Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management and Prevention of Community-Acquired Pneumonia in Immunocompetent Adults

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Joint Statement of PSMID • PCCP • PAFP • PCR
METHODOLOGY

The evidence-based approach and formal consensus techniques (nominal group technique and the Delphi technique) employed in this year’s update were similar to those used during its initial development. This approach includes the initial phase on preparation of the evidence-based report followed by the preparation of the interim report. The interim report was the result of review, discussion of the evidence-based report, and consensus of the group. Consensus was defined as 70% of votes cast, either by written ballots or by raising of hands.

The third phase was the preparation of the draft guidelines, which resulted from an expert panel review of the interim report. This year, the draft of the revised guidelines were presented in the following conventions to gather comments, suggestions and opinions from the other specialists and practitioners.

- 2008 Annual Convention of the Philippine Society for Microbiology and Infectious Diseases (PSMID)
- 2009 Annual Convention of the Philippine Academy of Family Physicians (PAFP)
- 2009 Annual Convention of the Philippine College of Chest Physicians (PCCP)

The same draft guidelines were forwarded to the offices of the following participants:

Organizations:
American College of Chest Physicians- Philippine

Chapter
Alliance for Prudent Use of Antibiotic Philippines, Inc
Critical Care Nurses Association of the Philippines
Philippine Academy of Family Physicians
Philippine Academy of Medical Specialist
Philippine College of Chest Physicians
Philippine College of Emergency Medicine and Acute Care
Philippine College of Physicians
Philippine College of Radiology
Philippine Health Insurance Corporation
Philippine Hospital Infection Control Society, Inc.
Philippine Medical Association
Philippine Nurses Association
Philippine Society for Microbiology and Infectious Diseases, Inc.
Philippine Tuberculosis Society, Inc.
Social Security System

Institutions
Armed Forces of the Philippines Medical Center
Cebu (Velez) General Hospital, Inc.
Davao Doctors' Hospital
Department of Health
East Avenue Medical Center
Lung Center of the Philippines
Makati Medical Center
Manila Doctors Hospital
Ospital ng Maynila Medical Center
University of Perpetual Help Rizal Medical Center
Philippine Heart Center
Research Institute for Tropical Medicine
San Lazaro Hospital
St. Luke's Medical Center
University of the East Ramon Magsaysay Memorial Medical Center
University of the Philippines – Philippine General Hospital
University of Santo Tomas Hospital
Veterans Memorial Medical Center

Pharmaceutical companies
Abbott Laboratories
AstraZeneca
Bayer Philippines, Inc.
Biomedis-Unilab
Cathay Drug Company, Inc.
GlaxoSmithKline
Janssen Pharmaceuticals
Merck Sharp & Dohme
Natrapharm
Novartis Healthcare Philippines
Orient Euro Pharmaceuticals
Pascual Laboratories
Pfizer Philippines Inc.
Roche Philippines, Inc.
Sanofi Pasteur
UAP-Medichem
United Laboratories
Westmont Pharma Inc.
Wyeth Philippines, Inc.
Zuellig Pharma.

The final phase was the preparation of the revised guidelines, which were presented in the annual convention of PSMID 2009.

The completion of this updated guideline is just the beginning of our continuing commitment to bring these clinical practice guidelines into the utilization phase. After all, “Guidelines do not implement themselves”.

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\text{Thelma E. Tupasi, MD, FPSMID} \\
\text{Adviser}
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PHILIPPINE CLINICAL PRACTICE GUIDELINES ON THE DIAGNOSIS, EMPIRIC MANAGEMENT AND PREVENTION OF COMMUNITY-ACQUIRED PNEUMONIA IN IMMUNOCOMPETENT ADULTS

2010 UPDATE

Joint Statement of PSMID • PCCP • PAFP • PCR
Algorithm for the Management -Oriented Risk Stratification of CAP among Immunocompetent Adults

1. CAP

2. Any of the ff:
   1. RR ≥30/min
   2. PR ≥125/min
   3. Temp. ≥40°C or ≤36°C
   4. SBP<90mmHg or DBP<60mmHg
   5. Altered mental status of acute onset
   6. Suspected aspiration
   7. Unstable co-morbid conditions
   8. Chest x-ray: multilobar, pleural effusion, abscess

3. Y
   - Any of the ff:
     1. Severe sepsis and septic shock
     2. Need for mechanical ventilation

4. Y
   - HIGH RISK CAP

5. N
   - ICU ADMISSION

6. N
   - LOW RISK CAP

7. N
   - MODERATE RISK CAP

8. N
   - WARD ADMISSION

9. N
   - OUT-PATIENT

FIGURE 1
INTRODUCTION

Pneumonia is the third leading cause of morbidity (2001) and mortality (1998) in Filipinos based on the Philippine Health Statistics from the Department of Health. These clinical practice guideline on community-acquired pneumonia (CAP), specific only for the empiric therapy of immunocompetent adults, were drafted to provide the clinician with practical approaches in the resolution of important issues in the diagnosis, management and prevention of CAP in adult patients.

This consensus is a collaborative undertaking of various medical specialty societies concerned with the care of patients with CAP:
- Philippine Society for Microbiology and Infectious Diseases (PSMID), Inc.
- Philippine College of Chest Physicians (PCCP)
- Philippine Academy of Family Physicians (PAFP)
- Philippine College of Radiology (PCR)

Inputs from other stakeholders and end users were also taken into account through discussions. These inputs were supplemented by questionnaires using the modified Delphi technique.

The recommendations were based on evidence derived from a critical review of the literature. A systematic search of the literature using computer-based search strategies was first undertaken. Then, relevant articles, including local data, were selected. A Medline search of the medical literature was conducted using combinations of query terms which included community-acquired pneumonia, signs, symptoms, chest radiography, microbiology, sputum Gram’s stain and culture, diagnosis, hospitalization, risk factors, treatment, mortality, outcome, prognosis, prevention, pneumococcal vaccine, and influenza vaccine.

The recommendations in this document incorporate updated information related to the issues addressed in these clinical practice guidelines on the diagnosis, treatment, and prevention of CAP. The summary of evidence after each recommendation serves as the basis for the consensus statements.

These guidelines are intended for the use of medical specialists in infectious diseases, pulmonology, family medicine, and general practitioners, clinical practitioners, nurses, administrators and policy makers.

EXECUTIVE SUMMARY

CLINICAL DIAGNOSIS

1. Can CAP be diagnosed accurately by history and physical examination?
   - Accuracy of predicting CAP by physicians’ clinical judgment is between 60-76%. (Grade B)
   - Clinical prediction rules combining history & physical examination findings may be utilized to presumptively identify patients with pneumonia. (Grade B)

2. Is there any clinical feature that can predict CAP caused by an atypical pathogen?
   - There is no clinical feature that can reliably distinguish pneumonia due to a typical or an atypical pathogen. (Grade A)

CHEST RADIOGRAPHY

3. What is the value of the chest radiograph in the diagnosis of CAP?
   - The Chest x-ray is essential in the diagnosis of CAP, in assessing severity, differentiating pneumonia from other conditions and in prognostication. (Grade A)

4. What specific views of chest radiograph should be requested?
   - Standing posteroanterior and lateral views of the chest in full inspiration comprise the best radiologic evaluation of a patient suspected of having pneumonia. (Grade A)

5. Are there characteristic radiographic features that can predict the likely etiologic agent from the chest radiograph?
   - There is no characteristic radiographic feature that can predict the likely etiologic agent in CAP. (Grade B)

6. How should a clinician interpret a radiographic finding of “pneumonitis”?
   - A radiographic reading of “pneumonitis” should always be correlated clinically. (Grade C)

7. What is the significance of an initial “normal” chest radiograph in a patient suspected to have CAP?
   - An initial “normal” chest x-ray may connote a radiographic lag phase.

8. Should a chest radiograph be repeated routinely?
   - Routine follow-up chest radiograph is not needed for patients with low risk CAP who are clinically improving. (Grade B)

9. What is the role of chest CT scan in CAP?
   - The chest CT scan has no routine role in the evaluation of CAP. (Grade B)

SITE-OF-CARE DECISIONS

10. Which patients will need hospital admission?
    - A management-oriented risk stratification of CAP based on the patient’s clinical presentation/condition, status of any co-morbid condition and chest x-ray findings should be utilized in the decision to determine the site of care for patients. (Grade A)
    - Patients with low-risk CAP are considered suitable for outpatient care in the absence of contraindications. (Grade A)
    - Patients with moderate- and high-risk CAP need to be hospitalized for closer monitoring and/or parenteral therapy. (Grade A)

MICROBIOLOGIC STUDIES

11. What microbiologic studies are necessary in CAP?
    - In Low risk CAP, microbiologic studies are optional. (Grade B)
    - In moderate- and high-risk CAP, blood cultures and Gram stain and culture with antibiotic sensitivity tests of respiratory specimens should be done in laboratories with quality assurance. (Grade A)
    - When possible, tests to document the presence of Legionella pneumophila are recommended in hospitalized CAP. (Grade B)

12. When should antibiotics be initiated for the empiric treatment of CAP?
Community-Acquired Pneumonia

- For patients requiring hospitalization, empiric therapy should be initiated as soon as possible after diagnosis of CAP is made. (GRADE B)
- For low risk CAP, treatment may be delayed. (GRADE C)

13. What initial antibiotics are recommended for the empiric treatment of CAP?
- For low-risk CAP without comorbid illness, amoxicillin remains the standard drug of choice (Grade A). Extended macrolides are recommended when atypical pathogens are suspected. (Grade A)
- For low-risk CAP with stable comorbid illness, β-lactam with β-lactamase inhibitor combinations (BLIC) (Grade A) or 2nd generation cephalosporins (Grade A) with or without extended macrolides are recommended. For patients who have completed first-line treatment (BLIC or 2nd generation cephalosporin) with no response, an extensive work-up should be done to identify the factors for failure of response. Work-up may include doing sputum Gram stain and culture. An alternative treatment is an oral 3rd generation cephalosporin (i.e., cefdinir, cefixime, cefpodoxime proxetil) with or without extended macrolides. (Grade C)
- For moderate-risk CAP, a combination of an IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) with either an extended macrolide or respiratory fluoroquinolone is recommended as initial antimicrobial treatment. (Grade B)
- For high-risk CAP without risk for Pseudomonas aeruginosa, a combination of an IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) with an extended macrolide and aminoglycoside (Grade A) or a combination of an IV antipseudomococcal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) and IV Ciprofloxacin or high dose IV Levofloxacin. (Grade B)

14. How can response to initial therapy be assessed?
- Temperature, respiratory rate, heart rate, blood pressure, sensorium, oxygen saturation and inspired oxygen concentration should be monitored to assess response to therapy.
- Response to therapy is expected within 24-72 hours of initiating treatment. Failure to improve after 72 hours of treatment is an indication to repeat the chest radiograph. (Grade A)
- Follow-up cultures of blood and sputum are not indicated for patients who are responding to treatment. (Grade A)

15. When should de-escalation of empiric antibiotic therapy be done?
- De-escalation of initial empiric broad-spectrum antibiotic or combination parenteral therapy to a single narrow-spectrum parenteral or oral agent based on available laboratory data is recommended once the patient is clinically improving, is hemodynamically stable and has a functioning gastrointestinal tract. (Grade B)

16. Which oral antibiotics are recommended for de-escalation or switch therapy from parenteral antibiotics?
- The choice of oral antibiotics following initial parenteral therapy is based on available culture results, antimicrobial spectrum, efficacy, safety and cost. In general, when switching to oral antibiotics, either the same agent as the parenteral antibiotic or the same drug class should be used.

17. How long is the duration of treatment for CAP?
- Duration of treatment is 5 to 7 days for low-risk uncomplicated bacterial pneumonia. (Grade B)
- For moderate- to high-risk CAP or for those with suspected or confirmed gram negative, Staphylococcus aureus or P. aeruginosa pneumonia treatment should be prolonged to 14 to 21 days. (Grade B)
- A 10 to 14-days treatment regimen is recommended for Mycoplasma and Chlamydia phila while Legionella is treated for 14 to 21 days. (Grade B)
- A 5-day course of oral or IV therapy for low-risk CAP and 10-day course for Legionella pneumonia are possible with new agents such as the azalides, which possess a long half-life and high tissue level prolonging their duration of effect. (Grade B)
- Patients should be afebrile for 48 to 72 hours with no signs of clinical instability before discontinuation of treatment. (Grade B)

18. What should be done for patients who are not improving after 72 hours of empiric antibiotic therapy?
- The clinical history, physical examination and the results of all available investigations should be reviewed. The patient should be reassessed for possible resistance to the antibiotics being given or for the presence of other pathogens such as Mycobacterium tuberculosis, viruses, parasites or fungi. Treatment should then be revised accordingly. (Grade B)
- Follow-up chest radiograph is recommended to investigate for other conditions such as pneumothorax, cavitation and extension to previously uninvolved lobes, pulmonary edema and acute respiratory distress syndrome. (Grade B)
- Obtaining additional specimens for microbiologic testing should be considered. (Grade B)

19. When can a hospitalized patient with CAP be discharged?
- In the absence of any unstable coexisting illness or other life-threatening complication, the patient may be discharged once clinical stability occurs and oral therapy is initiated. (Grade A)
- A repeat chest radiograph prior to hospital discharge is not needed for a patient who is clinically improving. (Grade B)
- A repeat chest radiograph is recommended during a follow-up visit, approximately 4 to 6 weeks after hospital discharge. The repeat chest radiograph will establish a new radiographic baseline and exclude the possibility of malignancy associated with CAP, particularly in older smokers. (Grade B)

PREVENTION

20. How can CAP be prevented?
- Influenza vaccination is recommended for the prevention of CAP. (Grade A)
- Pneumococcal vaccination is recommended for the prevention of invasive pneumococcal disease (IPD) in adults. (Grade A)
- Smoking cessation is recommended for all persons with CAP who smoke. (Grade A)

PART ONE: CLINICAL DIAGNOSIS

1. Can CAP be diagnosed accurately by history and physical examination?
- Accuracy of predicting CAP by physicians’ clinical judgment is between 60-76%. (Grade B)
- Clinical prediction rules combining history & physical examination findings may be utilized to presump tively identify patients with pneumonia. (Grade B)
Community-Acquired Pneumonia

CAP is a lower respiratory tract infection acquired in the community within 24 hours to less than 2 weeks. It commonly presents with an acute cough, abnormal vital signs of tachypnea (RR >20 breaths per minute), tachycardia (cardiac rate >100/minute), and fever (T >37.8°C) with at least one abnormal chest finding of diminished breath sounds, rhonchi, crackles or wheeze.

However, no particular clinical symptom or abnormal finding is sufficiently sensitive or specific to confirm or exclude the diagnosis of CAP from other acute lower respiratory tract infections. Clinical prediction rules combining history and physical examination findings may be utilized to presumptively identify patients with pneumonia.

The accuracy of predicting CAP by these clinical findings is only between 60-76%. Uncommon presentations of CAP (i.e., minimal physical findings and extrapulmonary symptoms) may partly explain such low accuracy.

Summary of evidence:
CAP is commonly defined as an acute infection of the pulmonary parenchyma with symptoms of acute illness accompanied by abnormal chest findings. Patients who acquire the infection in hospitals or long-term facilities are typically excluded from the definition. There is reported significant inter-observer agreement among physicians in obtaining clinical symptoms and signs in diagnosing patients with possible CAP. Furthermore, elderly patients may not present with the classical symptoms of fever, cough, and dyspnea. Like the history in Table 1, abnormal lung findings depend on the cut-off value set by studies in defining abnormal findings. 

Prospective cohort trials evaluated the sensitivity and specificity of the clinical history in pneumonia. Using the chest radiograph as the reference for the diagnosis of pneumonia, none of the trials proved that symptoms are important in ruling in or ruling out the diagnosis of pneumonia.

In a recent review by Metlay et al. symptoms of fever and cough do not distinguish between community acquired pneumonia and other causes of respiratory illness. As shown in Table 1, the positive likelihood ratio (LR+) for the presence of pneumonia and the negative likelihood ratio (LR-) for the absence of pneumonia are close to 1. This indeterminate ratio of 1 does not generate moderate or large shifts in disease probability.

Physical Examination

Vital sign abnormalities on the probability of pneumonia depend on the cut-off value set by studies in defining an abnormal result. A respiratory rate greater than 20 breaths/min resulted in a likelihood ratio of only 1.2 in one study but a respiratory rate greater than 25 breaths/min increased the likelihood ratio to 1.5 to 3.4. In contrast, one study has shown that normal vital signs (respiratory rate, heart rate, and temperature) significantly decreased the probability of CAP (negative likelihood ratio = 0.18). This result reduced the pretest odds by more than fivefold.

Like the history in Table 1, abnormal lung findings (e.g., crackles) increase the probability of pneumonia by only a small amount. Egophony (LR+ 2.0 – 8.6) may significantly increase the likelihood of pneumonia. However, its impact may only be modest with a positive predictive value ranging from as low as 20% to no higher than 56%. Normal chest examination findings have little effect on the probability of pneumonia with a likelihood ratio of only 0.6.

Table 1. Accuracy of history and physical examination for the diagnosis of community-acquired pneumonia*

<table>
<thead>
<tr>
<th>Type of Finding**</th>
<th>Positive Likelihood Ratio ‡</th>
<th>Negative Likelihood Ratio §</th>
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<tr>
<td>Medical History</td>
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<tr>
<td>Fever</td>
<td>1.7 - 2.1</td>
<td>0.6 - 0.7</td>
</tr>
<tr>
<td>Chills</td>
<td>1.3 - 1.7</td>
<td>0.7 - 0.9</td>
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<tr>
<td>Vital Signs</td>
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<tr>
<td>Tachypnea *</td>
<td>1.5 - 3.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Tachycardia *</td>
<td>1.6 - 2.3</td>
<td>0.5 - 0.7</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>1.4 - 4.4</td>
<td>0.6 - 0.8</td>
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<tr>
<td>Chest Examination</td>
<td></td>
<td></td>
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<tr>
<td>Dullness</td>
<td>2.2 - 4.3</td>
<td>0.8 - 0.9</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>2.3 - 2.5</td>
<td>0.6 - 0.8</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>1.4 - 1.5</td>
<td>0.8 - 0.9</td>
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<tr>
<td>Egophony</td>
<td>2.0 - 8.6</td>
<td>0.8 - 1.0</td>
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</table>

* Adapted from Metlay et. al. ** Only findings that were statistically significantly associated with the presence and absence of pneumonia in at least two studies were included (p<0.05 in a two-tailed chi-square or Fisher exact test). ‡ Positive likelihood ratio for pneumonia when finding is present (sensitivity/1 – specificity) and raises probability of disease (LR >1). Negative likelihood ratio for pneumonia when finding is absent (1 – sensitivity/specificity) and lowers probability of disease (LR <1). As explained in this study LR greater than 0.5 or less than 0.2 generate moderate to large shifts in disease probability LR of 2 to 5 and 0.5 to 0.2 generate small changes in disease probability LR of 1 to 2 and 0.5 to 1 generate rarely important changes in disease probability § Tachypnea defined as respiratory rate >25 breaths/minute. ¶ Tachycardia defined as heart rate >100 beats/minute in 2 studies and >120 beats/min in a third study.

Combination of History and Physical Examination

Prediction rules combining history and physical examination significantly affect the probability of pneumonia. Table 2 shows the accuracy of predicting pulmonary infiltrates utilizing the Gennis et. al. rule and Heckerling et al. score. Application of the two studies results in better prediction of CAP exceeding that of physician’s clinical judgment. These prediction rules may be utilized to help physicians identify patients who may have pneumonia and therefore need a chest x-ray.

Table 2. Accuracy of predicting pneumonia by physicians’ clinical judgment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decision Basis</th>
<th>Physician’s Clinical Judgment</th>
<th>Heckerling et. al. Score (threshold was 2 points)</th>
<th>Gennis et.al. Rule (threshold was 1 point)</th>
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</thead>
<tbody>
<tr>
<td>History Physical findings</td>
<td>Temperature of 37.8°C</td>
<td>Pulse of &gt;100/minute</td>
<td>• Temperature of 37.8°C</td>
<td>• Respiration of &gt;20/minute</td>
</tr>
<tr>
<td></td>
<td>Rate decreased breath sounds</td>
<td>Absence of asthma</td>
<td>60%</td>
<td>68%</td>
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Three studies have proven that combinations of history and physical examination findings significantly affect the probability of pneumonia. Assuming a baseline prevalence of pneumonia of 5%, a prediction rule may
be applied to a patient with an acute cough, fever, tachycardia and crackles. In this case, the revised probability of pneumonia increases within the range of 18% to 42%. In contrast, the probability of pneumonia is estimated to range only from 1% to 13% in a patient with an acute cough but with normal vital signs.10

2. Is there any clinical feature that can predict CAP caused by an atypical pathogen?
- There is NO clinical feature that can reliably distinguish pneumonia due to a typical or an atypical pathogen. (Grade A)

The initial CAP guidelines by the American Thoracic Society have clearly stated that symptoms cannot be reliably used to establish the etiologic diagnosis of pneumonia (typical or atypical pathogen)15. According to these guidelines, the clinical presentation of pneumonia may vary because of three reasons: the virulence factors of the pathogens; the advanced age of the host; and the presence of coexisting illnesses of the host. These reasons result in an overlap of clinical symptoms among the pathogens 10. Furthermore, mixed organisms may cause approximately 5 to 38% cases of CAP16.

Summary of Evidence

Atypical pathogens are a common cause of CAP in all regions of the world with a global incidence of 22%.16 The main feature differentiating atypical from typical CAP pathogens is the presence of extrapulmonary findings14. Pneumonia caused by typical pathogens (Streptococcus pneumoniae, Hemophilus influenzae or Moraxella catarrhalis) present with clinical findings limited to the lungs. Each of the atypical pathogens commonly implicated in CAP (Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila) has a predilection for certain extrapulmonary organ systems (GI, cutaneous). Therefore, the presence of the extrapulmonary findings can help the clinician narrow down the diagnostic possibility of CAP due to an atypical pathogen.

However, most studies in the literature have been unable to clearly differentiate pneumonia caused by a typical pathogen from pneumonia caused by an atypical pathogen based on individual clinical findings.17-21 As a result of this clinical dilemma, Cunha has proposed a weighted syndromic approach, based on the relative clinical specificity of characteristic findings.16,17,20 (See Appendix 2)

Suspect Legionella in hospitalized CAP because it is the most important atypical pathogen in terms of severity. Infection with Legionella spp. ranks among the three most common causes of severe pneumonia and is isolated in 1-40% of cases of hospital-acquired pneumonia.23 Legionella can be differentiated from Chlamydia pneumoniae and Mycoplasma pneumoniae because its extrapulmonary manifestations are very distinct from them.16 However, it is not possible to clinically distinguish patients with Legionnaire’s disease from patients with pneumococcal pneumonia. Several prospective studies have shown that the two diseases have nearly similar clinical and radiologic findings and that laboratory tests results cannot differentiate between the two diseases.24-26 Strong suspicion for Legionella should be considered with unexplained confusion, lethargy, loose stools or watery diarrhea, abdominal pain, relative bradycardia and lack of response to B-lactams.27,29

REFERENCES:
12. Jaeschke R, Guyatt G, Sackett DL. Users’ guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-based medicine working group. JAMA 1994; 271: 742-745.

II. CHEST RADIOGRAPHY

3. What is the value of the chest radiograph in the diagnosis of CAP?
- The Chest x-ray is essential in the diagnosis of CAP, assessing severity, differentiating pneumonia from other conditions and in prognostication. (Grade A)

A new parenchymal infiltrate in the chest radiograph remains the reference diagnostic standard for pneumonia.
A chest X-ray should be done in patients suspected to have CAP to confirm the diagnosis. However, in settings with limited resources, a chest x-ray may not be routinely done in patients strongly suspected to have CAP with the following conditions:
1. Healthy individuals or those with stable co-morbid conditions, AND
2. Normal vital signs and physical examination findings, AND
3. Reliable follow-up can be ensured.

In addition to confirming the diagnosis of pneumonia, an initial chest radiographic examination is essential in assessing the severity of disease and the presence of complications. Chest radiographs are sometimes useful for suggesting the etiologic agent, prognosis, alternative diagnosis, and associated conditions. Findings of bilateral or multilobar involvement, progression of infiltrates within 24 hours of the initial chest x-ray, pleural effusion, and lung abscess are suggestive of severe disease, poor prognosis; these findings indicate the need for hospital admission.

4. What specific views of chest radiograph should be requested?
   • Standing posteroanterior and lateral views of the chest in full inspiration comprise the best radiologic evaluation of a patient suspected of having pneumonia. (Grade A)

A posteroanterior radiograph places the patient with his or her chest against the film, minimizing the magnification of the heart and the mediastinum on the image, thus minimizing the amount of lung obscured by these structures. Similarly, on the lateral view, the size of the heart on the image is minimized if the left side is against the film. The left-lateral is therefore the preferred position for the lateral view.1 If pneumonia is localized on the postanterior view, the specific lateral view should be requested. Additional supplemental views such as lordotic, coned, or oblique views may be done to further evaluate regions that may not be readily seen in the routine studies.

5. Are there characteristic radiographic features that can predict the likely etiologic agent from the chest radiograph?
   • There is no characteristic radiographic feature that can predict the likely etiologic agent in CAP. (Grade B)

Pneumonia caused by atypical pathogens such as Mycoplasma, Legionella, and Chlamydia, creates a daunting task of differentiation from those produced by bacterial or viral etiologies due to overriding clinico-radiologic features. The radiographic presentations in general are non-specific, varying from interstitial or reticulonodular pattern to patchy consolidations which may be seen separately or sequentially, segmental or lobular. These pathogens are rarely associated with pleural effusion and lymphadenopathy. There is a greater weight given to the importance of comparative follow-up studies in arriving at the diagnosis considering most of said etiologies do not respond to conventional antimicrobials, hence, remains radiographically stable despite prompt and adequate treatment.

6. How should a clinician interpret a radiographic finding of "pneumonitis"?
   • A radiographic reading of "pneumonitis" should always be correlated clinically. (Grade C)

A radiographic reading of "pneumonitis" does not always denote an infectious process. Non-infectious causes of pneumonitis may include fibrosis (immunologic, occupational lung disease), thus a pneumonitis finding should always be correlated clinically. If pneumonitis is infectious in nature, it could relate to the first stage in the process of pneumonia. This is the congestive phase, where infection is contained within the interstitial compartment or peribronchial region before it extends to involve the alveoli (consolidation).

7. What is the significance of an initial "normal" chest radiograph in a patient suspected to have CAP?
   • An initial "normal" chest x-ray may connote a radiographic lag phase.

A "normal" chest radiograph connotes an absence of any overt parenchymal lesion. It is possible to have a "normal chest" in a background of significant symptomatology specifically in an early phase of pneumonia, that is referred to as a "radiographic lag phase". For patients who are hospitalized for suspected pneumonia but who have initial negative chest radiography findings, it may be reasonable to treat their condition presumptively with antibiotics and repeat the imaging in 24 to 48 hours.3

8. Should chest radiograph be repeated routinely?
   • Routine follow-up chest radiograph is not needed for patients with Low Risk CAP who are clinically improving. (Grade B)

In patients with Low Risk CAP who are recovering satisfactorily, a repeat chest x-ray is not needed. However, if the patient with CAP is not clinically improving or shows progressive disease, the chest x-ray should be repeated as needed based on the clinician's judgment.

In the absence of any unstable coexisting illness or other life-threatening complication, the patient may be discharged once clinical stability occurs and oral therapy is initiated. There is no need to repeat a chest radiograph prior to hospital discharge in a patient who is clinically improving. However, a repeat radiograph is recommended during a follow-up office visit, approximately 4 to 6 weeks after hospital discharge. The repeat radiograph will establish a new radiographic baseline and to exclude the possibility of malignancy associated with CAP, particularly in older smokers.3

9. What is the role of chest CT scan in CAP?
   • The chest CT scan has no routine role in the evaluation of CAP. (Grade B)

The role of CT scan imaging in CAP is minimal considering that this modality is dependent on morphologic features present in a wide latitude of pathologies. It is, however, helpful in excluding other pathologies (i.e., neoplastic, interstitial disease or granulomatous) masquerading as infectious and for the further evaluation of nonresolving or progressive pneumonia seen on follow-up chest x-ray.

Summary of Evidence
Physicians' ability to assess CAP on clinical grounds is low and cannot replace chest radiographs.4 Consensus statements from professional organizations strongly recommend the need for chest radiography to confirm the diagnosis of CAP.5,6 In addition, the chest radiograph is requested to detect associated lung disease, to gain insight into the causative agent (in some cases), to assess severity and to obtain a baseline to assess response.5 A different recommendation from a British study suggests that chest radiographs be performed only when
Community-Acquired Pneumonia

there are focal chest signs, when the symptoms worsen with antibiotic therapy, or when recovery is slower than expected.7

A study by O’Brien et al9 showed that vital sign and physical examination findings are useful screening parameters for CAP, demonstrating a sensitivity of 95%, a specificity of 56%, and an odds ratio of 24.9 in the presence of vital sign or physical examination abnormalities. The data suggest that chest radiographs are unnecessary in patients with acute respiratory symptoms who present with normal vital signs and physical examination findings. Because approximately 5% of cases would be missed, however, these criteria are useful only for patients with reliable follow-up and a low likelihood of morbidity if CAP is not detected initially.8

Although inter-observer variability in the interpretation of x-ray patterns has been cited in the literature, there is general agreement among radiologists as to the presence or absence of infiltrate.9 In a multivariate analysis of patient outcome, radiographic spread or bilateral involvement of pneumonia was related to mortality (Table 3).10 In a meta-analysis of prognosis and outcome of patients with CAP multi-lobar radiographic pulmonary infiltrates (OR = 3.1; 95% CI, 1.9-5.1) was shown to be significantly associated with mortality.11

Chest radiographic findings usually clear more slowly than clinical findings and multiple radiographs are generally not required.12 Follow-up chest X-ray should not be done too early as pneumonia infiltrates may persist unless the patient fails to respond. Follow-up Chest X-ray during hospitalization may be indicated to assess the position of an endotracheal tube or central line and to exclude pneumothorax after central line placement or to determine other reasons for failure to respond.13 In addition to progression of disease, possible pulmonary complications such as pleural effusion (10.6%), empyema (5.2%), lung abscess, or atelectasis should be assessed.13,14

Table 3. Chest radiographic findings which may predict a complicated course

<table>
<thead>
<tr>
<th>Chest radiographic findings</th>
<th>Odd Ratio</th>
<th>95 % C.I *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilobar radiographic pulmonary infiltrate</td>
<td>3.1</td>
<td>1.9 - 5.1</td>
</tr>
<tr>
<td>Bilateral pleural effusion</td>
<td>2.8</td>
<td>1.4 - 5.8</td>
</tr>
</tbody>
</table>

* Confidence Interval

REFERENCES:


III. SITE OF CARE DECISIONS

10. Which patients will need hospital admission?

• A management-oriented risk stratification of CAP based on the patient’s clinical presentation/condition, status of any co-morbid condition and chest x-ray findings should be utilized in the decision to determine the site of care for patients. (Grade A)

• Patients with low-risk CAP are considered suitable for out-patient care in the absence of contraindications. (Grade A)

• These patients with moderate- and high-risk CAP need to be hospitalized for closer monitoring and/or parenteral therapy. (Grade A)

The physician’s decision to hospitalize a patient is generally based on the stability of the patient’s clinical condition, the presence or absence of other active medical problems, the risk of death and complications, and sometimes psychosocial considerations. Disease-specific prognostic indicators may be used to assess the initial severity of pneumonia and may help guide the physician to determine the site of care: the out-patient, a medical ward or ICU. However, these guidelines should always be applied in conjunction with the physician’s clinical judgment, supplemented by objective findings; the initial decision may be altered depending on the clinical course. Patients with CAP can be classified into three risk categories (Table 4) to help determine the need for hospitalization. Figure 1 shows the algorithm for the management-oriented risk stratification of CAP in immunocompetent adults.

Recognition of patients at low risk of complications and therefore suitable for treatment out of the hospital has the potential to reduce inappropriate hospitalization and consequently inherent morbidity and costs. When hospital admission is required, further management is also influenced by the illness severity. Early identification of patients at high risk of death allows initiation of appropriate antibiotic therapy and admission to an intensive care setting where assisted ventilation and other support can be readily initiated if necessary.

Low Risk CAP

Adult patients with stable vital signs (Respiratory Rate (RR) <30 breaths/minute, Pulse rate (PR) <125 beats/minute, Temperature >36°C or <40°C, Systolic Blood Pressure (SBP) >90 mmHg, and Diastolic Blood Pressure (DBP) >60 mmHg) are associated with low morbidity and
mortality rate of 1-3% and are thus categorized as Low Risk CAP. These patients are considered suitable for out-patient care in the absence of contraindications.

Clinically immunocompetent patients with CAP and with stable or medically controlled co-morbid conditions such as diabetes mellitus, neoplastic disease, neurologic disease, congestive heart failure (CHF) class I, coronary artery disease (CAD), renal insufficiency, chronic obstructive pulmonary disease (COPD) and/or Asthma, chronic liver disease, and chronic alcohol abuse, are also classified under this risk category. There should be no altered mental status of acute onset or evidence of aspiration. Ability to safely and reliably take oral medication should also be taken into consideration. Chest x-ray findings should show localized infiltrates with no evidence of pleural effusion or abscess. These patients may be treated as out-patients if there is reasonable assurance for follow-up.

Moderate Risk CAP

Patients with any one of the following physical findings: RR>30 breaths/ minute, pulse rate ≥125 beats/minute, or temperature ≥36°C or ≥40°C; DBP ≤60 mmHg and SBP <90 mmHg; those with suspected aspiration; or those with altered mental status of acute onset have a higher mortality rate of 8-10% and are thus categorized as Moderate Risk CAP. Decompensated co-morbid conditions (as described previously) which may aggravate or be aggravated by the pneumonia are included in this category. Radiographic findings include bilateral or multilobar involvement, pleural effusion, or abscess. These patients need to be hospitalized for closer monitoring and/or parenteral therapy.

High Risk CAP

Patients with any one of the criteria under the moderate risk CAP category plus signs of severe sepsis/septic shock or who need for mechanical ventilation are associated with higher mortality rate of 20-30% and are thus categorized as High Risk CAP warranting admission in the intensive care unit.

Summary of Evidence

The decision regarding site of care- whether the patient should be treated as an outpatient, in a hospital ward, or in the ICU carries with it a number of important implications. It often determines the type and extent of diagnostic testing, the choice, spectrum and route of administration of antimicrobial therapy, the intensity of clinical observation, and the overall treatment costs.12,3

The evidence for risk stratification comes from several researches which studied the effects of the implementation of a risk-based triage protocol in the admission of patients with CAP. Objective site of care criteria has been developed.4-6 These include severity-of- illness assessment scores such as the CURB score and its modifications (CURB 65 criteria - confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater; the CRB-65, which omits the blood urea measurement) or prognostic models such as the Pulmonary Severity Index (PSI). Local studies had looked into these.7-10 These objective tools or scoring systems can also serve as an aid to improve the validity of clinical decision making in conjunction with clinical judgment.

As advancing age has consistently been shown to be associated with higher mortality from CAP in all studies to date, inclusion of age to assess CAP severity would seem to be appropriate.11,12 Several studies have shown a direct association between age and mortality4 with an OR of 2.7; 85% CI 1.4-4.1 for age ≥65 years as an independent predictor of a complicated course.13

However, a prediction rule based on the Pneumonia Severity Index (PSI) validated in more than 50,000 patients from a variety of inpatient and outpatient protocols has emphasized that an age of more than 65 years alone is not an indication for admission.14 A study by Halm et al15 has also confirmed that selected low-risk elderly patients with pneumonia can be treated as outpatients with good results. A review by Ewig and Welte16 stated that although age is a strong predictor of death from CAP, it is not a good argument in favor of hospital admission in the absence of other severity criteria.

Although the statistical risk of death is clearly independently increased by age it should not be the sole criterion for hospital admission as other severity criteria should also be considered. A review of pneumonia in the older patient by Niederman and Brito17 showed that older patients with CAP should have multiple factors such as signs of severe illness, decompensated co-morbidities or high risk of death as defined by prognostic scoring systems to be included in the evaluation of need of hospitalization and mortality risk supportive of clinical judgment. Kothe et al12 examined the role of ageing as a cause of increased CAP mortality. Using a large German database from the Community Acquired Pneumonia Competence Network (CAPNETZ) study, the investigators found that age ≥65 years itself was a risk factor for mortality.

Whether ageing itself adds to this mortality risk or whether the adverse outcomes of CAP in the elderly are consequences of other factors, some of which might be modified, such as the presence of co-morbid illnesses and the therapies required to manage them, or the delays in the diagnosis of pneumonia that result from indistinct clinical presentations in the elderly remains to be resolved.13

Pneumonia can also lead to worsening or exacerbation of chronic underlying medical illnesses, which by themselves may require hospital admission irrespective of the severity of Pneumonia.4,13 The presence of co-existing illnesses or other findings such as chronic obstructive airway disease19,20,21,22, diabetes Mellitus21,22, congestive heart failure15,21,22, chronic renal failure, chronic liver disease23 or chronic alcohol abuse or malnutrition are specific risk factors for mortality or a complicated course of Pneumonia.23

The presence of decompensated comorbid conditions as basis for admission is validated by the study of Minohue et al. which showed that 7.5% of initially ambulatory patients were subsequently hospitalized within 30 days due to factors related to CAP or due to co-morbidity.24 Cerebrovascular disease was also identified as an independent risk factor for mortality in the elderly patient population.17 The co-existence of neurological and gastrointestinal diseases may account for increased risk of aspiration as a common mechanism of infection.13 Approximately 10% of CAP cases are due to aspiration pneumonia.25,26

In a prospective study involving 1068 patients presenting to the hospital with the diagnosis of pneumonia, various clinical features were analyzed for their association with 30 day mortality. These features include the follow-
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...acute confusion (OR=8.1; 95% CI 4.8-13.7); BUN >19.6 mg/dL or >7 mmol/L (OR=5.6; 95% CI 3.1-10); RR >30 (OR=1.7; 95% CI 1.07-2.8); low BP (SBP <90 or DBP <60) (OR 2.4; 95% CI 1.4-3.8 and age >65 years (OR=5.5; 95% CI 2.8-10.9).\(^{30}\) Chalmers JD et al noted on multivariate logistic regression that reduced admission systolic BP <90 mmHg, diastolic BP <60 mmHg, mean arterial pressure <70 mm Hg and pulse pressure <40 mmHg were identified as independent predictors of 30 day mortality and mechanical ventilation and/or inotropic support. However, admission systolic BP alone was found superior to other hemodynamic predictors of 30 day mortality and the need for mechanical ventilation and/or inotropic support. In CAP\(^{31}\) Confusion was defined as new-onset disorientation to person, place or time that is not known to be chronic.\(^{4}\)

In a meta-analysis by Metlay JP et al, 3 laboratory test abnormalities and 1 radiographic finding were found to have statistically significant association with death. These include azotemia (in which the median definition was BUN >7.14 mmol/L (20 mg/dL) (OR=7.9; 95% CI 2.6-24); leukocytosis (in which the median definition was leukocyte count (>10 x 10\(^9\) cells/L); leukopenia (in which the median definition was leukocyte count (<10 x 10\(^9\) cells/L); and multilobar infiltrate on chest radiograph with each associated with an increased odds of death between 2.7 to 5.1.\(^{32}\) In the Australian CAP Study (ACAPS) involving 882 CAP episodes, they found statistically significant association of requirement for intensive respiratory or vasopressor support (IRVS) with low systolic BP (<90 mmHg), multilobar chest radiography involvement, low albumin level (<3.5 g/dL), high RR (>25/min for those <50 years of age; and >30/min for those >50 years of age), tachycardia (>125/min), confusion (new onset), poor oxygenation (PaO\(_2\) <70 mmHg; O\(_2\) sat <93%; PaO\(_2\)/FiO\(_2\) <333; if age 50 or <60 mmHg; O\(_2\) sat <90%; PaO\(_2\)/FiO\(_2\) <250; if >50 years of age) and low arterial pH (<7.35). This SMART-COP scoring tool could also help identify patients with CAP who will require IRVS.\(^{33}\) The above findings were also noted as part of the minor criteria for severe CAP in the IDSA ATS 2007 CAP guidelines, which also included thrombocytopenia (platelet count <100,000 cells/mm\(^3\)).\(^{4}\)

Studies which found urea >7 mmol/L to be an independent predictor of mortality included a larger number of younger patients.\(^{34-38}\) However, it may not be a good measure in predicting severity of CAP, esp. in older people, where the urea level may be confounded by multiple factors such as dehydration, hypertension, and diabetes, the prevalence of which are high in an older population.\(^{39}\) Leukopenia (WBC <4,000 cells/mm\(^3\)) resulting from CAP has consistently been associated with excess mortality and as increased risk of complications such as acute respiratory distress syndrome (ARDS).

Another severity assessment scoring system based on the PIRo (Predisposition, Insult, Response, and Organ Dysfunction) concept including the presence of the following variables: co-morbidities, age >70 years; multilobar opacities in chest radiograph; shock, severe hypoxemia; acute renal failure; bacteremia and acute respiratory distress syndrome has been developed. It was designed to stratify critically ill patients with CAP at ICU within 24 hours from admission.\(^{39}\) Espana et al also tried to develop a more specific scoring system for ICU admission. The need for ICU admission was defined by the presence of one of two major criteria: arterial pH <7.3 or Systolic BP <90 mm Hg. In the absence of the major criteria, severe CAP also could be identified by the presence of 2 of 3 minor criteria as follows: confusion, BUN >30 mg/dL; RR >30/min; PaO\(_2\)/FiO\(_2\) ratio <250, multilobar infiltrates and age of at least 80 years.\(^{38-39}\)

Patients with severe pneumonia are more hypoxic. Respiratory failure is a leading cause of death among patients admitted with CAP.\(^{40,41}\) Multivariate analysis showed that PaO\(_2\) <60 mmHg (OR=7.95; 95% CI:3.4-27.5), PaCO\(_2\) >45 mmHg (OR=4.6; CI:2.3-15.1); RR >30/minute (OR=12.25; CI:3.45-35.57), pleural effusion (OR=8.6; 95% CI 2.01-24.7), septic shock (OR=12.6; 95% CI: 3.4-45.66) and renal failure (OR=13.4; 95% CI: 3.2-37.8)\(^{20}\) were significantly related to mortality. The need for mechanical ventilation as well as higher risk for morbidity and mortality are associated with the following: An arterial saturation of <90%, low PaO\(_2\) <60 mmHg and low PaO\(_2\)/FiO\(_2\) or PF Ratio <250 mmHg also indicate severity and complication of pneumonia.\(^{4,11,38,44-45}\) Arterial PCO\(_2\) levels higher than 45 mmHg or progressively increasing PCO\(_2\) levels, are also reflective of increasing severity of respiratory failure, requiring mechanical ventilation.

Sepsis is defined as infection plus systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced acute organ dysfunction or tissue hypoperfusion. Septic shock is defined as sepsis induced hypotension (SBP of <90 mmHg or mean arterial pressure <70 mmHg or SBP decrease >40 mmHg or <2 standard deviation below normal for age in the absence of other causes of hypotension) persisting despite adequate fluid resuscitation.\(^{41}\) Even in CAP due to different etiologies, the frequency of severe sepsis may exceed 50%.\(^{34}\) Septic shock is a known risk factor for mortality from pneumococcal infection.\(^{50}\) Severe CAP (Risk Ratio 6.8 95% CI 4.6-10.1) and the presence of either septic shock with need for vasopressors (Risk Ratio 7.0 95% CI 4.1-11.9) or mechanical ventilation (Risk Ratio 6.9 95% CI 4.2-11.5) had the strongest association with mortality.\(^{2}\) Mechanical ventilation with endotracheal intubation and septic shock requiring vasopressors are absolute indications for admission to an ICU.\(^{2}\)

However, despite the numerous studies on the initial site of treatment for CAP, some studies on non-adherence to recommendations were noted. In the emergency department, some of the commonly reported reasons for admitting low risk CAP patients were the presence of a co-morbid illness; abnormal laboratory value, vital sign, or symptom or radiographic abnormalities precluding outpatient care; request for hospitalization by other treating physician, the patient or the patient’s family; the physician’s perception that the case of pneumonia was more severe than indicated by the guideline; the physician’s aversion to risk; and prior or anticipated failure of outpatient treatment. Important medical and psychosocial contraindications to outpatient care has to be considered. Administering oral antibiotics to patients with intractable vomiting in an outpatient setting is not an option. Patients who are intravenous drug users, alcohol abusers or those with severe psychiatric conditions or with severely impaired cognitive dysfunction may require hospitalization to ensure compliance with treatment, regardless of severity of illness. As such, this emphasizes that guidelines should not supersede a physician’s judgment; confirming that physicians apply their clinical judgment to appropriately override guideline recommendations.\(^{16,17,51-53}\)

In the emergency department, although higher risk patients with CAP were infrequently treated as outpatients, this decision is often based on the patient or family physician’s recommendation, despite the physician’s recommendation for admission; request of the patient’s involved family physician; the patient’s initial hypoxemia rapidly improved;
the admission diagnosis changed; or the patient was discharged to a nursing home.51, 54 A number of biomarker tests and inflammatory markers have been demonstrated to be independent prognostic factors for mortality. These include procalcitonin, trigger-receptor expressed on myeloid cells-1 (TREM-1), CD14, proadrenomedullin, C-reactive protein, pro-atrial natriuretic peptide, pro-vasopressin and D-dimers. Review of literature still showed need for further validation studies. Furthermore, determination of these tests are not widely or routinely available at present.51 In the future, measurements of serum biomarkers may augment the information provided by prognostic scoring tools to also help guide management decisions for patients with CAP.29

REFERENCES:

8. Pasambo CQ, Cadena EV. The Applicability of CURB-65 as a Prognostic Tool in CAP Among In-patients in the Medical Ward of Dr. Jose Reyes MMC: a 3 Year Retrospective Study. (unpublished).

Table 4. Clinical Features of Patients with CAP according to Risk Categories

<table>
<thead>
<tr>
<th>Low Risk CAP</th>
<th>Moderate Risk CAP</th>
<th>High Risk CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of</td>
<td>Any of the following:</td>
<td>Any of the criteria under Moderate Risk CAP category plus</td>
</tr>
<tr>
<td>Stable vital signs: RR&gt;30 breaths/min • PR&lt;125 beats/min • Temp &gt;36°C or &lt;40°C; SBP &gt;90 mmHg • DBP &gt;60 mmHg</td>
<td>Unstable vital signs: RR ≥30 breaths/min • PR ≥125 beats/min • Temp ≥40°C or ≤36°C; SBP ≥90 mmHg • DBP ≥60 mmHg</td>
<td>Severe Sepsis and Septic Shock</td>
</tr>
<tr>
<td>No altered mental state of acute onset</td>
<td>Altered mental state of acute onset</td>
<td>Need for mechanical ventilation</td>
</tr>
<tr>
<td>No suspected aspiration</td>
<td>Suspected aspiration</td>
<td></td>
</tr>
<tr>
<td>No or stable comorbid conditions</td>
<td>Decompensated co-morbid condition</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray: - localized infiltrates - no evidence of pleural effusion, abscesses</td>
<td>Chest X-ray: - multifocal infiltrates - pleural effusion or abscesses</td>
<td></td>
</tr>
</tbody>
</table>
Gram stain and culture may not be done except when there is failure of clinical response to previous antibiotics and the patient has clinical conditions wherein drug resistance may be an issue.

**Moderate- and High-Risk CAP**

In hospitalized patients, there are more pathogens to consider in addition to the above organisms (enteric Gram negatives, *P. aeruginosa*, *S. aureus*, *L. pneumophila*). In these patients, 2 sites of blood cultures are recommended prior to starting any antibiotic treatment. Although of low sensitivity, a positive blood culture is specific and is considered the gold standard in the etiologic diagnosis of bacterial pneumonia. Gram stain and culture of appropriate respiratory secretions should also be part of the initial work up.

Among the atypical pathogens, *L. pneumophila* causes severe pneumonia with the majority of patients requiring intensive care. The associated case fatality rate is high at 5 to 30%. The greatest risk of death occurs in the elderly and immunocompromised patients and delay in treatment is associated with increased mortality. Thus, for hospitalized patients with CAP, it is recommended that the presence of *L. pneumophila* is documented through urine antigen test (UAT) or direct fluorescent antigen test (DFA) of respiratory secretions.

The main disadvantage of extensive microbiologic testing is the cost effectiveness which is driven by the low yield of blood cultures (5-15%) and the poor quality of samples in respiratory specimens.

Diagnostic testing is recommended when the results are likely to change the standard empiric antibiotic management. The cost effectiveness of the diagnostic tests should also be taken into consideration.

### Atypical pathogens

Atypical pathogens are a term for a group of pathogens (*M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*) rather than a constellation of clinical symptoms. These pathogens do not grow on routine culture isolation in the laboratory.

Data on the incidence of atypical pathogens among different regions of the world vary due to the lack of standardization among the different laboratories and the difficulty in isolating these organisms despite recommended laboratory methods.

The incidence of atypical pathogens from 4,337 CAP patients (outpatient and inpatient) evaluated from around the world were the following: North America (22%), Europe (28%), Latin America (21%) and Asia/Africa (20%).

In Asian studies wherein the Philippines contributed 5.8% of the patients, the incidence of atypical pathogens among 955 cases of CAP (outpatient and inpatient) was 25.2%. Mixed infection was found in 17.2%. Another study showed an overall prevalence of 23.5% in Asian countries.

The Philippine prevalence data of atypical pathogens is 43% in hospitalized patients (inpatient). They occurred either as sole pathogens in 11% or as part of mixed infection (32%).

This data shows that atypical pathogens can be found as the etiologic agents in all risk classes of CAP (Table 5).
on expectorated sputum of good quality (PMN>25/low power field, squamous cells <10/ low power field) reflect cultures of the lower respiratory tract and provide good information. A physician aided by the predominant microorganism morphology seen from Gram-stained sputum could theoretically select the appropriate monotherapy in approximately 94% of the time. The sputum specimen should be rapidly transported and processed in the laboratory within 1 to 2 hours of collection.15

Cultures of expectorated sputum are more difficult to interpret. These may be contaminated with resident flora of the upper airways which may be potential pathogens thus leading to false positive results. They are not sensitive in patients who have taken previous antibiotics, in those unable to expectorate good quality sputum and in those with delays in the processing of the specimens. Nevertheless, cultures of appropriate specimens may be clinically significant. S. pneumoniae was isolated in the sputum in 64% (29/45) of patients with presumed pneumococcal pneumonia based on the finding of Gram positive diplococci compared to 6% (2/31) of patients without Gram-positive diplococci.17

A rapid diagnostic test for the detection of S. pneumoniae in the urine is now available locally (S. pneumoniae UAT). It is an immunochromatographic assay to detect the C polysaccharide in the bacterial cell wall. The sensitivity of S. pneumoniae UAT compared against the standard for diagnosis (blood, sputum and pleural fluid cultures) range from 82-88% (95% CI 74-95) and the specificity is 96-97% (95% CI 86.5-99.5).18,19 Test sensitivity was increased in patients who have not received previous antibiotics.

Invasive procedures such as transtracheal aspiration, bronchoalveolar lavage, protected specimen brush and lung aspiration are associated with complications and are not routine procedures. These should only be done in patients with nonresolving pneumonia, immunocompromised patients, and in those without adequate respiratory specimens despite routine diagnostic testing.20,21

Atypical pathogens: Data on the incidence of atypical organisms in CAP vary widely due to the use of different methods of isolation employed. Each has its own sensitivity and specificity which affect the incidence of these organisms in different studies (Table 6).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tests for M. pneumoniae</td>
<td>&gt;90</td>
<td>50-90</td>
</tr>
<tr>
<td>Respiratory or Tissue Culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology (Complement Fixation, ELISA)</td>
<td>75-80</td>
<td>80-90</td>
</tr>
<tr>
<td>PCR</td>
<td>95</td>
<td>95-99</td>
</tr>
<tr>
<td>Diagnostic tests for C. pneumonia</td>
<td>&gt;90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Respiratory or Tissue Culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>50-90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>(Microimmunofluorescence)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>&gt;90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Diagnostic tests for L. pneumophila</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum Culture</td>
<td>75-99</td>
<td>100</td>
</tr>
<tr>
<td>Serology</td>
<td>40-75</td>
<td>95</td>
</tr>
<tr>
<td>Urine antigen test</td>
<td>60-70</td>
<td>99</td>
</tr>
<tr>
<td>PCR</td>
<td>&gt;90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Direct Fluorescent</td>
<td>25-75</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

Summary of Evidence

Definite etiology: The etiologic diagnosis is considered definite when the pathogen is isolated from normally sterile or uncontaminated specimens (blood, pleural fluid or secretions obtained from transtracheal or transthoracic aspiration). Pathogens such as M. tuberculosis, L. pneumophila, viruses and fungi are not normal colonizers of the upper airways, thus, they are considered definite etiologic agent of pneumonia when isolated from respiratory secretions.15

Probable etiology: Pathogens demonstrated by smear or culture isolated in moderate to heavy quantity from respiratory secretions (e.g., expectorated sputum, bronchoscopic aspirate, quantitatively cultured bronchoalveolar lavage fluid or brush catheter specimen) are considered probable etiologic agents. Although with some limitations, Gram stain and culture when done
REFERENCES:


5. Ortiz MF, Comia CT. Adherence of the Physicians at Mediatrix Medical Center to the 2004 Philipppines Guidelines on the Management of Patients Hospitalized for CAP. (unpublished)


V. TREATMENT

12. When should antibiotics be initiated for the empiric treatment of community-acquired pneumonia CAP?

- For patients requiring hospitalization, empiric therapy should be initiated as soon as possible after diagnosis of CAP is made. (GRADE B)

- For low-risk CAP, treatment may be delayed (GRADE C)

Antibiotics, the mainstay for the treatment of pneumonia, should be initiated as soon as a diagnosis of CAP is made. The 2004 PCPG1 for CAP recommended a maximum 4 hour window from diagnosis to antimicrobial initiation. This recommendation was based on studies which showed a reduced in-hospital mortality when anti-microbial therapy was initiated within the first four hours of admission and diagnosis of CAP. The 2007 IDSA ATS Guidelines2, however, found an internal inconsistency between the group that received antibiotics within the first 2 hours and that which received antibiotics two to four hours after diagnosis. For this reason, the present guideline does not favor a specific time interval between diagnosis and antibiotic administration for patients.

13. What initial antibiotics are recommended for the empiric treatment of community-acquired pneumonia?

For low risk CAP without comorbid illness, Amoxicillin remains the standard drug of choice (Grade A). Extended macrolides are recommended when atypical pathogens are suspected. (Grade B)

For low risk CAP with stable comorbid illness, β-lactam with β-lactamase inhibitor combinations (BLIC) (Grade A) or 2nd generation cephalosporins (Grade A) with or without extended macrolides are recommended. For patients who have completed first line treatment (BLIC or 2nd generation cephalosporin) with no response, an extended work up should be done to identify the factors for failure of response. Work-up may include doing sputum Gram stain and culture. An alternative treatment is an oral 3rd generation cephalosporin (i.e., cefdinir, cefixime, cepodoxime proxetil) with or without extended macrolides. (Grade C)

For moderate risk CAP, a combination of an IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) with either an extended macrolide or respiratory fluoroquinolone is recommended as initial antimicrobial treatment. (Grade B)

For high risk CAP without risk for Pseudomonas aeruginosa, a combination of an IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) with an extended macrolide and aminoglycoside (Grade A) OR a combination of an IV antipseudomonal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) and IV Ciprofloxacin or high dose IV levofloxacin. (Grade B)

Antimicrobial management of a patient with community-acquired pneumonia is based on an assessment of pneumonia severity, the ability of the patient to comply with oral therapy and the social circumstances and available care for the individual.

Literature says that only minimal cases of pneumonias are defined microbiologically at initial assessment and hence most prescribing is empirical, especially when managed in the community. Even in severe pneu-
nia, despite extensive laboratory testing, the causative pathogen remains unknown in 40-70% of cases. Thus, most patients with pneumonia are treated successfully in the community in the absence of any microbial definition of an infecting micro-organism(s). Selection of antibiotic therapy should be directed against the likely pathogens. However, this initial empiric therapy should be accordingly revised if antimicrobial culture and susceptibility results are available. The dosages of recommended antibiotics in adults weighing 50–60 kg with normal renal and liver functions are shown in Table 8.

LOW RISK CAP: In previously healthy adult patients judged to have low risk CAP, Streptococcus pneumoniae and Haemophilus influenzae are the predominant etiologic agents in more than half of the cases where a pathogen is identified. Amoxicillin is considered to be the standard regimen for these patients’ outpatient care.

Table 9 shows a continuing increase in the rates of resistance of S. pneumoniae and H. influenzae to co-trimoxazole. For this reason, the use of co-trimoxazole for CAP is not recommended. When presenting clinical features suggest the etiologic organism to be atypical organisms such as Mycoplasma pneumoniae and Chlamydia pneumoniae, the use of extended macrolides or azalides is appropriate.

In patients with stable comorbid illnesses or in those with recent antibiotic therapy, Gram-negative bacilli may co-exist with the above potential pathogens. Hence, β-lactamase inhibitor combinations or BLIC (i.e., amoxicillin-clavulanic acid, amoxicillin-sulbactam, sulbactamin), second generation oral cephalosporins (i.e., cefaclor, cefuroxime axetil), with or without extended macrolides or azalides are recommended. For patients who have completed first line treatment (BLIC or 2nd generation cephalosporin) with no response, an extensive work up should be done to identify the factors for failure of response. Work up may include doing sputum gram stain and culture. An alternative treatment is an oral 3rd generation cephalosporin (i.e., cefditin, cefixime, cefpodoxime proxetil) with or without extended macrolides. In patients with hypersensitivity to β-lactams, the extended macrolides may cover for S. pneumoniae and H. influenzae while respiratory fluoroquinolones has added coverage (i.e., levofloxacin, moxifloxacin) for Gram-negative bacilli.

MODERATE RISK CAP: In patients with moderate-risk CAP, in addition to S. pneumoniae and H. influenzae, Gram-negative enteric bacilli are important etiologic considerations. For those with risk of aspiration, infection with anaerobes should also be considered. For this 2010 guideline, the empiric regimen of a parenteral non-antipseudomonal β-lactam (BLIC, cephalosporin, carbapenem) in addition to an extended macrolide or respiratory fluoroquinolone is recommended. Although there are numerous papers supporting the use of mono-therapy of respiratory fluoroquinolones for non-ICU CAP, an increasing resistance rate of our local enteric Gram-negative bacilli (Table 10) to respiratory fluoroquinolone (e.g., levofloxacin) has been observed. Monotherapy with respiratory fluoroquinolone might not be optimum in the treatment of moderate risk CAP. Parenteral non-antipseudomonal β-lactams include cephalosporins such as cefuroxime sodium, ceftriaxone or cefotaxime. Cefoxitin, cefizoxime or ertapenem are options that also have anaerobic activity. Agents which combine a β-lactam with β-lactamase inhibitor include amoxicillin-clavulanic acid, ampicillin-sulbactam. In the higher dose range, these agents also have anaerobic activity.

Combination of any of the above regimens with extended macrolides or respiratory fluoroquinolone is now recommended as a significant prevalence of Legionella was noted among hospitalized patients. Although the newer anti-pneumococcal quinolones such as levofloxacin or moxifloxacin are also options for therapy, it is recommended that they be reserved as potential second line agents for the treatment of pulmonary tuberculosis, particularly for multi-drug resistant tuberculosis. Frequent outpatient fluoroquinolone use for CAP was associated with fluoroquinolone resistant tuberculosis. For suspected aspiration especially in those with depressed sensorium or seizure episodes, a β-lactam with anaerobic activity or adding clindamycin or metronidazole to the regimen is advised.

HIGH RISK CAP: Empirc coverage for patients at high risk of mortality from CAP remains essentially the same as that for moderate risk patients. Due to the severity of the condition which may result in a low perfusion state, the parenteral route is recommended for all antimicrobial administration. Modifications to the empiric antibiotic recommendations may be made when the patient is suspected to be at risk of infection by one or more of the following:

P. aeruginosa. Patients who are at risk of infection with P. aeruginosa include those with history of chronic or prolonged (>7 days within the past month) use of broad-spectrum antibiotic therapy, with severe underlying bronchopulmonary disease (COPD, bronchiectasis), malnutrition or chronic use of steroid therapy >7.5 mg/day. For these patients, the recommended empiric therapy should include regimens with a parenteral antipseudomoccal, antipseudomonal β-lactam plus a parenteral extended macrolide and aminoglycosides OR a combination of a parenteral antipseudomoccal, antipseudomonal β-lactam plus either parenteral ciprofloxacin or high dose levofloxacin. Antipseudomoccal, antipseudomonal cephalosporins include cefepime and ceftipirome. Carabapenems such as meropenem or imipenem-cilastatin have anaerobic activity. Parenteral antipseudomonal β-lactams with β-lactamase inhibitors include piperacillin-tazobactam, ticarcillin-clavulanic acid and cefoperazone-sulbactam.

Staphylococcus. In patients shown or suspected to have lung abscesses, pneumatoceoles or pyothorax the addition of specific antistaphylococcal agents such as oxacillin should be considered. If community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) is suspected or isolated, vancomycin or linezolid may be added to the regimen.

Anaerobes. In suspected aspiration, clindamycin or metronidazole covers for anaerobes. If aspiration with microaerophilic streptococci from upper airways is considered, clindamycin has an advantage over metronidazole. On the other hand, metronidazole has an added advantage over clindamycin to cover Bacteroides fragilis.

OTHER NEW ANTIBIOTICS AND NEW DRUG FORMULATION POTENTIAL FOR USE IN CAP: This section summarizes the information about other antibiotics that are available in the Philippine market that have the po-
Potential for use in the treatment of respiratory tract infection but with limited clinical data.

Azithromycin dihydrate microspheres oral extended-release formulation. A new formulation of extended macrolide is available locally as azithromycin dihydrate 2 gm suspension. This 2 gm suspension is administered as single dose preparation and is considered another option for better compliance among low-risk CAP and among patients who are on nasogastric tube feeding for which oral tablet of azithromycin dihydrate can not be administered without pulverizing. This is the ONLY antibacterial agent approved in the USA as a single-dose one-day regimen for the treatment of adult patients with mild CAP or Acute bacterial sinusitis.9 As of this writing, no head-on study is available comparing the extended-release and immediate-release formulations of azithromycin in the treatment of CAP.

Azithromycin monohydrate. Azithromycin monohydrate is a new form of azithromycin containing a new chemical entity that was approved by Department of Health – Bureau of Food and Drugs in 2007. Characterization of the different hydrates of azithromycin using solubility studies showed that there was NO significant difference in the equilibrium solubility of monohydrate and dihydrate.7 A single-center, open randomized two-way cross over bioequivalence study on film coated azithromycin monohydrate vs azithromycin dihydrate tablet in healthy volunteers showed bioequivalence after single oral dose administration.8 However, clinical data on use of azithromycin monohydrate on CAP are very limited.

Parenteral amoxicillin-sulbactam. Parenteral amoxicillin-sulbactam combination is available in the Philippine market. It is active against both β-lactamase producer and nonproducer strains, and is effective against common pathogens in respiratory tract infections such as S. pneumoniae, H. influenzae, M. catarrhalis and others Gram-negative bacilli).9 However, clinical data of parenteral amoxicillin-sulbactam on respiratory tract infection in adults is limited. The only local data available is a multicenter randomized controlled trial comparing the efficacy and safety of oral preparations of amoxicillin-sulbactam vs amoxicillin-clavulanic acid in the treatment of low-risk CAP among adult Filipino patients.10

Tigecycline. Another drug that has been recently approved by USA FDA is tigecycline, a glycylcycline antibiotic, for pathogen-directed therapy of CAP (except P. aeruginosa). Its advantage when used as monotherapy is that it will cover for typical, atypical & anaerobic pathogens. This drug may be reserved for patients with history of β-lactam allergy, OR for patients with drug resistant isolates such as drug-resistant S. pneumoniae (DRSP), mecillin-resistant S. pneumoniae (MRSA), extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacilli, OR patients with suspected multiple organisms such as stroke patients who develop CAP or patients who have been on multiple antibiotics like the COPD and asthmatic patients.

Doripenem. Doripenem is the newest of the carbapenem to be approved for the management of infections in the United States. Compared with other carbapenem, doripenem had the lowest MIC90 against isolates of P. aeruginosa and was two-fold more active than meropenem but two-fold less active than imipenem against Acinetobacter spp. It has poor activity against Stenotro-

phomonas maltophilia and has activity similar to the other carbapenem against other Gram-negative bacilli. Since doripenem is stable for up to 8 hours in intravenous fluids (normal saline), use of a prolonged infusion time may help optimize therapy in patients infected with more-resistant Gram-negative organisms. In phase III trials, doripenem is noninferior to imipenem and piperacillin-tazobactam in the treatment of nosocomial pneumonia and ventilator-associated pneumonia. It is also noninferior compared with meropenem in the treatment of complicated intra-abdominal infections and also noninferior compared with levofloxacin in the treatment of complicated urinary tract infections.11 Currently, available data on doripenem is limited on hospital-acquired pneumonia, ventilator-associated pneumonia, urinary tract infection and intra-abdominal infections. There is still no published data on its use in CAP, though its activity against pneumococci and other streptococci is excellent.12

Summary of Evidence

Initial management decisions on an empiric basis must be made rapidly with a presumptive diagnosis of CAP.13 S. pneumoniae, H. influenzae and atypical pathogens have been demonstrated as the most common causes of low-risk CAP suitable for outpatient care.

Most of these studies14-18 demonstrated that S. pneumoniae remains to be a common pathogen in patients with CAP treated on outpatients. Similarly the presence of the atypical pathogens was also identified.14-18 Extended macrolides and azalides provide coverage against these potential pathogens. Woodhead19 as well as Mundy et. Al20 isolated atypical organisms from sputum samples of patients with low risk CAP. Notably, no deaths occurred in this group despite no specific treatment against them. Hence, in the outpatient setting, amoxicillin, which is directed against presumed pneumococcal or H. influenzae infection, is considered an adequate regimen.21,22 Other regimens such as co-amoxiclav, sulamycin, amoxicillin-sulbactam, second-generation oral cephalosporins may be given to patients with CAP who have stable comorbid conditions or those with recent antibiotic therapy.23,24,25 An extended macrolide may cover for possible atypical pathogens.26

The Antimicrobial Resistance Surveillance Program (ARSP)27 of the Department of Health collects antibiotic resistance reports from sentinel hospitals all over the country and publishes a compilation report yearly. Tables 9 show the resistance rates for S. pneumoniae and H. influenzae in the last 5 years. In 2008, S. pneumoniae resistance rate to penicillin was 0%. Thus, unlike other countries, drug resistant S. pneumoniae is still not a concern in the Philippines. We can see that the resistance to cotrimoxazole is increasing at 23.3% and resistance to erythromycin is at 3.9%. In the same year, H. influenzae resistance to Ampicillin was 10.3%.

Judicious use of fluoroquinolones as an alternative agent in the out-patient setting is advised. A study in the Philippines28 shows that ciprofloxacin and ofloxacin are now significantly less effective alternative therapy in tuberculosis, particularly MDR-TB, a locally hyperendemic disease. This decreased susceptibility of Mycobacterium tuberculosis to fluoroquinolones was attributed to a selection pressure from the widespread use of these agents in the community for various infections.29,30 A case-control study on fluoroquinolone use was performed by the group of Long et al. among patients with culture proven
pulmonary TB before diagnosis of TB was made. Single fluoroquinolone prescriptions were not associated with fluoroquinolone resistant *M. tuberculosis*, whereas multiple fluoroquinolone prescriptions were associated with fluoroquinolone resistance.\(^5\)

Studies on etiology among patients with CAP admitted for hospital care showed the predominance of *S. pneumoniae* as well as the occurrence of Gram-negative bacilli.\(^31,35\) The Asia CAP study among hospitalized CAP patients noted atypical pathogens in 43% of isolates.\(^56\) Among the atypical agents, morbidity is significantly increased with *Legionella pneumonia*; hence, empiric therapy against *Legionella* is recommended as part of the regimen for hospitalized patients with CAP along with beta-lactam agents which are also effective against Gram-negative bacilli.\(^56-63\) Parenteral erythromycin has been the standard regimen for severe *Legionella pneumonia*. Currently, extended macrolides and the fluoroquinolones have been shown to be active against *Legionella*. The extended macrolides may be given orally alongside parenteral beta-lactam agents among patients with moderate risk CAP if with good gastrointestinal absorption. Newer extended macrolide agents such as azithromycin dihydrate, and clarithromycin or the respiratory fluoroquinolones such as levofloxacin or moxifloxacin are considered alternatives.\(^64-72\)

In the Philippines, respiratory fluoroquinolones remains active against *S. pneumoniae* and *H. influenzae*. However, recent data of ARSP\(^27\) (Table 10) showed increasing rate of resistance of common Gram-negative bacilli against levofloxacin. Thus, among non-ICU admitted patients, combination therapy is recommended for optimum coverage of potential Gram-negative bacilli using

<table>
<thead>
<tr>
<th>Table 7. Empiric Antimicrobial Therapy in CAP</th>
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<tbody>
<tr>
<td><strong>Risk Stratification</strong></td>
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<tr>
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</tbody>
</table>
| Low Risk CAP               | *Streptococcus pneumoniae*  
  *Haemophilus influenzae*  
  *Chlamydia pneumoniae*  
  *Mycoplasma pneumoniae*  
  *Moraxella catarrhalis*  
  Enteric Gram-negative bacilli (among those with co-morbid illness) | Previously healthy:  
  *Amoxicillin*  
  OR  
  Extended macrolides\(^a\) (suspected atypical pathogen)  
  *With stable comorbid illness:*  
  \(\beta\)-lactam/\(\beta\)-lactamase inhibitor combination (BLIC)\(^b\) or 2\(^{nd}\) generation oral cephalosporins\(^c\) +/- Extended macrolides  
  Alternative:  
  3\(^{rd}\) generation oral cephalosporin\(^d\)  
  +/- Extended macrolide |
| Moderate Risk CAP           | *Streptococcus pneumoniae*  
  *Haemophilus influenzae*  
  *Chlamydia pneumoniae*  
  *Mycoplasma pneumoniae*  
  *Moraxella catarrhalis*  
  Enteric Gram-negative bacilli  
  *Legionella pneumonia*  
  Anaerobes (among those with risk of aspiration) | IV non-antipseudomonal \(\beta\)-lactam (BLIC, cephalosporin or carbapenem)\(^e\)  
  + Extended macrolide  
  OR  
  IV non-antipseudomonal \(\beta\)-lactam (BLIC, cephalosporin or carbapenem)\(^e\)  
  + Respiratory fluoroquinolones\(^f\) (FQ) |
| High Risk CAP               | *Streptococcus pneumoniae*  
  *Haemophilus influenzae*  
  *Chlamydia pneumoniae*  
  *Mycoplasma pneumoniae*  
  *Moraxella catarrhalis*  
  Enteric Gram-negative bacilli  
  *Legionella pneumonia*  
  Anaerobes (among those with risk of aspiration)  
  *Staphylococcus aureus*  
  *Pseudomonas aeruginosa* | No risk for *P. aeruginosa*:  
  IV non-antipseudomonal \(\beta\)-lactam (BLIC, cephalosporin or carbapenem)\(^e\)  
  +  
  IV Extended macrolide or IV Respiratory FQ  
  With risk for *P. aeruginosa*:  
  IV antipseudomoccal antipseudomonal \(\beta\)-lactam (BLIC, cephalosporin or carbapenem)\(^g\)  
  +  
  IV Extended macrolide + aminoglycoside\(^h\)  
  OR  
  IV antipseudomoccal antipseudomonal \(\beta\)-lactam (BLIC, cephalosporin or carbapenem)\(^g\) + IV Ciprofloxacin / Levofoxacin (high dose) |

\(^a\) Extended Macrolides - Azithromycin dihydrate, Clarithromycin  
\(^b\) Oral \(\beta\)-lactam/\(\beta\)-lactamase inhibitor combination (BLIC) - Amoxicillin-clavulanic acid, Amoxicillin-sulbactam, Sultamicillin  
\(^c\) Oral Second generation cephalosporin - Cefaclor, Cefuroxime axetil  
\(^d\) Oral Third generation cephalosporin - Cefdinir, Cefixime, Cefpodoxime proxetil  
\(^e\) IV non-anti-pseudomonal \(\beta\)-lactam (BLIC, cephalosporin or carbapenem) - Amoxicillin-clavulanic acid, Ampicillin-sulbactam, Cefotiam, Cefoxitin, Cefuroxime Na, Cefotaxime, Ceftriaxone, Ertapenem  
\(^f\) Respiratory fluoroquinolones - Levofloxacin, Moxifloxacin  
\(^g\) IV Anti-pseudomoccal, anti-pseudomonal \(\beta\)-lactam (BLIC, cephalosporin or carbapenem) - Cefoperazone-sulbactam, Piperacillin-tazobactam, Ticarcillin-clavulanic acid, Cefipime, Cefpirome, Imipenem-clastatin, Meropenem  
\(^h\) Aminoglycosides - Gentamicin, Tobramycin, Netilmicin, Amikacin
Community-Acquired Pneumonia

Table 8. Usual recommended dosages of antibiotics in 50-60 KBW adults with normal liver and renal functions

<table>
<thead>
<tr>
<th>Antibiotic Dosage</th>
<th>Antibiotic Dosage</th>
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<tbody>
<tr>
<td><strong>Low Risk CAP (All taken orally)</strong></td>
<td><strong>2nd Generation Cephalosporin</strong></td>
</tr>
<tr>
<td><strong>β-lactams:</strong></td>
<td>Cefaclor</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg TID or</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td>Cefuroxime axetil</td>
</tr>
<tr>
<td>Azithromycin dihydrate</td>
<td>500 mg BID</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg BID</td>
</tr>
<tr>
<td><strong>β-lactam with β-lactamase inhibitor combination (BLIC)</strong></td>
<td><strong>3rd Generation Cephalosporin</strong></td>
</tr>
<tr>
<td>Amoxicillin-Clavulanic acid</td>
<td>625 mg TID or</td>
</tr>
<tr>
<td>1 gm BID</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-sulbactam</td>
<td>1 gm TID</td>
</tr>
<tr>
<td>Sultamicillin</td>
<td>750 mg BID</td>
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<table>
<thead>
<tr>
<th><strong>Moderate Risk CAP</strong></th>
<th><strong>2nd Generation Cephalosporin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolides</strong></td>
<td>Cefotiam, IV</td>
</tr>
<tr>
<td>Azithromycin dihydrate, PO/IV</td>
<td>1 gm q48</td>
</tr>
<tr>
<td>Clarithromycin, PO/IV</td>
<td>1-2 gm q48</td>
</tr>
<tr>
<td>erythromycin, PO/IV</td>
<td>1.5 gm q48</td>
</tr>
<tr>
<td><strong>Antipneumococal Fluoroquinolones</strong></td>
<td><strong>3rd Generation Cephalosporin</strong></td>
</tr>
<tr>
<td>Levofloxacin PO/IV</td>
<td>Cefotaxime, IV</td>
</tr>
<tr>
<td>500-750 mg q24h</td>
<td>1-2 gm q48</td>
</tr>
<tr>
<td>Moxifloxacin PO/IV</td>
<td>Ceftriaxone, IV</td>
</tr>
<tr>
<td>400 mg q24h</td>
<td>1-2 gm q24h</td>
</tr>
<tr>
<td><strong>β-lactam with β-lactamase inhibitor combination (BLIC)</strong></td>
<td><strong>Carbapenem</strong></td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid, IV</td>
<td>1.2 gm q8h</td>
</tr>
<tr>
<td>Ampicillin-sulbactam, IV</td>
<td>1.5 gm q8h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>High Risk CAP (All routes are intravenous IV)</strong></th>
<th><strong>Non-anti-pseudomonal Carbapenem</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolides</strong></td>
<td>Ertapenem</td>
</tr>
<tr>
<td>Azithromycin dihydrate</td>
<td>1 gm q24h</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Anti- pseudomonal</td>
</tr>
<tr>
<td>erythromycin</td>
<td>Anti-pseudomonal</td>
</tr>
<tr>
<td>0.5-1 gm q6h</td>
<td>β-lactams (BLIC,</td>
</tr>
<tr>
<td><strong>Antipneumococal Fluoroquinolones</strong></td>
<td>Cephalosporin, Carbapenem)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1.5-3 gm q8-12h</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Pipercillin-Tazobactam</td>
</tr>
<tr>
<td>400 mg q24h</td>
<td>2.25-4.5 gm q8-8h</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>Ticarcillin-clavulanic acid</td>
</tr>
<tr>
<td>Amikacin</td>
<td>3.2 gm q6h</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Cefepime</td>
</tr>
<tr>
<td>3 mg/kg q24h</td>
<td>2 gm q8-12h</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>Cefpirome</td>
</tr>
<tr>
<td>7 mg/kg q24h</td>
<td>2 gm q12h</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Imipenem-cilastatin</td>
</tr>
<tr>
<td>3 mg/kg q24h</td>
<td>0.5-1 gm q6-8h</td>
</tr>
<tr>
<td><strong>Non-antipseudomonal BLIC</strong></td>
<td>Meropenem</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>1-2 gm q8h</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>1.2 gm q8-8h</td>
</tr>
<tr>
<td><strong>Non-antipseudomonal 3rd Generation Cephalosporin</strong></td>
<td><strong>Others:</strong></td>
</tr>
<tr>
<td>Cefotaxime IV</td>
<td>400 mg q12h</td>
</tr>
<tr>
<td>Ceftriaxone IV</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td>(with anaerobic activity)</td>
<td>750 mg q24h</td>
</tr>
<tr>
<td><strong>Antipneumococal Fluoroquinolones</strong></td>
<td>Oxacillin (Staphylococcus)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1-2 gm q4-6h</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td></td>
<td>600 mg q6-8h</td>
</tr>
<tr>
<td>Metronidazole (Anaerobes)</td>
<td>(Staphylococcus and Anaerobes)</td>
</tr>
<tr>
<td>Linezolid (MRSA)</td>
<td>500 mg q6-8h</td>
</tr>
<tr>
<td>Vancomycin (MRSA)</td>
<td>600 mg q12h</td>
</tr>
</tbody>
</table>

Either non-antipseudomonal β-lactam plus extended macrolides or non-antipseudomonal β-lactam plus respiratory fluoroquinolone.

A retrospective study comparing β-lactam and macrolide (BL + M) combination versus fluoroquinolone (F) monotherapy among hospitalized patients with CAP showed lower 14-day and 30-day mortality with BL+M than with F with no difference in length of stay among PSI class V patients. Likewise, in the study of Metersky among bacteremic pneumonia, the use of macrolide in therapy was strongly associated with improved outcome and may have advantages over a fluoroquinolone combination.

The most consistent finding across the retrospective studies favouring combination therapy is that it is the addition of a macrolide to a third-generation cephalosporin that has the best outcome.

Table 10. Levofloxacin (LVX) Resistance Pattern among Enterobacteriaceae (ARSP 2008)²⁷

<table>
<thead>
<tr>
<th>Escherichia coli</th>
<th>Enterobacter spp</th>
<th>Klebsiella spp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of isolates</td>
<td>3,047</td>
<td>1,688</td>
</tr>
<tr>
<td>LVX Number</td>
<td>667</td>
<td>571</td>
</tr>
<tr>
<td>LVX % Resistance Rate</td>
<td>22.3%</td>
<td>25.0%</td>
</tr>
</tbody>
</table>
Azithromycin monohydrate is a new form of azithromycin containing a new chemical entity that was approved by Department of Health – Bureau of Food and Drugs in 2007. Characterization of the different hydrates of azithromycin using solubility studies showed that there was NO significant difference in the equilibrium solubility of monohydrate and dihydrate. In the same study, the anhydrous form of azithromycin seemed to be unstable since it converted to dihydrate on storage at room temperature. On the other hand, monohydrate in the presence of moisture can convert to the more stable dihydrate form. Therefore, the most stable form of azithromycin is dihydrate form. It is important to select the appropriate form of azithromycin and also control the moisture levels during various processing operations involved in the formulation of solid dosage forms.

Parenteral amoxicillin-sulbactam combination is available in the Philippine market. It is active against both β-lactamase producer and nonproducer strains, and is effective against common pathogens in respiratory tract infections such as S. pneumoniae, H. influenzae, M. catarrhalis and others Gram-negative bacilli. However, clinical data of parenteral amoxicillin-sulbactam on respiratory tract infection in adults is limited.

Another drug that has been recently approved by US FDA is tigecycline. Tigecycline is a semisynthetic derivative of minocycline and is the first glycylcycline antibiotic available for clinical use. With the exception of P. aeruginosa, it is highly active in vitro against most common Gram-positive and Gram-negative pathogens, anaerobes and atypical pathogens. Integrated results of two phase III studies comparing tigecycline and levofloxacin in community-acquired pneumonia showed tigecycline appeared to be safe and achieved cure rate similar to levofloxacin in hospitalized patients with CAP. The drug-related adverse events of nausea and vomiting were significantly higher in tigecycline although the discontinuation rates for adverse events were low for both treatment groups.

Doripenem is the newest of the carbapenems to be approved for the management of infections in the United States. In phase III trials, doripenem is noninferior to imipenem (Clinical cure rate 68.3% for doripenem vs 64.8% for Imipenem) and piperacillin-tazobactam (Clinical cure rate 81.3% for doripenem and 79.8% for piperacillin-tazobactam) in the treatment of nosocomial pneumonia and ventilator-associated pneumonia. It is also noninferior compared with meropenem in the treatment of complicated intra-abdominal infections (clinical cure rate 83.9% for doripenem vs 85.9% meropenem) and also noninferior compared with levofloxacin in the treatment of complicated urinary tract infections (95.1% cure rate for doripenem vs 90.2% for levofloxacin).

### 14. How can response to initial therapy be assessed?

- Temperature, respiratory rate, heart rate, blood pressure, sensorium, oxygen saturation and inspired oxygen concentration should be monitored to assess response to therapy.
- Response to therapy is expected within 24-72 hours of initiating treatment. Failure to improve after 72 hours of treatment is an indication to repeat the chest radiograph. (Grade A)
- Follow-up cultures of blood and sputum are not necessary.
Community-Acquired Pneumonia

Most patients with uncomplicated bacterial pneumonia will respond to treatment within 24 to 72 hours; re-evaluation of patients, therefore, should be done after 72 hours of initiating therapy. A patient is considered to have responded to treatment if fever decreases within 72 hours, temperature normalizes within 5 days and respiratory signs, particularly tachypnea, return to normal. In patients with low risk CAP showing good therapeutic response; a follow-up chest x-ray is not necessary. Follow-up cultures of blood and sputum are also not indicated for patients who respond to therapy.

15. When should de-escalation of empiric antibiotic therapy be done?
• De-escalation of initial empiric broad-spectrum antibiotic or combination parenteral therapy to a single narrow spectrum parenteral or oral agent based on available laboratory data is recommended once the patient is clinically improving, is hemodynamically stable and has a functioning gastrointestinal tract. (Grade B)

16. Which oral antibiotics are recommended for de-escalation or switch therapy from parenteral antibiotics?
• The choice of oral antibiotics following initial parenteral therapy is based on available culture results, antimicrobial spectrum, efficacy, safety and cost. In general, when switching to oral antibiotics, either the same agent as the parenteral antibiotic or an antibiotic from the same drug class should be used.

Table 12 summarizes the usual recommended dosages of the oral antibiotics for switch therapy in adults weighing 50 to 60 kg with normal renal and liver function. Switch therapy to an oral agent will allow early discharge from the hospital as early as the fourth day of hospitalization and will lead to cost-savings. Table 13 shows the benefits of intravenous to oral switch therapy.

17. How long is the duration of treatment for CAP?
• Duration of treatment is 5-7 days for low risk uncomplicated bacterial pneumonia. (Grade B)
• For moderate- and high-risk CAP or for those with suspected or confirmed Gram negative, *S. aureus* or *P. aeruginosa* pneumonia treatment should be prolonged to 14-21 days. (Grade B)
• A treatment regimen of 10 to 14 days is recommended for *Mycoplasma* and *Chlamydia pneumonia* treatment should be for 14 to 21 days. (Grade B)
• A 5-day course of oral or IV therapy for low-risk CAP and 10-day course for *Legionella* pneumonia is treated for 14 to 21 days. (Grade B)
• A treatment regimen of 10 to 14 days is recommended for *Mycoplasma* and *Chlamydia pneumonia* treatment should be for 14 to 21 days. (Grade B)
• A 5-day course of oral or IV therapy for low-risk CAP and 10-day course for *Legionella* pneumonia is treated for 14 to 21 days. (Grade B)
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• A treatment regimen of 10 to 14 days is recommended for *Mycoplasma* and *Chlamydia pneumonia* treatment should be for 14 to 21 days. (Grade B)
• A 5-day course of oral or IV therapy for low-risk CAP and 10-day course for *Legionella* pneumonia is treated for 14 to 21 days. (Grade B)
• A treatment regimen of 10 to 14 days is recommended for *Mycoplasma* and *Chlamydia pneumonia* treatment should be for 14 to 21 days. (Grade B)
and the drug continued. If the dose is inadequate, the dose should be corrected. If the choice is among the recommended options and the dose is correct but the patient has not improved after 72 hours, the antibiotic should be changed. If the dose is inadequate, the dose should be corrected and the drug continued.

### Table 14. Duration of antibiotic use based on etiology

<table>
<thead>
<tr>
<th>Etiologic Agent</th>
<th>Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most bacterial pneumonia except enteric gram (-) pathogens, S. aureus, and P. aeruginosa</td>
<td>5-7; 3-5 (azalides) for S. pneumoniae</td>
</tr>
<tr>
<td>Enteric gram (-) pathogens, S. aureus, and P. aeruginosa</td>
<td>14</td>
</tr>
<tr>
<td>Mycoplasma and Chlamydia phila</td>
<td>10-14</td>
</tr>
<tr>
<td>Legionella</td>
<td>14-21; 10 (azalides)</td>
</tr>
</tbody>
</table>

### Table 15. Factors to consider for nonresponding pneumonia or failure to improve

Nonresponding pneumonia or failure to improve may be due to:

1. Incorrect diagnosis or presence of a complicating noninfectious condition e.g., pulmonary embolism, congestive heart failure, vasculitis, myocardial infarction.
2. A resistant microorganism or an unexpected pathogen not covered by the antibiotic choice.
3. Antibiotic is ineffective or causing an allergic reaction i.e., poor absorption of the oral antibiotic, certain drug interactions, inadequate dose, patient not taking or receiving the prescribed antibiotic.
4. Impaired local or systemic host defenses e.g., aspiration, endobronchial obstruction, bronchiectasis, systemic immune deficiency.
5. Local or distant complications of pneumonia e.g., parapneumonic effusion, empyema, lung abscess, ARDS, metastatic infection, endocarditis.
6. Overwhelming infection.
7. Slow response in the elderly patient; S. pneumoniae and L. pneumophila may cause slow resolution of pneumonia in the elderly.
8. Exacerbation of comorbid illnesses.

In patients seen after the antibiotic therapy has already been initiated, if the choice is among the recommended options and the dose is correct but the patient has not improved after 72 hours, the antibiotic should be changed. If the dose is inadequate, the dose should be corrected and the drug continued.

### Table 16. Recommended Hospital Discharge Criteria

During the 24 hours before discharge, the patient should have the following characteristics (unless this represents the baseline status):

1. Temperature of 36-37.5°C
2. Pulse <100/min
3. Respiratory rate between 16-24/minute
4. Systolic BP >90 mmHg
5. Blood oxygen saturation >90%
6. Functioning gastrointestinal tract

**Summary of Evidence**

Parameters of treatment response. Predicted response to antibiotic treatment takes into account the immunologic capacity of the host, the severity of the illness, the pathogen and chest radiographic findings. Specifically, the clinical response to treatment depends on a combination of several factors particularly host factors (e.g., immune status and comorbid conditions), bacteriologic factors (e.g., virulence, susceptibility to antibiotics and amount of inoculum), disease factors (e.g., extent of illness and physiologic compromise and the degree of disease progression at the time of diagnosis), and treatment factors (e.g., timing and adequacy of treatment, pharmacokinetics of the selected antibiotic). In immunocompetent CAP patients, subjective response is usually noted within 1 to 3 days of initiation of treatment. Among the clinical parameters of response to therapy, the most carefully documented response is fever or time to defervescence. Fever associated with severe pneumonia has been observed to decline in 72 hours and to completely lyse in 5 days.

Leukocytosis usually resolves by day 4. In a prospective multicenter evaluation of more than 1400 patients with CAP admitted to 15 Spanish hospitals, the median time to clinical stability was 4 days with stability defined as absence of fever (temperature <37.2°C), heart rate of <100 beats/min, respiratory rate of <24 breaths/min, systolic blood pressure of >90 mmHg and oxygen saturation of >90% or arterial oxygen partial pressure of >60 mmHg. In this observational study the initial factor associated with earlier clinical stability was adherence to antibiotic treatment guidelines. At the time of admission, the factors found to be independently associated with slower clinical stability were presence of dyspnea, confusion, multilobar involvement, high pneumonia severity index and pleural effusion. During the course of the pneumonia, treatment failure, admission to the ICU and complications such as renal, cardiac or respiratory insufficiency delayed the time to reach clinical stability.
Community-Acquired Pneumonia

Chest radiographic findings usually clear more slowly than clinical findings and multiple radiographs are generally not required. Follow-up chest radiography should not be done too early as pneumonia infiltrates may persist unless the patient fails to respond. Follow-up radiography during hospitalization may be indicated to assess the position of an endotracheal tube or central line and to exclude pneumothorax after central line placement or to determine other reasons for failure to respond. In addition to progression of disease, possible pulmonary complications such as pleural effusion (10.6%), empyema (5.2%), lung abscess, or atelectasis should be assessed.  

Observational studies have shown that host factors particularly age and presence or absence of comorbid illness are important determinants of the rate of radiographic resolution. The speed of resolution of radiographic infiltrates was inversely related to age, comorbidity and number of lobes involved. Cumulative clearance was noted in 51% of patients examined at 2 weeks, 67% at 4 weeks, 77% at 6 weeks, 84% at 8 weeks, 90% at 12 weeks, 93% at 20 weeks and 94% at 24 weeks. Radiographs of patients less than 50 years old with pneumonia due to *S. pneumoniae* cleared by 4 weeks in only 60% of patients. In the elderly, patients with underlying illness (particularly alcoholism or COPD) or patients with extensive pneumonia on presentation, the rate of resolution slowed considerably with only 20 to 30% clearing by 4 weeks. *L. pneumophila* infection may take substantially longer to clear; only 55% of such infections show complete resolution by 12 weeks.

Delayed resolution of radiographic abnormalities was independently associated with multiorgan disease (odds ratio 2.87); dullness (odds ratio 6.94); high C-reactive protein level, defined as >200 mg/L (odds ratio 4.24); and high respiratory rate at admission, defined as >25 breaths/min (odds ratio 2.42) in a prospective study of 288 patients with severe CAP. Routine short-term follow-up obtained within <28 days after hospital admission of patients with severe CAP did not seem to provide additional clinical value in those responding to initial therapy.

**De-escalation of antibiotic therapy.** Cost considerations favor streamlining of initial parenteral empiric broad-spectrum therapy in patients who show adequate clinical response to a narrow spectrum parenteral agent or an oral agent after 2 to 3 days. The choice should be based on bacteriologic studies if available. Determining when to change from intravenous to oral therapy requires clinical judgement and is likely to depend on the individual patient. In general the following parameters should be taken into account in deciding to change to oral treatment: no clinical indication to continue intravenous antibacterial therapy; decrease in leukocyte count or returning to normal; normal gastrointestinal absorption; no diarrhea; improved or resolving signs and symptoms of infection; temperature returning to normal; and oral medication is feasible for the patient.

In hospitalized patients with CAP without clinical indications of meningitis or endocarditis, the presence of *S. pneumoniae* bacteremia at the time of hospital admission is not a contraindication for switching a clinically stable patient from intravenous to oral therapy. For pneumonia due to confirmed or suspected Enterobacteriaceae, sequential therapy with fluoroquinolones or a 3rd generation oral cephalosporin is appropriate due to their optimal pharmacodynamics: their serum concentration exceeds the MIC₉₀ for many common pathogens responsible for CAP. The improved bioavailability of the newer antibiotics allows oral preparations to rapidly achieve adequate serum levels in patients with a functioning gastrointestinal tract. Compliance is a key issue with oral therapy and thus agents chosen should have minimum side effects, once or twice daily dosing, and be cost-effective.

**Non-response or failure to improve.** Two patterns of unacceptably poor response are seen in hospitalized patients. First is progressive pneumonia or clinical deterioration, with acute respiratory failure and/or septic shock within the first 72 hours of admission. Deterioration more than 72 hrs after initial treatment is often related to intercurrent complications, deterioration in the underlying disease or development of nosocomial superinfection. The second most common reason for deterioration after 72 hours is persistent or nonresponding pneumonia. Nonresponse is considered when patients do not respond clinically within 72 hours despite antibiotic treatment or the patient deteriorates after an initial response. Important causes of nonresponse related to antimicrobial failure include a pathogen resistant to the antimicrobial treatment or a superinfection. In such situations, microbiologic studies including blood cultures should be repeated. Unusual pathogens such as *M. tuberculosis* may be the cause of treatment failure. Special stains of lower respiratory secretions for *M. tuberculosis* atypical mycobacteria, *P. jiroveci* and endemic fungi and antigen detection for Legionella species, should thus be performed. For severe lung infections, microbiologic studies should be done on bronchoalveolar lavage specimens or samples obtained by protected specimen brush.

Hemodynamic monitoring and clinical evaluation should be undertaken in high risk CAP to assess for possible severe sepsis with multi-organ failure, disseminated intravascular, ARDS, hepatic failure, congestive heart failure and gastrointestinal bleeding. Other non-infectious complications including pulmonary embolism, myocardial infarction, lung cancer or other unrecognized immune-suppression may also cause non-response and clinical worsening.

Independent risk factors for failure to improve that have been identified include multilobar involvement, cavitation pneumonia, a pleural effusion, coexisting liver disease, malignancy or neurological disease, aspiration pneumonia, *Legionella* pneumonia, gram negative pneumonia, high disease severity on admission, leucopenia and inappropriate antimicrobial therapy.

**Duration of treatment.** The presence of coexisting illness and/or bacteremia, the severity of illness at the onset of antibiotic therapy, and the subsequent hospital course should be considered in determining the duration of antibiotic therapy. Studies have been done to evaluate 5 to 7 days treatment among outpatients and 7 to 10 days for inpatients. Generally, *S. pneumoniae* pneumonia and other bacterial infections should be treated for 5 to 10 days; there is no data showing that a longer duration of therapy is needed for bacteremic patients who have shown good clinical response. Patients with intracellular pathogens such as *M. pneumoniae* and *C. pneumoniae* may need longer therapy ranging from 10 to 14 days.
Immunocompetent patients with Legionnaire’s disease should receive treatment for 14 days, whereas immunocompromised patients or those chronically treated with corticosteroids may require 14 days or longer. Drugs that attain high concentrations in pulmonary tissues with prolonged duration of effect such as the azalides may allow a 3-5 day course for low-risk CAP. 1,2,13-18 and a 10-day course for Legionella pneumonia in immunocompetent patients. In a open-label non-comparative trial of 25 hospitalized immunocompetent patients with Legionella pneumonia, 14 days of parenteral azithromycin followed by 4 days of oral azithromycin, 22 patients were clinically cured. 13 Well-designed randomized controlled trials to establish the optimal duration of CAP are lacking.

REFERENCES:
8. Center for Pharmacology and Analysis (CEPHA s.r.o.). A single center, open, randomized, two way, cross over bioequivalence study on azithromycin 500mg film-coated tablets (Novartis Enterprises Private Ltd., India) versus azatromax 500mg tablet (Pfizer Italia S.p.A., Italy) in healthy volunteer. 2002. (Unpublished).
10. Galvez BB. A multicenter randomized clinical trial comparing the efficacy and safety of oral preparations of amoxicillin (500mg) + sulbactam (500mg) vs amoxacillin (500mg) + clavulanate (125mg) in the treatment of low-risk community-acquired pneumonia in adult Filipino patients. 2009 (Unpublished).
23. Ortiz MF, Coria CT. Adherence of the Physicians at Mary Mediatric Medical Center to the 2004 Philippine Guidelines on the Management of Patients Hospitalized for CAP. (unpublished)
27. Ortiz, M and Coria, C. Adherence of the Physicians at Mary Mediatric Medical Center to the 2004 Philippine guidelines on the Management of Patients Hospitalized for Community-acquired Pneumonia (CAP)
33. Leesik H, Ani U, Johan A Altaira A. Microbial pathogens of adult CAP in Southern Estonia


VI. PREVENTION

20. How can CAP be prevented?

- Influenza vaccination is recommended for the prevention of CAP. (Grade A)

- Pneumococcal vaccination is recommended for the prevention of invasive pneumococcal disease (IPD) in adults. (Grade A)

- Smoking cessation is recommended for all persons with CAP who smoke. (Grade A)

The mainstay of CAP prevention is pneumococcal and influenza vaccination. Both pneumococcal and influenza vaccines may be useful in preventing secondary pneumococcal infections and reducing illness and death. Both pneumococcal and influenza infections may be prevented by the use of currently available pneumococcal and influenza vaccines.

Cigarette smoking is a risk factor for pneumonia. Smoking cessation, particularly in patients who have had pneumonia, remains an important preventive strategy for CAP. The Philippine CAP Task Force reviewed the current guidelines for pneumococcal and influenza vaccines of the following groups: (1) Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (Atlanta, Georgia); (2) Philippine Society for Microbiology and Infectious Diseases with the Philippine Foundation for Vaccination (PFV); (3) Philippine College of Chest Physicians Council on Pulmonary Infections; and (4) Department of Health Technical Working Group for Influenza Prevention and Management.
Pneumococcal Vaccine

The pneumococcal vaccine is a 23-valent preparation containing purified capsular polysaccharide of the serotypes responsible for at least 85% to 90% of invasive pneumococcal infections in the US. In the Philippines, surveillance data of invasive isolates of Streptococcus pneumoniae among children with bacteremia/meningitis showed that 92% were vaccine types.

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended for the following high risk persons listed in Table 16.

In 2008, the ACIP recommended the inclusion of asthma and cigarette smoking as indications for the use of PPSV23 in adults aged 19 to 64 years. Asthma is an independent risk factor for IPD. Adults who smoke cigarettes are at substantially increased risk for IPD. All people who have existing indications for PPSV23 should continue to be vaccinated according to these current recommendations during the outbreak of novel influenza A(H1N1).

While the ACIP recommends universal vaccination of PPSV23 for all adults 65 years of age and older, the recommended age in the Philippines is 60 years of age and older. This is because the projected life expectancy in the country is lower. According to the DOH 2001 Statistics, the average life expectancy is 66.6 years for Filipino males and 71.9 years for Filipino females. In the 2009 update of the “Handbook on Adult Immunization for Filipino males and 71.9 years for Filipino females.” vaccination of PPSV23 is recommended for persons >50 years old.

The PPSV23 is administered intramuscularly or subcutaneously as a single 0.5 mL dose. Routine revaccination of immunocompetent persons previously vaccinated with 23-valent polysaccharide vaccine is not recommended.

However, revaccination once is recommended for persons who are at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody levels, provided that 5 years have elapsed since receipt of the first dose of pneumococcal vaccine. Because of limited data on the safety of multiple doses and on the duration of protection provided by polysaccharide vaccine, recommendation is for a single revaccination 5 years after the initial dose. These recommendations have been misinterpreted as suggesting revaccination every 5 years.

Revaccination may be given to the following: (1) persons >65 years who received their first dose more than 5 years ago and before they reached age 65, and (2) persons <64 years old who received the vaccine more than 5 years ago and who have asplenia, HIV, leukemia, lymphoma, generalized malignancy, multiple myeloma, chronic renal failure or nephritic syndrome; (3) persons receiving immunosuppressive chemotherapy (including corticosteroids), and (4) who received solid organ or bone marrow transplant.

Pneumococcal vaccine is not recommended for persons who have a history of serious allergic reaction to a vaccine component, have moderate or severe acute illness, or are pregnant. The vaccine is considered generally safe based on clinical experience. Approximately half of persons who received pneumococcal vaccine develop mild, local side effects (e.g., pain at the injection site, erythema, and swelling). Moderate systemic reactions (e.g., fever and myalgias) and severe systemic reactions (e.g., anaphylactic reactions) have rarely been reported. No neurologic disorders (e.g., Guillain-Barre Syndrome) have been associated with the administration of pneumococcal vaccine.

There is no evidence that PPSV is harmful to either a pregnant woman or her fetus. However, as a precaution, women with conditions that put them at risk for pneumococcal disease should be vaccinated before becoming pregnant, if possible.

### Table 16. Recommendations for Pneumococcal Vaccination

<table>
<thead>
<tr>
<th>Indications</th>
<th>Precautions / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Persons aged &gt;60 years of age</td>
<td>• Immediate anaphylactic reaction to a previous dose of pneumococcal vaccine</td>
</tr>
<tr>
<td>• Persons with chronic illnesses: chronic pulmonary diseases</td>
<td>• Allergy to a vaccine component: anaphylaxis to phenol or thimerosal</td>
</tr>
<tr>
<td>(chronic obstructive pulmonary disease, bronchiectasis, chronic</td>
<td>• Moderate to severe illness with or without a fever</td>
</tr>
<tr>
<td>pulmonary tuberculosis, cardiovascular (including congestive</td>
<td></td>
</tr>
<tr>
<td>heart failure and cardiomyopathies), diabetes mellitus, chronic</td>
<td></td>
</tr>
<tr>
<td>alcoholism, chronic liver disease, chronic renal failure or nephritic</td>
<td></td>
</tr>
<tr>
<td>syndrome, cerebrospinal fluid leaks, functional or anatomic asplenia</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised persons: HIV/AIDS, lymphoma, leukemia,</td>
<td></td>
</tr>
<tr>
<td>multiple myeloma, generalized malignancy, those receiving immunosuppressive</td>
<td></td>
</tr>
<tr>
<td>chemotherapy or corticosteroids, solid organ or bone marrow transplant</td>
<td></td>
</tr>
<tr>
<td>Persons receiving immunosuppressive therapy including corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Persons who received solid organ or bone marrow transplant</td>
<td></td>
</tr>
</tbody>
</table>

Influenza Vaccine

Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications. Influenza vaccine is recommended for all persons at increased risk for complications from influenza (Table 17).

The vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalizations and death among adults >65 years with or without high-risk medical conditions. Persons 50 to 64 years of age who do not have high-risk conditions also benefit from vaccination through decreased rates of influenza, decreased absenteeism from work, and decreased need from medical visits and medication, including antibiotics.

Each year, the seasonal influenza vaccine contains three influenza virus strains: one influenza A (H3N2) virus, one influenza A (H1N1) virus, and one influenza B virus. The influenza virus strains in the vaccine are selected each year based on surveillance-based forecasts about what
virus strains are most likely to cause illness in the coming season. Therefore, each year's vaccine is designed to protect against the influenza viruses expected to cause disease during that influenza season.\textsuperscript{14} Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.\textsuperscript{4}

The viruses used in making flu vaccine each year are based on information gathered over the previous year about the strains of flu viruses that are infecting pandemic and how they are changing. Circulating influenza strains and information on disease trends are gathered by 122 national influenza centers in 94 countries and the viruses and other data are further tested and combined data are analyzed by the four World Health Organization (WHO) Collaborating Centers for Reference and Research on Influenza located in Atlanta, London, Melbourne and Tokyo.

Based on this information, experts forecast which viruses are likely to circulate the following season and WHO recommends specific virus strains that can be used to make vaccines to protect against them. For vaccines being made for the Northern Hemisphere, the recommendation is made by WHO in February each year. For vaccines being made for the Southern Hemisphere, the recommendation is made by WHO in September.

Each country then can use the recommendations made by WHO to assist with national decisions about which viruses to use in influenza vaccines for their country.\textsuperscript{14} For the Philippines, current recommendations now state that the formulation for the Southern Hemisphere be used.

The pandemic influenza A(H1N1) virus emerged in March, 2009. It spread rapidly throughout the world, leading to the declaration of an influenza pandemic by WHO on June 11, 2009. Limited data from serologic studies of persons who received vaccination with seasonal influenza vaccines suggest that seasonal influenza vaccines will not provide protection against novel influenza A(H1N1) virus.\textsuperscript{15} Vaccination of people at high risk of contracting influenza is of utmost importance during the period of pandemic H1N1 infection. This is aimed at reducing the number of pneumonia cases caused by seasonal influenza to lower the possibility of misdiagnosing seasonal influenza as pandemic influenza A (H1N1) infection.

The WHO has issued recommendations that influenza vaccines for the 2010 southern hemisphere season contain the following viruses: an A/Perth/16/2009 (H3N2)-like virus, a B/Brisbane/60/2008-like virus and an A/California/7/2009 (H1N1)-like virus. This group of recommended influenza vaccine viruses will cover both pandemic and seasonal influenza. The A/California/7/2009 (H1N1)-like virus covers current pandemic influenza viruses, and the other two recommended vaccine viruses cover seasonal influenza viruses for 2010 in the southern hemisphere. Recommendations on the presentation of the vaccines – whether the viruses should be contained in a single vaccine or in one for pandemic (H1N1) 2009 influenza and another for seasonal influenza – will be provided later.\textsuperscript{16}

In the Philippines, influenza is characterized by several epidemics each year, with two main peaks. A large peak occurs during the rainy season from June to September, particularly from July to August. A smaller peak is noted during the months of December to January.\textsuperscript{16} Based on 5-year epidemiologic data (from February 1998 to September 2003) from the Influenza Virus Surveillance program of the Research Institute of Tropical Medicine, increased influenza activity can be seen from July to October. It is therefore recommended that vaccination should be given once a year 2 - 3 months before the start of the influenza season (preferably from February to June).\textsuperscript{7}

The risk for exposure to influenza during international travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year, while in the temperate regions of the Southern Hemisphere most activity occurs from April through September.

Influenza outbreaks have been reported among persons who travel from the northern hemisphere to the southern hemisphere and among persons from the northern hemisphere on groups tours. Any traveler who wants to reduce the risk for influenza infection should consider influenza vaccination, preferably at least 2 weeks before departure. Influenza vaccination is recommended before travel for persons at high risk for complications of influenza if they plan to travel to the tropics at any time of the year, travel with organized tourist groups at any time of the year, or travel to the Southern Hemisphere during April to September.\textsuperscript{3}

The influenza vaccine should be stored at 2°C – 8°C and should not be frozen. For adults, the influenza vaccine is administered at a dose of 0.5 mL intramuscularly every year. Annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination.

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. The vaccine, although purified, is produced in hens’ eggs and may contain residual egg protein. However, persons who have a history of anaphylactic hypersensitivity to vaccine components and who are also at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization.\textsuperscript{3}

The most frequent side effect of vaccination is soreness at the vaccination site (affecting 10-64%) that lasts for less than 2 days. Among older persons and healthy young adults, administration of influenza vaccine is not associated with higher rates of systemic symptoms (e.g., fever, malaise, myalgia and headache) when compared to placebo.\textsuperscript{18,19}

The previous 1976 swine influenza vaccine was associated with increased frequency of Guillain-Barre Syndrome. Evidence for a causal relation of Guillain-Barre Syndrome with subsequent vaccines prepared from other influenza viruses is unclear. The likelihood of coincidentally experiencing Guillain-Barre Syndrome after influenza vaccination is expected to be greater among persons with a history of Guillain-Barre Syndrome than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of Guillain-Barre Syndrome is unknown. Therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced Guillain-Barre Syndrome
Community-Acquired Pneumonia

within 6 weeks after a previous influenza vaccination is prudent. 3

Both pneumococcal and influenza vaccines can be administered simultaneously at different sites without increasing side effects. There is no contraindication for use of either pneumococcal or influenza vaccine immediately after an episode of pneumonia.

Table 17. Recommendations for Influenza Vaccination

<table>
<thead>
<tr>
<th>Indications</th>
<th>Precautions / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>All persons aged ≥65 yrs</td>
<td>Anaphylactic reaction to a previous dose of influenza vaccine</td>
</tr>
<tr>
<td>Chronic illness: chronic pulmonary (including asthma), chronic cardiorespiratory (except hypertension), renal, hepatic, neurological/ neuromuscular, hematological or metabolic disorders (including diabetes mellitus)</td>
<td>Allergy to eggs or to a vaccine component</td>
</tr>
<tr>
<td>Immunocompromised: HIV, malignancies, immunosuppressive drug, radiation therapy, organ or bone marrow transplantation</td>
<td>Moderate or severe acute illness with or without a fever</td>
</tr>
<tr>
<td>Pregnancy in the 2nd or 3rd trimester</td>
<td>Active neurologic disorder or a history of developing neurologic symptoms or illness following a previous dose</td>
</tr>
<tr>
<td>Residents of nursing homes &amp; other chronic care facilities</td>
<td>History of Guillain-Barre Syndrome</td>
</tr>
<tr>
<td>Household contacts (including children) and caregivers of children aged &lt;5 years and adults aged ≥50 years</td>
<td></td>
</tr>
<tr>
<td>Household contacts (including children) &amp; caregivers of persons with medical conditions that put them at high risk for severe complications from influenza</td>
<td></td>
</tr>
</tbody>
</table>

Adult Dose

- 0.5 mL intramuscularly once a year

Precautions / Contraindications

- Anaphylactic reaction to a previous dose of influenza vaccine
- Allergy to eggs or to a vaccine component
- Moderate or severe acute illness with or without a fever
- Active neurologic disorder or a history of developing neurologic symptoms or illness following a previous dose
- History of Guillain-Barre Syndrome

Smoking Cessation

Cigarette smoking, both active and passive, is a recognized independent risk factor for CAP. In addition to pneumococcal immunization, promotion of smoking cessation will also help curtail the incidence of pneumococcal disease. Smoking cessation is recommended for all patients with CAP who are current smokers.

Summary of Evidence

A. Pneumococcal Vaccine

The pneumococcal vaccine is both cost effective and protective against IPD. 2 Postlicensure epidemiologic studies have documented the vaccine’s efficacy in preventing IPD among the elderly and individuals with certain chronic medical conditions. 20 Only one case-control study failed to demonstrate effectiveness against bactereemic disease, 19 possibly because of study limitations such as small sample size and incomplete ascertainment of patients’ vaccination status. Moreover, the severity of underlying clinical conditions of case patients may not have been comparable to that of the controls, creating a potentially biased underestimate of vaccine effectiveness. The overall efficacy against IPD among immunocompetent persons 65 years of age and older is 75%; however efficacy seems to decrease with advancing age. 22

A study by Jackson et al 23 conducted in a large population of older adults, support the effectiveness of the pneumococcal polysaccharide vaccine for the prevention of bacteremia 0.56 (0.33-0.93). There was no significant association between vaccination and the risk of outpatient pneumonia and death, but vaccination was associated with a significantly higher risk of hospitalization with community-acquired pneumonia, which underscores the critical need to evaluate other vaccine formulations for the prevention of noninvasive pneumococcal infections in adults.

Prior vaccination against pneumococcus is associated with improved survival, decreased chance of respiratory failure or other complications, and decreased length of stay among hospitalized patients with CAP. In the study of Fisman et al 24 composed of 62,918 adults hospitalized with CAP between 1999-2003, 7390 (12%) had a record of prior pneumococcal vaccination. Vaccine recipients were less likely to die of any cause during hospitalization than were individuals with no record of vaccination (adjusted odds ratio [OR], 0.50; 95% confidence interval [CI], 0.43-0.59). Vaccination also lowered the risk of respiratory failure (adjusted OR, 0.67; 95% CI, 0.59-0.76) and other complications. Prior pneumococcal vaccination was associated with reduced median length of stay by 2 days compared with nonvaccination (4.5 days for prior vaccination and 6.5 days for nonvaccination, P <.001).

In a large population-based cohort study of patients hospitalized with pneumonia, Johnstone et al 25 found that previous pneumococcal vaccination was associated with a significant 40% relative reduction in hospital mortality or need for ICU admission.

In a 2-year retrospective cohort study of elderly persons with chronic lung disease, Nichol et al 26 found that pneumococcal vaccination was associated with significantly lower risks for pneumonia hospitalization (adjusted risk ratio [RR], 0.57; 95% CI, 0.38-0.84; P=.005) and for death (adjusted RR, 0.71; 95% CI, 0.56-0.91; P=.008). Over the 2-year outcome period, pneumococcal vaccination was also associated with direct medical care cost savings.

A recent meta-analysis was undertaken by Moberley et al 27 to assess the effectiveness of PPV in preventing disease or death in adults. Their meta-analysis of randomized controlled trials found strong evidence of PPV's efficacy against IPD with no statistical heterogeneity (OR 0.26, 95% CI 0.15 0.46). Efficacy against all-cause pneumonia was inconclusive with substantial statistical heterogeneity (OR 0.71, 95% CI 0.52 to 0.97). PPV was not associated with substantial reductions in all-cause mortality (OR 0.87, 95% CI 0.69 to 1.10). Vaccine efficacy against primary outcomes appeared poorer in adults with chronic illness but the difference was not statistically significant. The authors concluded that this meta-analysis provides evidence supporting the recommendation for PPV to prevent IPD in adults. The evidence from randomized controlled trials was less clear with respect to adults with chronic illness. This might be because of the lack of effect or lack of power in the studies.

B. Influenza Vaccine

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. 2 The vaccine prevents influenza illness in approximately 70–90% of healthy adults aged <65 years. 28,29 Influenza vaccination reduces the rates of visits to physicians, sick leaves, and
antibiotic use attributable to influenza-like illness by 34 to 44%, 32 to 45%, and 25%, respectively. 20

A meta-analysis by Jefferson et al 25 evaluated the effects of vaccines against influenza in healthy adults. Inactivated parenteral vaccines were 30% effective (95% CI 17% to 41%) against influenza-like illness, and 80% (95% CI 56% to 91%) efficacious against influenza when the vaccine matched the circulating strain and circulation was high, but decreased to 50% (95% CI 27% to 65%) when it did not. Vaccination had a modest effect on time off work, but there was insufficient evidence to draw conclusions on hospital admissions or complication rates. The authors concluded that influenza vaccines are effective in reducing cases of influenza, especially when the content predicts accurately circulating types and circulation is high.

Older persons with certain chronic diseases might develop lower post-vaccination antibody titers than healthy young adults and thus remain susceptible to influenza related upper respiratory infection. A randomized trial by Govaert et al 18 among non-institutionalized persons >60 years reported a vaccine efficacy of 58% against respiratory illness, but indicated that efficacy might be lower among those aged >70 years.

A meta-analysis of 20 cohort studies by Gross et al 11 showed that influenza vaccine reduces the risk for pneumonia, hospitalization and death among elderly persons during an influenza epidemic if the vaccine strain is identical or similar to the epidemic strain. Pooled estimates of vaccine efficacy were 53% (95% CI = 35%-66%) for preventing pneumonia, 56% (95% CI = 39%-68%) for preventing respiratory illness, 50% (95% CI = 28%-65%) for preventing hospitalization, and 68% (95% CI = 56% -76%) for preventing death. Vaccine efficacy from case-control studies ranged from 32%-45% for preventing hospitalization due to pneumonia, 31%-65% for preventing hospital deaths from pneumonia and influenza, 43%-50% for preventing hospital deaths from all respiratory causes, and 27%-30% for preventing death from all causes.

In years when the vaccine strains and the virus strains are well-matched, the vaccine can reduce the chances of getting the influenza by 70% to 90% in healthy adults. The vaccine may be somewhat less effective in elderly persons, but vaccination can still prevent serious complications from the flu. 10 In a study by Herrera et al 31 among persons 50-64 years of age during the 2003-2004 season, when the vaccine strains were not optimally matched, inactivated influenza vaccine effectiveness against laboratory-confirmed influenza was 60% among persons without high-risk conditions, and 48% among those with high-risk conditions. Vaccine effectiveness was 90% and 36% against influenza-related hospitalization for persons without and with high-risk conditions, respectively.

A recent meta-analysis by Rivetti et al 35 reviewed the evidence of efficacy, effectiveness and safety of influenza vaccines in the elderly (aged 65 years or older). In homes for elderly individuals (with good vaccine match and high viral circulation) the effectiveness of vaccines against influenza-like illness (ILI) was 23% (6% to 36%) and non-significant against influenza (RR 1.04: 95% CI 0.43 to 2.51). Well matched vaccines prevented pneumonia (VE 46%; 30% to 58%), hospital admission (VE 45%; 16% to 64%) and deaths from influenza or pneumonia (VE 42%, 17% to 59%). In elderly individuals living in the community, vaccines were not significantly effective against influenza (RR 0.19: 95% CI 0.02 to 2.01), ILI (RR 1.05: 95% CI 0.58 to 1.89), or pneumonia (RR 0.88; 95% CI 0.64 to 1.20). Well matched vaccines prevented hospital admission for influenza and pneumonia (VE 26%; 12% to 38%) and all-cause mortality (VE 42%; 24% to 55%).

C. Smoking Cessation

Data suggest that cigarette smoking is the major avoidable risk factor for acute pneumonia in adults. 24 In a population-based case-control study by Nuorti et al 35, cigarette smoking was identified as the strongest independent risk factor for IPD among immunocompetent, nonelderly adults. IPD was associated with cigarette smoking (OR, 4.1; 95% CI 2.4 to 7.3) and with passive smoking among nonsmokers (OR 2.5; 95% CI 1.2 to 5.1).

A prospective study by Baik et al 37 also identified smoking as a risk factor for CAP among men and women. Compared with never smokers, current smoking was associated with risk of CAP among men (RR 1.46; 95% CI 1.00-2.14) and women (RR 1.55; 95% CI 1.15-2.10). Similarly, a study by Almiral et al 38 confirmed cigarette smoking as an independent risk factor for CAP in multivariable analysis.

Because of consistent data on the association of cigarette smoking with increased risk of CAP and IPD, smoking cessation should be part of the therapeutic plan for persons with CAP who are current smokers.

REFERENCES:

1. Centers for Disease Control and Prevention. Interim guidance for use of 23-valent pneumococcal polysaccharide vaccine during novel influenza A(H1N1) outbreak. www.cdc.gov/h1n1flu/guidance/pppv_h1n1.htm

Learn to access drug info on your cellphone. Send PPD to 2600 for Globe/Smart/Sun users.
Community-Acquired Pneumonia


Appendix I

Grading System for the Strength of the Recommendations and Quality of Evidence

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of recommendation</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for or against use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for or against use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation for or against use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong></td>
<td>Evidence from ≥1 properly randomized trial</td>
</tr>
<tr>
<td><strong>Level II</strong></td>
<td>Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from &gt;1 center); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td><strong>Level III</strong></td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees</td>
</tr>
</tbody>
</table>


APPENDIX II

Modified Winthrop-University Hospital Infectious Disease Division’s Point System for Diagnosing Legionnaire’s Disease in Adults

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Clinical features</th>
<th>Point score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Acute onset</td>
<td>+1</td>
</tr>
<tr>
<td>Mental confusion / encephalopathic</td>
<td>Not drug-induced</td>
<td>+4</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Acute onset</td>
<td>+3</td>
</tr>
<tr>
<td>Ear pain</td>
<td>Acute onset</td>
<td>-3</td>
</tr>
<tr>
<td>Nonexudative pharyngitis / sorethroat</td>
<td>Acute onset</td>
<td>-3</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Acute onset</td>
<td>-3</td>
</tr>
<tr>
<td>Sputum</td>
<td>Purulent</td>
<td>-2</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Mild/Moderate</td>
<td>-3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Pleuritic</td>
<td>-2</td>
</tr>
<tr>
<td>Loose stools / watery diarrhea</td>
<td>Not drug-induced</td>
<td>+4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>With/Without diarrhea</td>
<td>+5</td>
</tr>
<tr>
<td>Relative bradycardia</td>
<td>Temperature &gt;102°F</td>
<td>+5</td>
</tr>
<tr>
<td>Lack of response to β-lactams</td>
<td>After 72 hours</td>
<td>+5</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Otherwise unexplained</td>
<td>+3</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Otherwise unexplained</td>
<td>-5</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Otherwise unexplained</td>
<td>-5</td>
</tr>
</tbody>
</table>

Laboratory tests

- **PO2 with**
- **Hypernatremia** Otherwise unexplained +1
- **Hypophosphatemia** Otherwise unexplained +5
- **ALT/AST (SGOT/SGPT)** (mild/transient) Otherwise unexplained +3
- **Ferritin (≥2 x normal)** Otherwise unexplained +5
- **Total bilirubin** Otherwise unexplained +1
- **CRP** Otherwise unexplained +4
- **CRP (≥30)** Otherwise unexplained +4
- **Cold Agglutinin titer (≥1:64)** Otherwise unexplained -5
- **Creatinine** Otherwise unexplained +1
- **Microscopic hematuria** Otherwise unexplained +2

Legionnaire’s disease likely: total points >10; Legionnaire’s disease possible: total points 5-10; Legionnaire’s disease unlikely: total points <5

- ALT alanine aminotransferase; AST aspartate aminotransferase; CPK creatine phosphokinase; CRP C-reactive protein;
- Acute onset associated with pneumonia and otherwise unexplained
- If not on β blockers, diltiazem, verapamil; no arrhythmias or pacemaker rhythms

REFERENCES:
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Social Security System: Victoria Poquiz, MD
UAP - Medichem: Ma. Antonieta Dial, MD
United Laboratories: Rodolfo Pagcatipunan

Secretariat
Iris K. Maranan
Rosa Lydia L. de Guzman
Community-Acquired Pneumonia

Index of Drugs Mentioned in the Guideline

This index os not part of the guideline. It lists the products and/or their therapeutic classes as mentioned in the guideline. For the doctor’s convenience, brands available in the PPD references are listed under each of the classes. For drug information, refer to PPD, PPD Pocket Version, PPD Text, PPD Tabs, and www.TheFilipinoDoctor.com.
Community-Acquired Pneumonia

Terlev
Voleca
Wiloxev
Winthrop Levofloxacin

**Moxifloxacin**
Avelox

**Carbapenems**
**Ertapenem**
Invanz

**Imipenem/Cilastatin**
Tienam
Hospira Imipenem + Cilastatin

**Meropenem**
Aropen
Dexpenem
Hospira Meropenem trihydrate
Menem IV
Meromax
Meronem
Merop
Mervex
Plemonem

**Other Antibiotics**
**Linezolid**
Zyvox

**Vancomycin**
Hospira Vancomycin
Vancocin CP
Vancomet

**Antiprotozoals**
**Metronidazole**
Dazomet
Flagyl
Metrolag
Protozole
RiteMED Metronidazole
Rodazid 125 mg/5 mL Suspension
Rodazid 500 mg Tablet
Triconex

**Vaccines for Active Immunization**
**Haemophilus influenzae (including Hib)**
Act-HIB
Easyfive-TT*
Hibrix
Infanrix Hexa*
Infanrix-IPV+Hib*
Pentaxim*
Synflorix*
Quinvaxem*
Vaxem Hib

**Influenza (Flu)**
Agrippal S1
Fluarix
Influvac
Vaxigrip

**Pneumococcal**
Pneumo 23
Pneumovax 23
Prevenar 13
Synflorix*