.clevelandclinicmeded.com/diseasemanagement/infectiousdisease/communitypneumonia/communitypneumonia.htm

Bacteriology

Bacteriology

Identified Pathogens in Community-acquired Pneumonia

Pathogen	Percentage of Cases
Streptococcus pneumoniae	20-60%
Haemophilus influenzae	3-10%
Staphylococcus aureus	3-5%
Gram-negative bacilli	3-10%
Legionella species	2-8%
Mycoplasma pneumoniae	1-6%
Chlamydia pneumoniae	4-6%
Viruses	2-15%
Aspiration	6-10%
Others	3-5%

http://www.clevelandclinicmeded.com/diseasemanagement/infectiousdisease/communitypneumonia/communitypneumonia.htm

Treatment: Inpatient vs Outpatient

Pneumonia Severity Index

Characteristic	Points assigned
Demographic factor	
Age	
Men	Age (yrs)
Women	Age (yrs) – 10
Nursing-home resident	+10
Co-existing illnesses	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical examination findings	
Altered mental status	+20
Respiratory rate ≥30 breaths/min	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature < 35°C (95°F) or ≥40°C(104°F)	+15
Pulse ≥125 beats/min	+10
Laboratory and radiographic findings (if study performed)	
Arterial blood pH < 7.35	+30
Blood urea nitrogen level ≥30 mg/dL	+20
Sodium level < 130 mmol/L	+20
Glucose level ≥250 mg/dL	+10
Hematocrit < 30%	+10
Partial pressure of arterial 0_2 < 60 mm Hg or 0_2 Sat < 90%	+10
Pleural effusion	+10

Pneumonia Severity Index

Class	Points	Mortality*
I	<51	0.1%
II	51-70	0.6%
III	71-90	0.9%
IV	91-130	9.5%
V	>130	26.7%

* From the PORT study validation cohort

Reference: Fine MJ, et. al. A prediction rule to identify low-risk patients with community acquired pneumonia *NEJM* 1997; 336: 243)

Antibiotic Choice

IDSA CAP Guidelines

Table 1. Categories for ranking recommendations in the therapeutic guidelines.

Category	Description
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from at least 1 randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial without randomization
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Initial Antibiotic Selection-Outpatient

Previously healthy	
No recent antibiotic therapy	A macrolide or doxycycline
Recent antibiotic therapy	A respiratory fluoroquinolone alone, an advanced macrolide plus high-dose amoxicillin, or an advanced macrolide plus high-dose amoxicillin-clavulanate.
Comorbidities (COPD, diabetes, renal or congestive heart failure, or malignancy)	
No recent antibiotic therapy	An advanced macrolide of a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	A β-lactam or a respiratory fluoroquinolone

Appropriateness of antibiotic

- Appropriate selection of initial antibiotic therapy
  - *Streptococcus pneumoniae* causes two-thirds of all cases of bacteremic pneumonia
  - Need to cover potentially resistant strains of *S. pneumoniae* and atypical organisms for patients admitted to ICU

Timing and Choice of Antibiotics

Antibiotic Timing at 4 hours cutoff: IDSA B-III recommendation.

Empiric Antibiotic Choice of Therapy: IDSA A-I recommendation.

Initial Antibiotic Selection- inpatient

Non-ICU

β-lactam (IV or IM) + macrolide (IV or Oral)

or

β-lactam (IV or IM) + doxycycline (IV or Oral)

or

Quinolone monotherapy (IV or Oral)

ICU

β-lactam (IV) + macrolide (IV)

or

β-lactam (IV) + quinolone (IV)

If documented β-lactam allergy:
Quinolone (IV) + Clindamycin (IV)

or

Quinolone (IV) + Vancomycin (IV)

Pseudomonal Risk*

*In addition to the antibiotics listed under ICU, if the patient had a secondary ICD-9 code of bronchiectasis, or a positive response to the bronchiectasis question, or malnutrition [as reflected by a serum albumin below 3], these antibiotics would also be considered acceptable:

Antipseudomonal β-lactam (IV) + Antipseudomonal quinolone (IV)

Or

Antipseudomonal β-lactam (IV) + Aminoglycoside (IV) + either a [Macrolide (IV) or Antipneumococcal quinolone (IV)]

If documented β-lactam allergy:Aztreonam (IV) + Aminoglycoside (IV) + Antipneumococcal quinolone (IV)

Adapted from IDSA: ***Update of Practice Guidelines for the Management of Community Acquired Pneumonia in Adults. CID 2003;37:1405-1432***

Initial Antibiotic Selection

30-day mortality - Community-dwelling Patients (14,150 patients)

Initial Antibiotics	30-day mortality N/D (%)	Adjusted Odds Ratio† aOR (95% CI)	P Value
3rd generation cephalosporin*	277/3072 (9.0)	Reference	Ref
Macrolide monotherapy‡	19/431 (4.4)	0.63 (.39-1.04)	0.069
2nd generation cephalosporin	73/844 (8.6)	1.13 (.85-1.51)	0.406
Quinolone monotherapy‡	121/1716 (7.1)	**0.78 (.62-.98)**	**0.037**
At least 1 aminoglycoside	80/445 (18.0)	**1.51 (1.11-2.04)**	**0.008**
Cephalosporin + macrolide‡	231/3618 (6.4)	**0.74 (.61-.89)**	**0.002**
Cephalosporin + quinolone‡	63/723 (8.7)	0.90 (.67-1.22)	0.506
ß-lactam/ß-lactamase inhibitor + macrolide‡	17/158 (10.8)	1.12 (.65-1.94)	0.689

***monotherapy with cefotaxime or ceftriaxone.**

†Results adjusted for age, gender, neoplastic disease, cardiovascular disease, altered mental status, respiratory rate ≥ 30/min, systolic BP < 90 mmHg, temperature < 35C or ≥ 40C, pulse ≥ 125/min, blood pH < 7.35, BUN > 10.7 mmol/L, sodium < 130 mEq/L, hematocrit < 30%, pO2 < 60 mmHg, pleural effusion, admission to ICU in the first 24 hours after arrival, antibiotics administered within the first 4 hours after arrival, and US census region.

‡These antibiotic combinations include patients receiving either oral or parenteral macrolides or quinolones.

Bratzler DW. Houck PM, et al. [abstract] American Thoracic Society, 2003.

Organisms Causing CAP in Hospitalized Patients Requiring ICU Admission

- Overall up to 10% of admitted patients with CAP are brought to the ICU
  - 30% caused by *Streptococcus pneumoniae*
  - 50-60% have an unknown etiology
  - Other reported organisms
    - *Legionella*
    - *H.influenza*
    - *S.aureus*
    - *P.aeruginosa* (underlying bronchiectasis)
    - Enterobacteriacae (underlying bronchiectasis)

American Thoracic Society 2001. ***Am J Respir Crit Care Med*** Vol.163.1730-1754.

Recommended Definition Severe CAP and Need for ICU Admission [1]

- Combination of 2 minor or 1 major criteria (retrospective analysis- sensitivity of 78% and Specificity of 94%) [2]
  - Minor:
    - RR>30/minute
    - PaO2/FiO2 ratio <250
    - Bilateral or multilobar pneumonia
    - Systolic BP<90 mmHg and diastolic BP<60 mmHg
  - Major
    - Need for mechanical ventilation
    - Increase in the size of infiltrates by 50% within 48hr
    - Septic shock or the need for pressors
    - Acute renal failure

1. American Thoracic Society 2001. ***Am J Respir Crit Care Med*** Vol.163.1730-1754.

2. Ewig et al. ***Am J Respir Crit Care Med*** 1998 Vol.158.1102-1108

Timing of antibiotics

- Bratzler et al; *Archives of Internal Medicine* 2004. In press
  - Retrospective study 13,771 patient from a random Medicare registry sample
    - CAP; Age >65; 7/1998-3/1999
    - Outcome Measures
      - Antibiotic administration within 4 hours
      - Mortality (severity-adjusted)
      - Readmission within 30 days
      - Length of stay (LOS)

Association between Antibiotic First Dose Timing and Outcomes

Outcome	Within 4 hours %	After 4 hours %	Adjusted Odds Ratio aOR (95% CI)	P value
30-day mortality	11.6	12.7	0.85 (.76-.95)	**0.005**
In-hospital mortality	6.8	7.4	0.85 (.74-.98)	**0.029**
Length of stay > 5 days	42.1	45.1	0.90 (.83-.96)	**0.003**
30-day readmission	13.1	13.9	0.95 (.85-1.06)	0.344

Using multivariate logistic regression [the model included the timing of antibiotic first dose, PSI score, ICU admission, US census region, race/ethnicity, other processes of care (oxygenation assessment, performance of blood cultures, and antibiotic selection)].

Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. *Arch Intern Med*. 2003 (In Press).

Early (within 4 hours) administration of antibiotics associated with decreased mortality and shorter LOS

First Dose Timing and Outcomes

Timing of First Dose Group 1 vs Group 2	Group 1 Mortality %	Group 2 Mortality %	Adjusted Odds Ratio aOR (95% CI)	P value
≤ 1 hour vs > 1 hour	12.9	12.0	0.99 (.81-1.21)	0.906
≤ 2 hours vs > 2 hours	12.5	11.9	0.94 (.83-1.06)	0.322
≤ 3 hours vs > 3 hours	11.7	12.3	0.88 (.79-.99)	**0.030**
≤ 4 hours vs > 4 hours	11.6	12.7	0.85 (.76-.95)	**0.005**
≤ 5 hours vs > 5 hours	11.6	13.0	0.86 (.76-.97)	**0.017**
≤ 6 hours vs > 6 hours	11.6	13.5	0.84 (.73-.95)	**0.008**
≤ 7 hours vs > 7 hours	11.7	13.5	0.87 (.76-1.01)	0.060
≤ 8 hours vs > 8 hours	11.7	13.8	0.85 (.73-.99)	**0.040**
≤ 9 hours vs > 9 hours	11.8	13.8	0.86 (.73-1.02)	0.075
≤ 10 hours vs > 10 hours	11.9	13.4	0.91 (.76-1.09)	0.327

Retrospective analysis: early antibiotic treatment associated with decreased odds of mortality

Using multivariate logistic regression [the model included the timing of antibiotic first dose, PSI score, ICU admission, US census region, race/ethnicity, other processes of care (oxygenation assessment, performance of blood cultures, and antibiotic selection)]. Patients who were on antibiotics prior to admission are excluded from this analysis. (Houck PM, Bratzler DW, et al. *Arch Intern Med*. In Press)

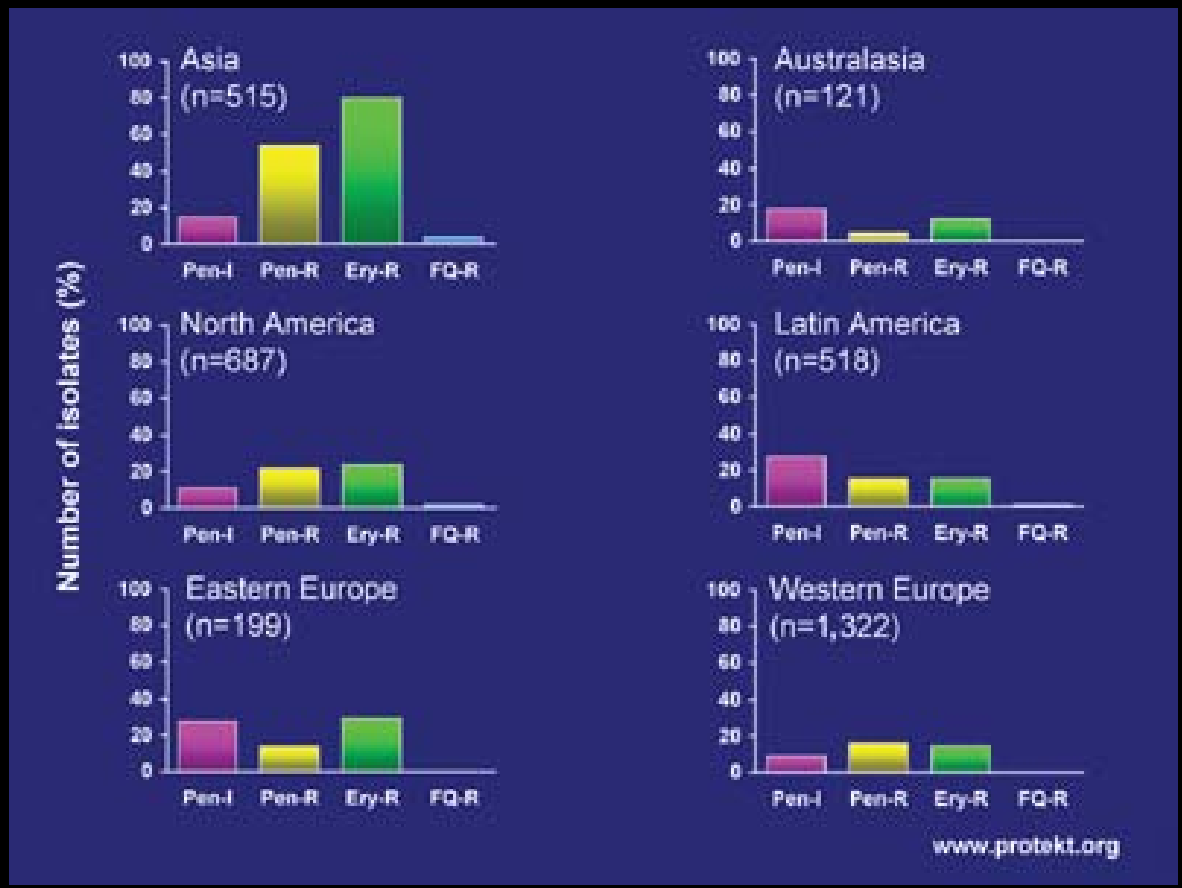
Initial Antibiotic Choice for CAP in an ICU Cohort: Outcome-Death

Variable	Relative OR	95%CI	P value
Underlying Diseases	**3.09**	**1.63-5.887**	**0.0007**
Shock	**2.85**	**1.23-6.61**	**0.016**
Bacteremia	**2.63**	**1.18-5.87**	**0.019**
Ineffective initial therapy	**4.71**	**2.85-8.58**	**0.0001**
Non-pneumonia related complications	**10.7**	**5.00-20.00**	**0.0001**

Retrospective clinical study with multivariate Analysis of 299 patients admitted to an ICU

Leroy et al. ***Intensive Care Medicine*** (1995) 21:24-31

S.pneumonia with reduced susceptibility to fluoroquinolones



PROTEKT study: Epidemiology of *Streptococcus pneumoniae* resistance (www.protekt.org).

Switching from IV Therapy to PO

- Most patients show a clinical response within 3 to 5 days of IV antibiotic therapy:

Criteria to consider when switching from IV to oral therapy:

- Patient's condition is treatable by oral form of medication.
- Patient has a functioning GI tract for adequate absorption.
- Patient is currently receiving a soft or regular diet and/or is taking other oral medications.
- Patient's condition is improving as indicated from clinical findings (e.g., temperature and white blood cell count).

Summary: Current Practice Guidelines

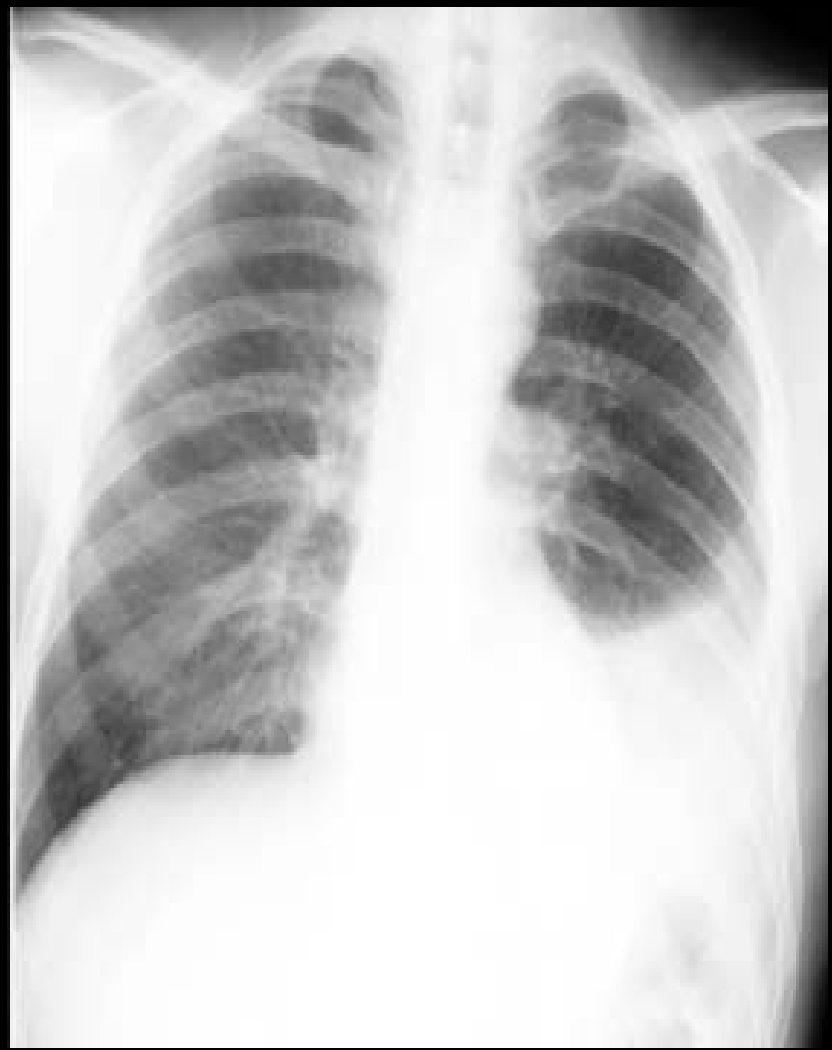
- Antibiotic timing and antibiotic choice represent practice guidelines based on best available current evidence
  - These are retrospective, observational trials and expert (committee) opinion.
    - In some studies the measure of effect, although, statistically significant may be small
  - These guidelines are not based on extensive prospective, randomized controlled trials
    - Antibiotic timing

Selected laboratory tests

- Sputum Gram stain and culture
- Blood cultures
- Legionella urinary antigen tests
- Pneumococcal Urinary Antigen

Parapneumonic Pleural Effusion

Management of Patients withParapneumonic Effusions			
Effusion	**Pleural Fluid Bacteriology**	**Pleural Fluid Chemistry**	**Drain?**
Minimal effusion (< 10 mm on lat. decub.); free-flowing	Cx and GS Unknown	pH unknown	No
Small-moderate effusion (> 10 mm to < 1/2 of hemithorax on lateral decub.); free-flowing	Negative Cx and GS	pH > 7.20	No
Large effusion (> 1/2 of hemithorax on lateral decub.) OR loculated fluid OR thickened pleura	Positive Cx or GS	pH < 7.20	Yes
Regardless	Pus	pH < 7.0	Yes
Cx = Culture; GS = Gram's Stain			

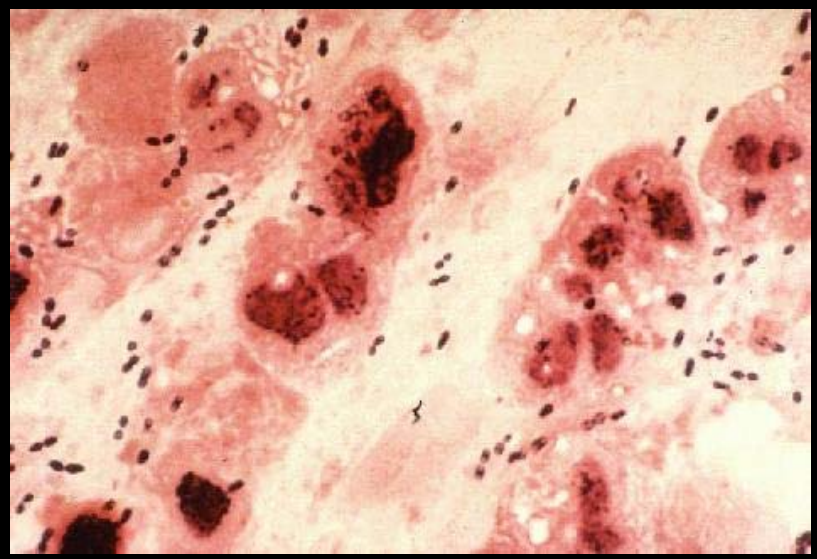


http://www.clevelandclinicmeded.com/diseasemanagement/pulmonary/pleuraldisease/pleuraldisease.htm

Sputum Gram Stain and Culture

IDSA B-II recommendation

Expectorated sputum should be deep cough specimen obtained before antibiotic treatment and it should be rapidly transported and processed withina few hours of collection.



Blood Culture Collection

IDSA B-III recommendation

National CAP Guidelines

- 2 sets of blood cultures should be drawn before initiation of antibiotic therapy
  - Infectious Diseases Society of America, 2000
  - American Thoracic Society, 2001

Blood Culture Collection:

- ***Increase the collection of blood cultures prior to first antibiotic dose***
  - **Blood cultures before antibiotics gives highest yield of identifying a pathogen**
- Increase the collection of blood cultures during the first 24 hours
  - Better late than never!

Rationale for Obtaining Blood Cultures in Patients with Pneumonia

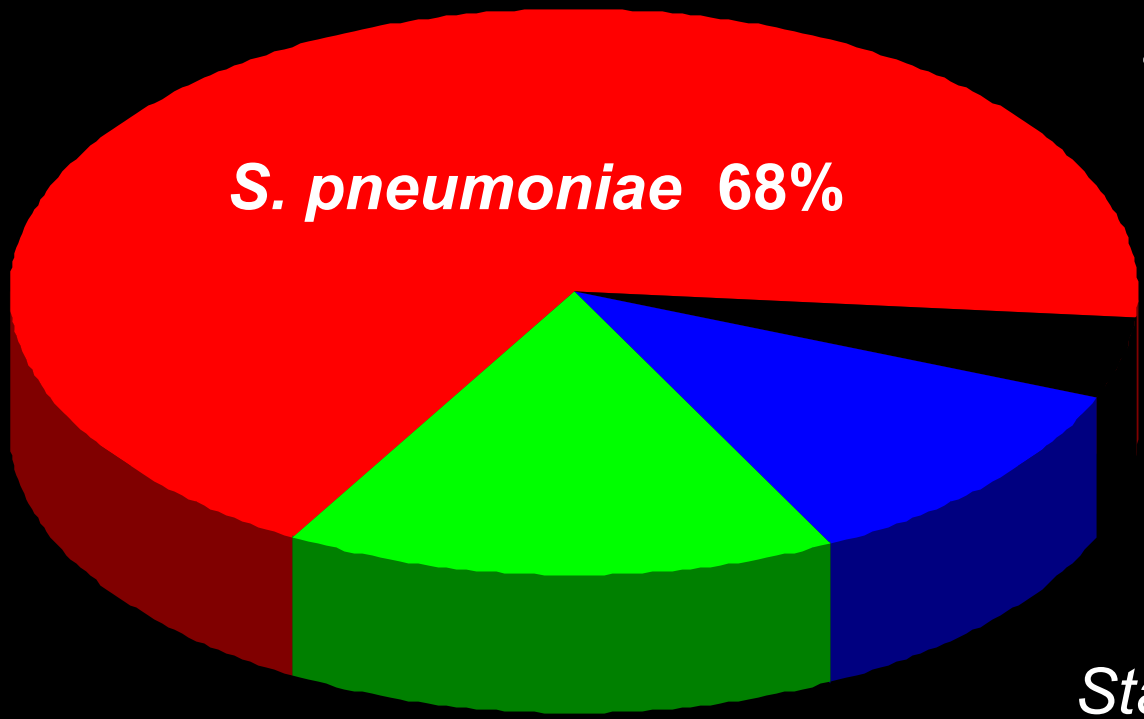
- Studies have shown that 2-14% of patients with pneumonia have positive blood cultures- *low yield diagnostic test*
- Chalasani NP et al. Chest 1995;108:932-936.
- A positive blood culture provides definitive evidence of the cause of pneumonia in most cases; provides greater certainty than sputum cultures or serology

Rationale for Obtaining Blood Cultures in Patients with Pneumonia

- Pneumonia patients with bacteremia have 3-fold increase in mortality
  Fine MJ et al. JAMA 1996;275:134.
- Establishing a microbiologic diagnosis allows streamlining of antibiotic therapy, which decreases potential for antibiotic resistance
- Collection of blood cultures associated with decreased mortality

Pathogens Retrieved by Blood Culture

- Prospective study
- 19 Canadian hospitals
- 760 patients
  - 43 with (+) blood cultures



Other 5%

Staph. aureus 11%

Enterobacteriacae 16%

Campbell SG et al. Chest 2003;123:1142-1150.

Performance of Microbiologic Studies in Pneumonia Patients

Multicenter (3,555 hospitals), retrospective cohort study, 1994-95; n=14,069

Test	%	Range by state
Blood culture within 24 hrs of admission	69	46-83%
Blood culture obtained before antibiotics	57	32-74%

Blood culture collection within 24 hours of arrival was associated with a 10% lower odds of 30-day mortality

Meehan TP et al. JAMA 1997;278:2080-2084.

Performance of Microbiologic Studies in Pneumonia Patients

Multicenter (38 academic hospitals), retrospective study, 1997-98; n=1,062

Test	%	Range
Blood culture obtained before antibiotics	72	9-100%
Blood culture within 24 hrs of admission	82	54-100%

Dedier J et al. Arch Intern Med 2001;161:2099-2104.

Legionella pneumophila urinary antigen test

- IDSA 2003: CIII recommendation
  - ***This test is recommended for patients with enigmatic pneumonia severe enough to be hospitalized in the ICU, in the presence of an epidemic, or failure to respond to a Beta-lactam antibiotic.***
- ***Legionella***
  - In case series represents 0.5% to 6.0% of hospitalized CAP
  - ***Legionella*** urinary antigen test
    - Detects ***Legionella*** serogroup 1 only
      - Accounts for 80-95% of cases of Legionella
      - Sensitivity 92%
      - Specificity 98%

Pneumococcal Urinary Antigen Test

- **IDSA BII recommendation**
  - *The pneuomococcal urinary antigen assay is an acceptable test to augment the standard diagnostic methods of blood culture and sputum Gram stain and culture, with the potential advantage of rapid results similar to those for sputum Gram stain.*

Pneumococcal Urinary Antigen Test

- Immunochromatographic membrane test (ICT) used to detect pneumococcal cell wall polysaccharide
- Sensitivity rages from 50%-80%
  - Highest sensitivity observed in cases with proven bacteremic pneumococcal disease
- Specificity 90%
- The potential advantage is for rapid result (15 minutes)
  - May assist in pathogen targeted therapy

Conclusion

- Sixth leading cause of death overall and the number one cause of death from infectious disease in the USA
- Even with modern medical care the case mortality is 12%
- Typical and a typical pathogens must be considered in the choice of antibiotic therapy.
  - PSI should be used for risk stratification
  - Initial antibiotic choice should take into account history, comorbidities and risk stratification.
- Diagnostic tests include sputum gram stain and culture, blood cultures, Legionella urinary antigen test and pneumococcal urinary antigen.
- For patients on parental antibiotics, a switch to oral therapy should be made as soon as possible.