Management of Community-Acquired Pneumonia (CAP): "Let's Revisit the Guidelines"

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Objectives

- **Formulate a comprehensive management plan that begins with site-of-care decision, recognition of the most common etiologic agents of CAP, identification of epidemiologic risk factors for specific pathogens, and a targeted diagnostic work-up.**
- **Recognize the recommended empiric and pathogen-directed antimicrobial regimens, optimal timing for transitioning from I.V. to P.O., optimal duration of therapy, and preventive measures.**

Background

- **~900,000 episodes of CAP/year in adults ≥ 65 years in the U.S.**
- **Significant cause of morbidity and mortality.**
- **Various studies have demonstrated that guideline-based management of CAP can lead to ↓ 30-day mortality, ↓ in unnecessary hospital admissions, and ↓ length of hospital stay (LOS).**
- **First joint IDSA/ATS guidelines for management of CAP published in 2007.**

Jackson et al. Clin Infect Dis 2004;39:1642-50
Feikin et al. Am J Public Health 2000;90:222-9
Dean et al. Am J Med 2001;110:451-7
Capelastegui et al. Clin Infect Dis 2004;39:955-63
Marrie et al. JAMA 2000:283:749-55.
Benenson et al. Acad Emerg Med 1999;6:1243-8
Mandell et al. Clin Infect Dis 2007;44:S27-72

Case 1

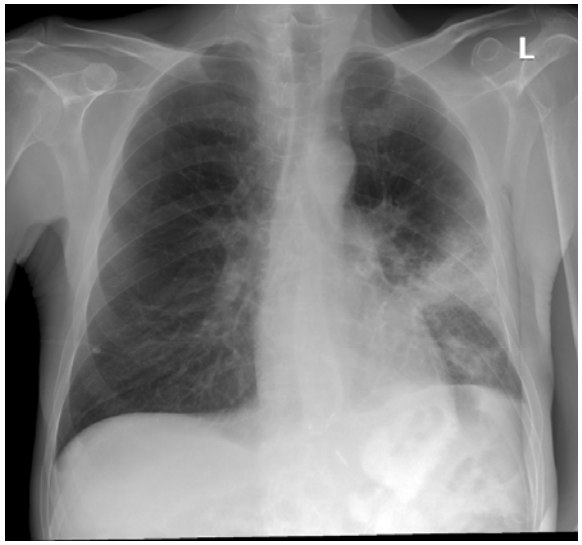
- **Patient "X" is a 68 y/o caucasian male with underlying insulin controlled DM and HTN.**
- **Presents with 3-day history of fevers, productive cough, left-sided pleuritic chest pain, generalized fatigue, and decreased oral intake.**
- **Admits to a remote 10 pack-year smoking history.**
- **Recently attended a 7-day business convention at a hotel in Philadelphia.**
- **Denies recent sick contacts.**

Case 1 Continued…

- VS: T_{max} 103ºF, P112, R22, BP117/68, SPO2 93% RA
- Gen: A / O x 3, Mildly tachypneic, but able to speak full sentences.
- HEENT: AT/NC, PEERLA, EOMI, Dry oral mucosa, No pharyngeal erythema or tonsillar exudates.
- Heart: Regular and Tachycardic. No M/G/R
- Lungs: Left basilar inspiratory crackles
- Abdomen: Soft, NT, ND, and normoactive BS
- Skin: No rashes
- Extremities: No pitting edema

Case 1 Continued…

- WBC 18,000/µL
- BUN 34mg/dL
- Cr 2.3mg/dL
- Glucose = 278mg/dL
- Nml LFT's



Outpatient vs. Inpatient Management: Severity of Illness Score; CURB-65

	Clinical Factor	Points
C	Confusion	1
U	Blood urea nitrogen > or = 20 mg/dL	1
R	Respiratory rate > or = 30 breaths/min	1
B	Systolic BP < 90 mm Hg or Diastolic BP < or = 60 mm Hg	1
65	Age > or = 65	1

- **CRB-65 → Simplified version to use in office.**

Total Score	Mortality %	Risk Level	Suggested Site-of-Care
0	0.6%	Low	Outpatient
1	2.7%	Low	Outpatient
2	6.8%	Moderate	Short inpatient / supervised outpatient
3	14.0%	Moderate to High	Inpatient
4 or 5	27.8%	High	Inpatient / ICU

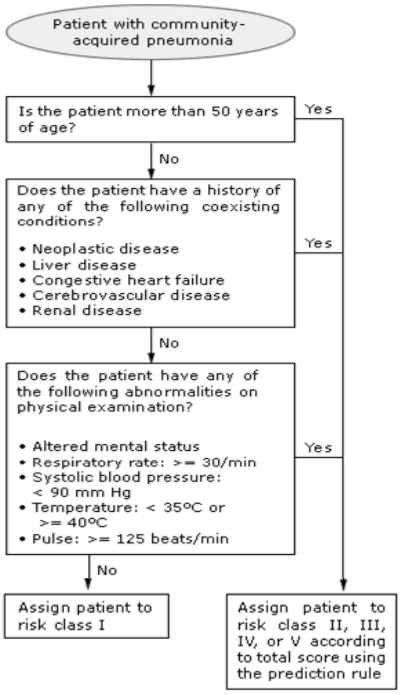
Lim et al. Thorax 2003;58:377-82
Capelastegui et al. Eur Respir J 2006;27:151-7
http://internalmedicine.osu.edu/pulmonary/cap/10674.cfm

Outpatient vs. Inpatient Management: Severity of Illness Score; Pneumonia Severity Index (PSI)

Stratification of Risk Score				
Risk	Risk Class	Score	Mortality	
Low	I	Based on algorithm	0.1%	Outpatient treatment
Low	II	<= 70	0.6%	
Low	III	71-90	0.9%	
Moderate	IV	91-130	9.3%	Hospital admission
High	V	>130	27.0%	

* Interactive tool from the Assessment of the Variation and Outcomes of Pneumonia: Pneumonia Patient Outcomes Research Team Final Report. AHRQ Publication No. 97-N009.

Fine et al. N Engl J Med 1997;336:243-50
http://internalmedicine.osu.edu/pulmonary/cap/10675.cfm



Demographic factors	
Age (in years)	
Men	
Women	-10
Nursing home resident	+10
Coexisting illnesses	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Findings on physical examination	
Altered mental status	+20
Respiratory rate >= 30/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35ºC or >= 40ºC	+15
Pulse >= 125 beats/min	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea mitrogen >= 30/mg/dl (11 mmol/liter)	+20
Sodium < 130 mmol/liter	+20
Glucose >= 250 mg/dl (14 mmol/liter)	+10
Hematocrit <30%	+10
Partial pressure of arterial oxygen < 60 mm Hg or oxygen saturation < 90%	+10
Pleural effusion	+10

Fine et al. N Engl J Med 1997;336:243-50
http://internalmedicine.osu.edu/pulmonary/cap/10675.cfm

Direct ICU Admission

Table 4. Criteria for severe community-acquired pneumonia.

Minor criteria[a]
- Respiratory rate[b] ⩾30 breaths/min
- PaO_2/FiO_2 ratio[b] ⩽250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN level, ⩾20 mg/dL)
- Leukopenia[c] (WBC count, <4000 cells/mm³)
- Thrombocytopenia (platelet count, <100,000 cells/mm³)
- Hypothermia (core temperature, <36°C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria
- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

NOTE. BUN, blood urea nitrogen; PaO_2/FiO_2, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

[a] Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

[b] A need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or a PaO_2/FiO_2 ratio <250.

[c] As a result of infection alone.

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- **1 Major Criteria**

OR

- **3 Minor Criteria**

Outpatient vs. Inpatient Management: Severity of Illness Score

- **CURB-65 and/or PSI criteria MUST ALWAYS be supplemented with physician judgment, especially with outpatient management decisions.**
- **Based on CURB-65 score and physician judgment, Patient "X" was admitted to the hospital for inpatient management.**

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Diagnostic Workup

- **Identifying a specific pathogen – "Pros"**
  - **Change in the antibiotic(s) prescribed**
  - **Unusual pathogens or those that have public health implications (i.e. TB, SARS, Legionnaire's disease, etc.)**
  - **↑ Risk of clinical failure and mortality associated with using wrong or in-effective antibiotic.**
  - **↓ Cost, drug adverse effects, and microbial resistance pressure associated with antibiotic de-escalation.**
  - **Periodic surveillance of antibiotic resistance profiles for common etiologies of CAP.**

Kollef et al. Chest 1999;115:462-74.
Ronson et al. Arch Intern Med 2004;164:502-8
Arancibia et al. Am J Respir Crit Care Med 2000;162:154-60
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

- **Identifying a specific pathogen – "Cons"**
  - **No difference in clinical failure (p = 0.74), LOS (p = 0.63), or mortality (p = 0.09) between pathogen-directed therapy and empiric therapy groups.**
  - **Pathogen-directed therapy was associated with improved mortality in ICU patients only (p = 0.02).**
  - **Cost ($$$$$) → poor quality samples and overall low-yield of positive cultures in certain patients with CAP.**

Van der Eerden et al. Thorax 2005;60:672-8
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

- **Sputum for Gram Stain and Culture**
  - **Perform on good-quality specimens only and before antibiotics are given if possible.**
  - **May suggest that broader coverage is needed until cultures finalized (i.e. GPC's in clusters or GNR's).**
  - **Highly predictive of and can validate f/u sputum culture results**
  - **~40% of patients are unable to produce sputum sample at all.**
  - **Meta-analysis demonstrated a relatively low-yield of sputum gram stain (presence of predominant morphotype).**

Mandell et al. Clin Infect Dis 2007;44:S27-72
Gleckman et al. J Clin Microbiol 1988;26:846-9
Van der Eerden et al. Thorax 2005;60:672-8
Reed et al. West J Med 1996;165:197-204
Garcia-Vazquez et al. Arch Intern Med 2004;164:1807-11.

Diagnostic Workup

- **Blood Cultures**
  - **Also relatively low yield of positive results (~5 – 14%)**
  - **Most common isolated pathogen is *S. pneumoniae*.**
  - **No data showing improvement in outcomes or antibiotic selection.**
  - **↑ LOS associated and ↑ use of vancomycin with false-positive results (i.e. coagulase-negative Staphylococcus).**
  - **Optional for those treated as outpatients**
  - **Should be performed selectively in hospitalized patients.**

Campbell et al. Chest 2003;123:1142
Waterer et al. Respir Med 2001;95:78-82
Yu et al. Clin Infect Dis 2003;37:230-7
Metersky et al. Am J Respir Crit Care Med 2004;169:342-7
Houck et al. Arch Intern Med 2004;164:637-44
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

- **Blood Cultures → Indications to obtain blood cultures:**
  - **Severe CAP (*S. aureus, P. aeruginosa, etc.)***
  - **Asplenia (congenital or acquired)**
  - **Complement deficiencies**
  - **Chronic liver disease**
  - **Leukopenia on presentation (< 4,000 cells/mm^3)**

- **Thoracentesis → Pleural fluid >5 cm (upright CXR).**
  - **Must send fluid for analysis + cultures (aerobic and anaerobic). Yield of cultures are low, but findings can influence choice of antibiotics, need for further drainage / decortication, and duration of antibiotic therapy.**

Metersky et al. Am J Respir Crit Care Med 2004;169:342-7
Metersky et al. Chest 2003;124:1129-32
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

- **Non-bronchoscopic Bronchoalveolar Lavage (BAL)**
  - **High % of positive results when performed in E.R. (~87%), even after antibiotic therapy, but not shown to be superior to tracheal aspirates.**
- **Bronchoscopic BAL, Protected Specimen Brush (PSB), or Transthoracic Lung Aspiration.**
  - **No prospective data evaluating their performance in the initial management of CAP**
- **Should consider for immunocompromised patients or those that have failed standard CAP therapy.**

Rodriguez et al. Ann Emerg Med 2001;38:357-63
Jimenez et al. Chest 1993;103:1023-7
Arancibia et al. Am J Respir Crit Care Med 2000;162:154-60
Van der Eerden et al. Eur J Clin Microbiol Infect Dis 2005;24:241-9
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

- ***S. pneumoniae* Urinary Antigen**
  - **Rapid (~15 minutes)**
  - **Sensitivity 50 – 80% & Specificity > 90%**
  - **Useful when cultures are not available or able to be obtained or when antibiotics have been given.**
  - **Cost ($$$$) → ~$30 / sample**
  - **False positive results → Children colonized with *S. pneumoniae* and/or episode of CAP within that last 3 months.**
- ***Legionella pneumophila* Urinary Antigen**
  - **Serogroup 1 only (~80 – 95% of CAP d/t *L. pneumophila)***
  - **Sensitivity 70 – 90% & Specificity 99%.**
  - **Remains positive for weeks**

Dominguez et al. Chest 2001;119:243-9
Gutierrez et al. Clin Infect Dis 2003;36:286-92
Murdoch et al. J Clin Microbiol 2001;39:3495-8
Navarro et al. J Clin Microbiol 2004;42:4853-5
Murdoch et al. Clin Infect Dis 2003;37:153-4
Helbig et al. J Med Microbiol 2001;50:509-16
Murdoch DR. Clin Infect Dis 2003;36:64-9
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

- **Influenza A/B Rapid Enzyme Immunoassay (EIA)**
  - **Point-of-care test (~30 minutes) w/ sensitivity 50 – 70% & specificity ~100%**
  - **Allows for early initiation of antiviral therapy and implementation of droplet isolation precautions.**
  - **Cost (~$30) and sensitivity (high rate of false-negative results) are a disadvantage.**

- **Direct Fluorescent Antibody (DFA) Tests**
  - **Results within ~2 hours**
  - **Influenza → ↑sensitivity compared to EIA (85 – 95%) and same specificity (100%). Can also detect influenza subtypes (i.e. Influenza A 2009 H1N1).**
  - **RSV → Not useful d/t poor sensitivity in adults (20 – 30%).**

Kaiser et al. J Clin Virol 1999;14:191-7
Bellei et al. J Virol Methods 2003;109:85-8
Landry et al. J Clin Virol 2004;31:113-5
Shetty et al. Pediatr Infect Dis J 2003;22:789-94
Charn et al. J Clin Microbiol 2002;40:1675-80
Casiano-Colon et al. J Clin Virol 2003;28:169-74
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

- **Acute and Convalescent Phase Serologies**
  - **Used to diagnose "atypical" pathogens (*Chlamydia pneumoniae, Mycoplasma pneumoniae,* and other Legionella spp.)**
  - **Single acute-phase testing is not reliable**
  - **For the most part, these are impractical**

- **Polymerase Chain Reaction (PCR)**
  - **Respiratory tract specimens (i.e. sputum, BAL, etc.)**
  - **Available for pathogens like *L. pneumophila**, *C. pneumoniae*, and *M. tuberculosis** (*FDA-approved)**
  - **Lack of standarization across laboratories for the majority of above PCR's is an issue.**

Littman et al. Clin Diagn Lab Immunol 2004;11:615-7
Bartlett et al. Infect Dis Clin North Am 2004;18:809-27
Dowell et al. Clin Infect Dis 2001;33:492-503
Templeton et al. Clin Infect Dis 2005;41:345-51
Mundy et al. Am J Repir Crit Care Med 1995;152:1309-15
Mandell et al. Clin Infect Dis 2007;44:S27-72

Diagnostic Workup

Table 5. Clinical indications for more extensive diagnostic testing.

Indication	Blood culture	Sputum culture	*Legionella* UAT	Pneumococcal UAT	Other
Intensive care unit admission	X	X	X	X	X[a]
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X[b]
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia (anatomic or functional)	X			X	
Recent travel (within past 2 weeks)			X		X[c]
Positive *Legionella* UAT result		X[d]	NA		
Positive pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X[e]

NOTE. NA, not applicable; UAT, urinary antigen test.

[a] Endotracheal aspirate if intubated, possibly bronchoscopy or nonbronchoscopic bronchoalveolar lavage.
[b] Fungal and tuberculosis cultures.
[c] See table 8 for details.
[d] Special media for *Legionella*.
[e] Thoracentesis and pleural fluid cultures.

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Case 1 Continued…

- **Sputum for gram stain and culture**
  - **Heavy purulence**
  - **No organisms seen**
  - **Culture – Pending**
- **Urine *S. pneumoniae* Antigen – Pending**
- **Urine *Legionella pneumophila* Antigen - Pending**
- **2 Sets of Blood Cultures – Pending**
- **Started on Levofloxacin 750mg IV q 24 hours in the ER.**

Microbial Etiology of CAP & Pathogen-Specific Risk Factors

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.

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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)

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Empiric vs. Directed Therapy

- Antibiotic resistance is an ongoing problem and physicians must be familiar with their local antibiotic resistance patterns.
- Drug-Resistant *S. pneumoniae* (DRSP)
  - Resistance to B-Lactams is ↓, while resistance to macrolides is ↑.
  - Clinical failures reported with macrolides (i.e. azithromycin) and older FQ's (i.e. ciprofloxacin and levofloxacin)
  - No clinical failures reported yet with the use of newer FQ's (i.e. moxifloxacin).

Waterer et al. Chest 2003;124:519-25
Perez-Trallero et al. AAC 2005;49:1965-72.
Musher et al. N Engl J Med 2002;346:630-1
Kelley et al. Clin Infect Dis 2000;31:1008-11
Lonks et al. Clin Infect Dis 2002;35:556-64
Chen et al. N Engl J Med 1999;341:233-9
Davidson et al. N Engl J Med 2002;346-747-50
Ho et al. JAC 2001;48:659-65
Davies et al. Postgrad Med 2008;20(3 Suppl 1):39-45
Mandell et al. Clin Infect Dis 2007;44:S27-72

Empiric vs. Directed Therapy

- Risk factors for DRSP
  - Age < 2 y/o OR > 65 y/o
  - Use of B-lactams in previous 3 months
  - Alcoholism
  - Medical comorbidities
  - Immunosuppression
  - Exposure to child in day care center

Yu et al. Clin Infect Dis 2003;37:230-7
Campbell et al. Clin Infect Dis 1998;26:1188-95
Clavo-Sanchez et al. Clin Infect Dis 1997;24:1052-9
Vanderkooi et al. Clin Infect Dis 2005;40:1288-97

Empiric vs. Directed Therapy

- **Community-Acquired MRSA (CA-MRSA)**
  - **↑ Incidence as etiology of CAP**
  - **SCC*mec* IV and Panton-Valentin leukocidin (PVL)**
    - **Necrotizing pneumonia**
    - **Acute Respiratory Failure**
    - **Septic Shock**
    - **Lung abscesses and empyemas**
  - **High yield of sputum and blood cultures**
  - **Seen as etiology of post-influenza bacterial pneumonia**

Gorak et al. Clin Infect Dis 1999;29:797-800
Dufour et al. Clin Infect Dis 2002;35:819-24
Mongkolrattanothai et al. Clin Infect Dis 2003;37:1050-8
Deresinski et al. Clin Infect Dis 2005;40:562-73
Fridkin et al. N Engl J Med 2005;352:1436-44
Micek et al. Chest 2005;128:2732-8

Empiric vs. Directed Therapy

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)
   - 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)

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Empiric vs. Directed Therapy

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

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)

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Empiric vs. Directed Therapy

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

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)

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Empiric vs. Directed Therapy

Table 9. Recommended antimicrobial therapy for specific pathogens.

Organism	Preferred antimicrobial(s)	Alternative antimicrobial(s)
Streptococcus pneumoniae		
Penicillin nonresistant; MIC <2 μg/mL	Penicillin G, amoxicillin	Macrolide, cephalosporins (oral [cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren] or parenteral [cefuroxime, ceftriaxone, cefotaxime]), clindamycin, doxycyline, respiratory fluoroquinolone[a]
Penicillin resistant; MIC ≥2 μg/mL	Agents chosen on the basis of susceptibility, including cefotaxime, ceftriaxone, fluoroquinolone	Vancomycin, linezolid, high-dose amoxicillin (3 g/day with penicillin MIC ≤4 μg/mL)
Haemophilus influenzae		
Non–β-lactamase producing	Amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin[b]
β-Lactamase producing	Second- or third-generation cephalosporin, amoxicillin-clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin[b]
Mycoplasma pneumoniae/Chlamydophila pneumoniae	Macrolide, a tetracycline	Fluoroquinolone
Legionella species	Fluoroquinolone, azithromycin	Doxycyline
Chlamydophila psittaci	A tetracycline	Macrolide

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Empiric vs. Directed Therapy

Table 9. Recommended antimicrobial therapy for specific pathogens.

Organism	Preferred antimicrobial(s)	Alternative antimicrobial(s)
Coxiella burnetii	A tetracycline	Macrolide
Francisella tularensis	Doxycycline	Gentamicin, streptomycin
Yersinisa pestis	Streptomycin, gentamicin	Doxycyline, fluoroquinolone
Bacillus anthracis (inhalation)	Ciprofloxacin, levofloxacin, doxycycline (usually with second agent)	Other fluoroquinolones; β-lactam, if susceptible; rifampin; clindamycin; chloramphenicol
Enterobacteriaceae	Third-generation cephalosporin, carbapenem[c] (drug of choice if extended-spectrum β-lactamase producer)	β-Lactam/β-lactamase inhibitor,[d] fluoroquinolone
Pseudomonas aeruginosa	Antipseudomonal β-lactam[e] **plus** (ciprofloxacin or levofloxacin[f] or aminoglycoside)	Aminoglycoside **plus** (ciprofloxacin or levofloxacin[f])
Burkholderia pseudomallei	Carbapenem, ceftazadime	Fluoroquinolone, TMP-SMX
Acinetobacter species	Carbapenem	Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin
Staphylococcus aureus		
Methicillin susceptible	Antistaphylococcal penicillin[g]	Cefazolin, clindamycin
Methicillin resistant	Vancomycin or linezolid	TMP-SMX
Bordetella pertussis	Macrolide	TMP-SMX

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Empiric vs. Directed Therapy

Table 9. Recommended antimicrobial therapy for specific pathogens.

Organism	Preferred antimicrobial(s)	Alternative antimicrobial(s)
Anaerobe (aspiration)	β-Lactam/β-lactamase inhibitor,[d] clindamycin	Carbapenem
Influenza virus	Oseltamivir or zanamivir	
Mycobacterium tuberculosis	Isoniazid plus rifampin plus ethambutol plus pyrazinamide	Refer to [243] for specific recommendations
Coccidioides species	For uncomplicated infection in a normal host, no therapy generally recommended; for therapy, itraconazole, fluconazole	Amphotericin B
Histoplasmosis	Itraconazole	Amphotericin B
Blastomycosis	Itraconazole	Amphotericin B

Mandell et al. Clin Infect Dis 2007;44:S27-72

Combination vs. Monotherapy for Bacteremic CAP due to *S. pneumoniae*

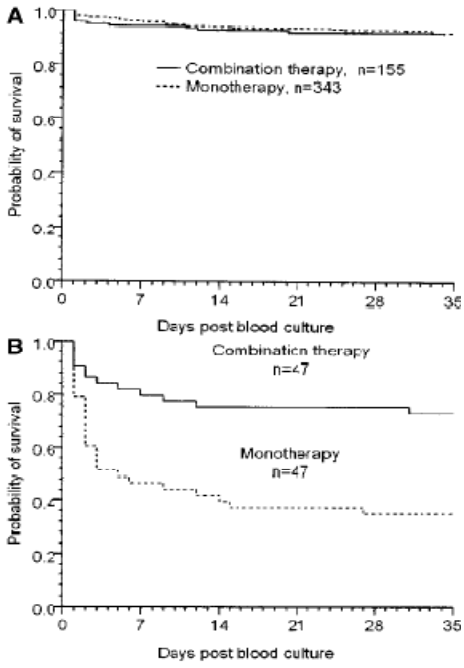
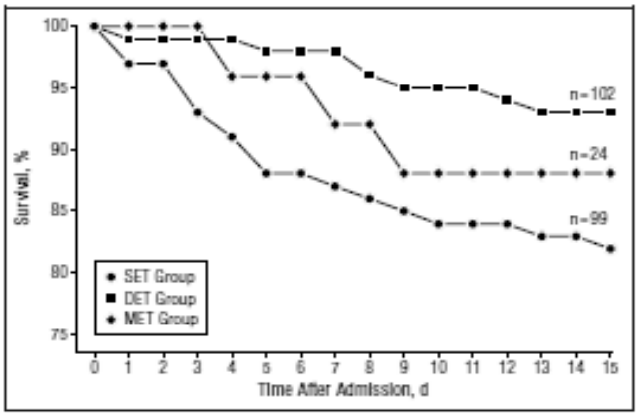


Figure 1. (*A* and *B*) Survival graphs stratified by severity of illness. (*A*) Kaplan–Meier survival plot for patients who were not critically ill as defined by the Pitt bacteremia score. (*B*) Kaplan–Meier survival plot for 94 patients who were critically ill as defined by the Pitt bacteremia score. Combination therapy was superior to monotherapy among critically ill patients ($p < 0.008$, Mantel Cox).

Baddour et al. Am J Repir Crit Care Med 2004;170:440-4

Combination vs. Monotherapy for Bacteremic CAP due to *S. pneumoniae*



Survival by antibiotic therapy group. SET indicates single effective therapy; DET, dual effective therapy; and MET, more than DET. For further explanation see the "Subjects, Materials, and Methods" section.

Waterer et al. Arch Intern Med 2001;161:1837-42

Combination vs. Monotherapy for Bacteremic CAP due to *S. pneumoniae*

Table 4. Prognostic factors independently associated with in-hospital mortality by logistic regression analysis.

Prognostic factor	OR (95% CI)	*P*
Age ⩾65 years	2.52 (1.12–5.67)	.025
Shock	18.3 (7.48–45)	<.0001
Receipt of empirical macrolide therapy	0.4 (0.17–0.92)	.03
Macrolide and penicillin resistance	3.1 (1.05–9.17)	.04

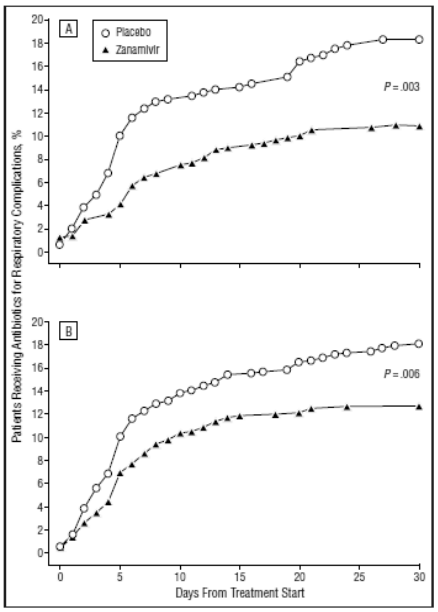
Martinez et al. Clin Infect Dis 2003;36:389-95

Combination vs. Monotherapy for Bacteremic CAP due to S. pneumoniae

- **Survival advantage for combination therapy in severely ill patients?**
  - **Undiagnosed co-infection w/ atypical pathogens?**
  - **Immunomodulatory effects of macrolides?**
    - **↓ Pro-inflammatory cytokines (IL-1,6,8, & TNF-α)**
    - **Inhibit Leukotrine B4 (↓ PMN migration to lung tissue & superoxide anion release)**
- **Recommendation are to use combination therapy in severely ill patients for at least 48hrs or until pathogen is identified.**

Tamaoki et al. Am J Med 2004;8(117):Suppl 9A :5S-11S
Mandell et al. Clin Infect Dis 2007;44:S27-72

Seasonal Influenza: Benefits of Treatment

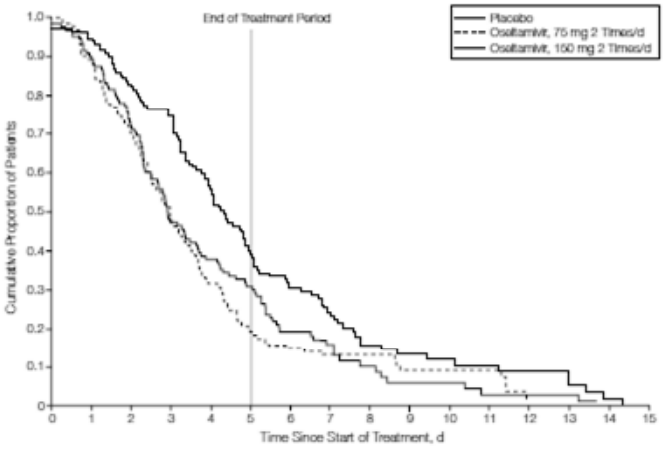


A, Time from treatment start (combined intranasal and inhaled zanamivir vs placebo) to antibiotic prescription for a respiratory tract complication in 1134 patients with laboratory-confirmed influenza illness. Placebo recipients, n=447; zanamivir recipients, n=687. B, Time from treatment start (inhaled zanamivir vs placebo) to antibiotic prescription for a respiratory tract complication in 1572 patients with laboratory-confirmed influenza illness. Placebo recipients, n=765; zanamivir recipients, n=807.

Kaiser et al. Arch Intern Med 2000;160:3234-40

Seasonal Influenza: Benefits of Treatment

Figure 2. Time to Alleviation of All Symptoms in Influenza-Infected Patients



Participants with missing values were censored. One patient (not shown, oseltamivir, 75-mg group) had a censored value of 20.3 days. $P<.001$ for placebo vs oseltamivir, 75 mg twice daily; $P = .006$ for placebo vs oseltamivir, 150 mg, twice daily.

Treanor et al. JAMA 2000;283(8):1016-24

Seasonal Influenza: Benefits of Treatment

Table 4. Number of Influenza-Infected Patients Experiencing Secondary Complications as a Result of Influenza Illness and Antibiotic Use Over the Treatment Period

Complication	Study Group, No.		
	Placebo (n = 129)	Oseltamivir, 75 mg (n = 124)	Oseltamivir, 150 mg (n = 121)
Otitis media	1	0	0
Sinusitis	11	6	4
Bronchitis	8	5	2
Pneumonia	1	0	0
Any secondary complication (%)	19 (15)	11 (9)*	6 (5)*
Antibiotic use (%)	14 (11)	8 (6)†	4 (3)†

*Combined oseltamivir results vs placebo (Fisher exact test), $P = .03$.
†Combined oseltamivir results vs placebo (Fisher exact test), $P = .05$.

- **A statistically significant # of patients returned to normal health and activities in the treatment group compared to placebo**
  - **Oseltamivir 75mg, p < 0.01**
  - **Oseltamivir 150mg, p = 0.03**

Treanor et al. JAMA 2000;283(8):1016-24

Seasonal Influenza: Benefits of Treatment

- Uncomplicated influenza (outpatient)
  - Treat within 48 hours after onset of symptoms
  - If symptoms present for > 48 hours, no benefit from treatment
- Complicated influenza (inpatient)
  - +/- Influenza pneumonia and/or superimposed bacterial pneumonia
  - Benefits of antiviral treatment are unclear given lack of well designed studies (No benefit in 1 retrospective study).
  - Suspect most experts would probably treat.
  - Infection control implications (viral shedding)

Nicholson et al. Lancet 2000;355:1845-50
Monto et al. J Infect Dis 1999;180:254-61
Kaiser et al. Arch Intern Med 2003;163:1667-72
Jefferson et al. Lancet 2006;367:303-13
Kaiser et al. Curr Clin Top Infect Dis 1999;19:112-34
Mandell et al. Clin Infect Dis 2007;44:S27-72

What about 2009 Influenza A H1N1?

Table 4. Factors associated with mortality in hospitalized patients with pandemic (H1N1) 2009: multivariate analysis

	Odds ratio	95% confidence interval	p Value
Age (< 50 years old)	3.36	0.66-17.1	.13
Comorbidities	9.80	1.22-78.6	.03
Time from onset of symptoms to oseltamivir administration (+ 1 day increase)	1.20	1.06-1.35	.004

- > 24 hour delay in administration of Oseltamivir after hospital arrival was associated with ↑ fever above median, LOS above median, need for mechanical ventilation, and mortality
- Oseltamivir may be beneficial even if started > 48 hours after admission.

Viasus et al. Chest 2011 [Epub ahead of print]

Time to 1st Antibiotic Dose

- 2 retrospective studies initially found a survival advantage when 1st dose of antibiotics was given < 8 and < 4 hours respectively.
- No survival advantage found in f/u prospective studies of "care-by-protocol" with pre-set time goals for 1st dose of antibiotics within 4 - 8 hours.
- Patients who present to ER should receive 1st dose of antibiotic while in the ER.
- Patients directly admitted to the hospital from an outpatient office, should receive the 1st antibiotic dose at the office if available.

Mehan et al. JAMA 1997;278:2080-4
Houck et al. Arch Intern Med 2004;164:637-44
Benenson et al. Acad Emerg Med 1999;6:1243-8
Marrie et al. Chest 2005;127:1260-70

Case 1 Continued…

- Sputum Culture – Oropharyngeal flora
- Blood Cultures – No growth
- Urine Antigen Testing
  - *S. pneumoniae* – Negative
  - *Legionella pneumophila* – Positive

Switch From I.V. to P.O & Duration of Antibiotic Therapy

- **Hemodynamic stability, clinical improvement, able to take P.O. medications, and functioning GI tract.**
  - **Up to 2/3 of non-ICU patients meet criteria for clinical stability by day 3 and most by day 7.**
- **Duration of therapy can be shorter than previously thought, but must ensure the following:**
  - **A minimun of 5 days of therapy are provided**
  - **Afebrile for 48-72 hours**
  - **≤ 1 CAP sign of clinical stability**

Mandell et al. Clin Infect Dis 2007;44:S27-72
Ramirez et al. Arch Intern Med 1995;155:1273-6
Dunbar et al. Clin Infect Dis 2003;37:752-60

Switch From I.V. to P.O & Duration of Antibiotic Therapy

Table 10. Criteria for clinical stability.

Temperature ≤37.8°C
Heart rate ≤100 beats/min
Respiratory rate ≤24 breaths/min
Systolic blood pressure ≥90 mm Hg
Arterial oxygen saturation ≥90% or pO_2 ≥60 mm Hg on room air
Ability to maintain oral intake[a]
Normal mental status[a]

NOTE. Criteria are from [268, 274, 294]. pO_2, oxygen partial pressure.

[a] Important for discharge or oral switch decision but not necessarily for determination of nonresponse.

Mandell et al. Clin Infect Dis 2007;44:S27-72

Duration of Antibiotic Therapy

Table 5. Clinical success rates for the clinically evaluable population at the 7–14-day posttherapy visit, according to the Pneumonia Severity Index (PSI) score.

Patient category	*n/N* (%)[a] 750 mg group[b] (*n* = 198)	500 mg group[c] (*n* = 192)	95% CI[d]
Evaluable patients	183/198 (92.4)	175/192 (91.1)	−7.0 to 4.4
Stratum I[e]			
Total	69/76 (90.8)	73/86 (84.9)	−16.5 to 4.7
PSI class III[f]	44/49 (89.8)	44/51 (86.3)	−17.2 to 10.2
PSI class IV[g]	25/27 (92.6)	27/32 (84.4)	−26.1 to 9.6
PSI class V[h]	0/0 (0.0)	2/3 (66.7)	Not applicable
Stratum II[i]	114/122 (93.4)	102/106 (96.2)	−3.4 to 9.0

[a] No. of patients in the category with clinically successful treatment/no. of patients in the category (%).
[b] Levofloxacin, 750 mg q.d. iv or po for 5 days.
[c] Levofloxacin, 500 mg q.d. iv or po for 10 days.
[d] Two-sided 95% CI around the difference (10-day levofloxacin regimen minus 5-day levofloxacin regimen).
[e] PSI classes III, IV, and V combined.
[f] PSI score, 71–90.
[g] PSI score, 91–130
[h] PSI score, >130.
[i] PSI classes I and II combined.

Dunbar et al. Clin Infect Dis 2003;37:752-60

Duration of Antibiotic Therapy

Table 6. Clinical success rates, by pathogen of primary interest, identified in ⩾5 clinically evaluable patients at the 7–14-day posttherapy visit.

Pathogen class, species	*n/N* (%)[a] 750-mg group[b]	500-mg group[c]
Typical pathogen[d]		
Haemophilus influenzae	12/13 (92.3)	13/14 (92.9)
Haemophilus parainfluenzae	12/12 (100.0)	9/10 (90.0)
Streptococcus pneumoniae	20/22 (90.9)	18/20 (90.0)
Atypical pathogen[e]		
Chlamydia pneumoniae	20/22 (90.9)	16/16 (100.0)
Legionella pneumophila	11/11 (100.0)	3/3 (100.0)
Mycoplasma pneumoniae	41/43 (95.3)	34/36 (94.4)

[a] No. of patients infected with the pathogen who had a clinical response of "cure" or "improvement"/no. of patients infected with the pathogen (%).
[b] Levofloxacin, 750 mg q.d. iv or po for 5 days.
[c] Levofloxacin, 500 mg q.d. iv or po for 10 days.
[d] Identified from respiratory-specimen cultures.
[e] Identified using serologic tests.

Dunbar et al. Clin Infect Dis 2003;37:752-60

Duration of Antibiotic Therapy

- **Which patients may NOT be candidates for short course (5-day) therapy?**
  - **Bacteremic *S. aureus* pneumonia**
  - **Pneumonia associated with deep-seated complications (i.e. endocarditis, meningitis, etc.)**
  - **Presence of cavities (i.e. lung abscess) or necrotizing process**
  - **Uncommon pathogens (i.e. endemic fungi)**
  - **Pneumonia due to *P. aeruginosa* ?? (↑ Relapse with 8-day vs. 15-day course for nosocomial pneumonia.)**

Mandell et al. Clin Infect Dis 2007;44:S27-72
Chastre et al. JAMA 2003;290:2588-98

Case 1 Continued…

- **Patient "X" became afebrile within 72 hours after admission and was able to tolerate oral intake without difficulty.**
- **Antibiotic regimen was changed to Levofloxacin 750mg PO q 24 hours.**
- **Received Pneumococcal Polysaccharide Vaccine and Inactivated Influenza Vaccine prior to discharge from the hospital.**
- **Completed a 10-day total course of therapy and returned to normal activities.**

Preventive Measures

Table 13. Recommendations for vaccine prevention of community-acquired pneumonia.

Factor	Pneumococcal polysaccharide vaccine	Inactivated influenza vaccine	Live attenuated influenza vaccine
Route of administration	Intramuscular injection	Intramuscular injection	Intranasal spray
Type of vaccine	Bacterial component (polysaccharide capsule)	Killed virus	Live virus
Recommended groups	All persons ≥65 years of age	All persons ≥50 years of age	Healthy persons 5–49 years of age,[a] including health care providers and household contacts of high-risk persons
	High-risk persons 2–64 years of age	High-risk persons 6 months–49 years of age	
	Current smokers[b]	Household contacts of high-risk persons	
		Health care providers	
		Children 6–23 months of age	

NOTE. Adapted from the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention [304].

[a] Avoid use in persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including diabetes, renal dysfunction, and hemoglobinopathies; persons with immunodeficiencies or who receive immunosuppressive therapy; children or adolescents receiving salicylates; persons with a history of Guillain-Barré syndrome; and pregnant women.

[b] Vaccinating current smokers is recommended by the Pneumonia Guidelines Committee but is not currently an indication for vaccine according to the Advisory Committee on Immunization Practices statement.

Mandell et al. Clin Infect Dis 2007;44:S27-72

Preventive Measures

Table 13. Recommendations for vaccine prevention of community-acquired pneumonia.

Factor	Pneumococcal polysaccharide vaccine	Inactivated influenza vaccine	Live attenuated influenza vaccine
Specific high-risk indications for vaccination	Chronic cardiovascular, pulmonary, renal, or liver disease	Chronic cardiovascular or pulmonary disease (including asthma)	Avoid in high-risk persons
	Diabetes mellitus	Chronic metabolic disease (including diabetes mellitus)	
	Cerebrospinal fluid leaks	Renal dysfunction	
	Alcoholism	Hemoglobinopathies	
	Asplenia	Immunocompromising conditions/medications	
	Immunocompromising conditions/medications	Compromised respiratory function or increased aspiration risk	
	Native Americans and Alaska natives	Pregnancy	
	Long-term care facility residents	Residence in a long-term care facility	
		Aspirin therapy in persons ≤18 years of age	

NOTE. Adapted from the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention [304].

[a] Avoid use in persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including diabetes, renal dysfunction, and hemoglobinopathies; persons with immunodeficiencies or who receive immunosuppressive therapy; children or adolescents receiving salicylates; persons with a history of Guillain-Barré syndrome; and pregnant women.

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Mandell et al. Clin Infect Dis 2007;44:S27-72

Preventive Measures

Table 13. Recommendations for vaccine prevention of community-acquired pneumonia.

Factor	Pneumococcal polysaccharide vaccine	Inactivated influenza vaccine	Live attenuated influenza vaccine
Revaccination schedule	One-time revaccination after 5 years for (1) adults ≥65 years of age, if the first dose is received before age 65 years; (2) persons with asplenia; and (3) immunocompromised persons	Annual revaccination	Annual revaccination

NOTE. Adapted from the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention [304].

[a] Avoid use in persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including diabetes, renal dysfunction, and hemoglobinopathies; persons with immunodeficiencies or who receive immunosuppressive therapy; children or adolescents receiving salicylates; persons with a history of Guillain-Barré syndrome; and pregnant women.

[b] Vaccinating current smokers is recommended by the Pneumonia Guidelines Committee but is not currently an indication for vaccine according to the Advisory Committee on Immunization Practices statement.

Mandell et al. Clin Infect Dis 2007;44:S27-72

Summary

- **There are available tools (i.e. CURB-65, PSI) to help decide whether a patient with CAP can be managed as an inpatient or outpatient.**
  - **Remember that these scores are NOT a substitute for clinical judgment.**
- **Diagnostic tests to determine etiology of CAP should be ordered only in selected patients to maximize yield.**
- **Recognize the common etiologies of CAP, the risk factors for those that are not, and local susceptibility patterns.**

Summary

- **Empiric therapy should always include coverage for the most common etiologies of CAP. Additional coverage should be based on specific risk-factors.**
- **Directed therapy should be undertaken if a responsible pathogen is identified.**
- **Change to oral therapy if available and once patient able to tolerate.**
- **Duration of therapy does not need to be a long one, but must be based on clinical response and physician judgment.**
- **Vaccination as a means of prevention whenever possible.**