Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia (CAP) in Immunocompetent Adults

2010 Update

Joint Statement of the
Philippine Society for Microbiology and Infectious Diseases
Philippine College of Chest Physicians
Philippine Academy of Family Physicians
Philippine College of Radiology

Task Force on Community-acquired Pneumonia

Manolito L. Chua, M.D.	PSMID	Chair
Ma. Lourdes A. Villa, M.D.	PSMID	Rapporteur
Marissa M. Alejandria, M.D.	PSMID	Member
Abundio A. Balgos, M.D.	PCCP	Member
Joselito R. Chavez, M.D.	PCCP	Member
Vilma M. Co, M.D.	PSMID	Member
Remedios F. Coronel, M.D.	PSMID	Member
Jose Paolo M. De Castro, M.D.	PAFP	Member
Raquel Victoria M. Ecarma, M.D.	PSMID	Member
Benilda B. Galvez, M.D.	PCCP	Member
Policarpio B. Joves, M.D.	PAFP	Member
Isaias A. Lanzona, M.D.	PCCP	Member
Myrna T. Mendoza, M.D.	PSMID	Member
Leonardo Joseph Obusan, M.D.	PCR	Member
Isabelita M. Samaniego, M.D.	PAFP	Member
Ma. Bella R. Siasoco, M.D.	PCCP	Member

Thelma E. Tupasi, M.D., FPSMID
Adviser

Panel of Experts

PSMID	Angeles Tan-Alora, M.D. Mediadora C. Saniel, M.D. Thelma E. Tupasi, M.D.
PCCP	Roberto A. Barzaga, M.D. Teresita S. de Guia, M.D. Camilo C. Roa, Jr., M.D.
PAFP	Cynthia L. Hipol, M.D. Zorayda E. Leopando, M.D. Reynaldo A. Olazo, M.D.
PCR	Emmanuel D. Almasan, M.D.

Table of Contents

Part Four: Microbiologic Studies

Part Five: Treatment

Part Six: Prevention

Appendices

Foreword

Since the *Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia (CAP)* was published in 1998, new developments in CAP have emerged. This document aims to provide our physicians with an evidence-based approach to the initial antimicrobial management of CAP in immunocompetent adults.

This 2010 version updates the 2004 guidelines. It incorporates new evidences for its recommendations on the diagnosis, empiric management, and prevention of CAP. The following are the major changes incorporated in this document:

- Updates on issues on clinical and radiographic diagnosis of atypical pneumonias.
- Updates on criteria for admitting patients with pneumonia case.
- New recommended initial empiric antibiotic treatment.
- Updates on recommendations on prevention of pneumonia.

It is important to reiterate to our colleagues that these guidelines, by their very nature, cannot encompass all eventualities. Care has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. Therefore, the authors, editors, and publisher of these guidelines disclaim any and all liability for errors or omission or for any consequence from the application of information in this document and make no warranty, expressed or implied, with respect to the contents of this publication. Under no circumstances will this guideline supersede the experience and clinical judgment of the treating physician.

The Task Force on Community-acquired Pneumonia

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 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 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 these updated guidelines 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.”

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 guidelines 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 the 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) and
- 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?
   - The accuracy of predicting CAP by physicians' clinical judgment is between 60-76%. (Grade B)
   - Clinical prediction rules combining history and 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, 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?
   - A 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 or 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 for hospitalized CAP. (Grade B)
    - Invasive procedures (i.e., transtracheal, transthoracic biopsy, bronchoalveolar lavage, protected brush specimen) to obtain specimens for special microbiologic studies for atypical pathogens (e.g., mycobacteria and other microorganisms that will not grow on routine culture) are options for non-resolving pneumonia, immunocompromised patients, and patients in whom no adequate respiratory specimens can be sent despite sputum induction and routine diagnostic testing. (Grade B)

Treatment

12. When should antibiotics be initiated for the empiric treatment of 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)

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 second-generation cephalosporins (Grade A) with or without extended macrolides are recommended. For patients who have completed first-line treatment (BLIC or second-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 either an IV extended macrolide or IV respiratory fluoroquinolone is recommended as an initial antimicrobial treatment. (Grade A)
    - For high-risk CAP with risk for *P. aeruginosa*, a combination of an IV antipneumococcal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) with an extended macrolide and aminoglycoside (Grade A) **or** a combination of an IV antipneumococcal, 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 to 72 hours of initiating treatment. Failure to improve afer 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 and 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-day treatment regimen is recommended for *Mycoplasma* and *Chlamydophila* 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 a 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 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 and physical examination findings may be utilized to presumptively identify patients with pneumonia. (Grade B)

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 (respiratory rate >20 breaths per minute), tachycardia (cardiac rate >100/minute), and fever (temperature >37.8ºC) 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.[1] There is reported significant inter-observer agreement among physicians in obtaining clinical symptoms and signs in diagnosing patients with possible CAP.[2,3,4] Furthermore, elderly patients may not present with the classical symptoms of fever, cough, and dyspnea.[5]

History: Prospective cohort trials evaluated the sensitivity and specificity of the clinical history in pneumonia.[6,7,8,9] 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.[10] 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.[11,12]

Physical examination: Vital sign abnormalities on the probability of pneumonia depend on the cut-off value set by studies in defining an abnormal result.[10] A respiratory rate greater than 20 breaths/ minute resulted in a likelihood ratio of only 1.2 in one study[7] but a respiratory rate greater than 25 breaths/minute increased the likelihood ratio to 1.5 to 3.4. [6,9] 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.[9]

Like the history in Table 1, abnormal lung findings (e.g., crackles) increase the probability of pneumonia by only a small amount.[10] 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. [7]

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

Type of Finding**	Positive Likelihood Ratio‡	Negative Likelihood Ratio‡
Medical History Fever	1.7 – 2.1	0.6 – 0.7
Chills	1.3 – 1.7	0.7 - 0.9
Vital signs		
Tachypnea ¶	1.5 – 3.4	0.8
Tachycardia §	1.6 – 2.3	0.5 – 0.7
Hyperthermia	1.4 – 4.4	0.6 – 0.8
Chest examination		
Dullness	2.2 – 4.3	0.8 – 0.9
Decreased breath sounds	2.3 – 2.5	0.6 – 0.8
Rhonchi	1.4 – 1.5	0.8 – 0.9
Egophony	2.0 – 8.6	0.8 – 1.0

* Adapted from Metlay et. al.[10]

** 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 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/minute in a third study.

Combination of history and physical examination: Prediction rules combining history and physical examination significantly affect the probability of pneumonia. [6,8,9] 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. [13] These prediction rules

may be utilized to help physicians identify patients who may have pneumonia and therefore need a chest x-ray.

Three studies have proven that combinations of history and physical examination findings significantly affect the probability of pneumonia. [6,8,9] 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]

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

Decision Basis	Physician's Clinical Judgment	Heckerling et. al. Score (threshold was 2 points)	Gennis et. al. Rule (threshold was 1 point)
Variables	History Physical findings	• Temperature of >37.8°C • Pulse of >100/minute • Rales • Decreased breath sounds • Absence of asthma	• Temperature of >37.8°C • Respiration of >20/minute
Accuracy in predicting pneumonia	60%	68%	76%

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)[13]. 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 5-38% cases of CAP[14].

Summary of Evidence

Atypical pathogens are a common cause of CAP in all regions of the world with a global incidence of 22%[15]. The main feature differentiating atypical from typical CAP pathogens is the presence of extrapulmonary findings[16]. Pneumonia caused by typical pathogens *(Streptococcus pneumoniae, Haemophilus pneumoniae*, or *Moraxella catarrhalis)* present with clinical findings limited to the lungs. Each of the atypical pathogens commonly implicated in CAP *(Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella)* 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, 17,22]. (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 *Chlamydophila* and *Mycoplasma* 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

1. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Practice Guidelines for the Management of Community-acquired Pneumonia in adults. Infectious Disease Society of America. Clin Infect Dis 2000; 31:347-82.

2. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA 1997; 278: 1440-5.

3. Wipf JE, Lipsky BA, Hirschmann JV, et al. Diagnosing pneumonia by physical examination: relevant or relic? Arch Intern Med 1999; 159: 1082-7.

4. Spiteri MA, Cook DG, and Clarke SW. Reliability of eliciting physical signs in examination of the chest. Lancet 1988; 1 (8590): 873-5.

5. Metlay JP, Schulz R, Li YH, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Arch Intern Med 1997; 157: 1453-9.

6. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough: a statistical approach. J Chronic Dis 1984; 37: 215-225.

7. Gennis P, Gallagher J, Falvo C, Baker S, Than W. Clinical criteria for the detection of pneumonia in adults: guidelines for ordering chest roentgenograms in the emergency department. J Emerg Med 1989; 7: 263-268.

8. Singal BM, Hodges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. Ann Emerg Med 1989; 18: 13-20.

9. Heckerling PS, Tape TG, Wigton RS, et al. Clinical prediction rule for pulmonary infiltrates. Ann Intern Med 1990: 113: 664-670.

10. Metlay JP, Fine MJ. Testing strategies in the initial management of patients with community-acquired pneumonia. Ann Intern Med 2003; 138: 109-118.

11. Sackett DL. A primer on the precision and accuracy of the clinical examination. JAMA 1992; 267 (19): 2638-2644.

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: 703-7.

13. Niederman MS, Mandell LA, Anzueto A. et al. American Thoracic Society Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy Am Rev Respir Dis 1993; 148: 1418-1426.

14. Armitage K, Woodhead M. New guidelines for the management of adult community-acquired pneumonia by Kathryn Armitage and Mark Woodhead. Curr Opin Infect Dis 20: 170-176 2007

15. Arnold FW, Summersgill JT, LaJole AS, Peyran P, Marrie TJ, Rossi P, Blasl F, Fernandez P, File TM, Rello J, Menendez R, Maezoratti L, Luna CM, Ramirez J, and the Community-acquired Pneumonia Organization (CAPO) Investigators. A worldwide perspective of atypical pathogens in community-acquired pneumonia. Am J Respir Crit Care Med 2007; 175: 1086-1093.

16. Cunha, Burke A. The atypical pneumonias: clinical diagnosis and importance. Clin Microbiol Infect 2006; 12: 12-24.

17. Marrie TJ, Peeling RW, Fine MJ. et al. Ambulatory patients with community-acquired pneumonia: The frequency of atypical agents and clinical course. Am J Med 1996; 101: 508-515.

18. Fang GD, Fine M, Orloff J. et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: A prospective multicenter study of 359 cases. Medicine (Baltimore) 1990; 69: 307-316.

19. Sopena N, Sabria-Leal M, Pedro-Botel ML et al. Comparative study of the clinical presentation of Legionella pneumonia and other community-acquired pneumonias. Chest 1998; 113: 1195-1200.

20. Mulazimoglu L, Yu VL. Can Legionnaire's disease be diagnosed by clinical criteria? A critical review. Chest 2001; 120: 1049-1053.

21. Fernandez-Sabe N, Roson B, Carratala B. Clinical diagnosis of Legionella pneumoniae revisited: evaluation of the community-based pneumonia incidence Study Group scoring system. Clin Infect Dis 2003; 15: 483-489

22. Cunha, Burke A. Severe Legionella pneumonia: rapid presumptive diagnosis with Winnthrop-University hospital's weighted point score system (modified). Heart Lung 2008; 37: 311-320.

23. Diederen BMW. Legionella spp. and Legionnaires' disease. Journal of Infection 2008; 56: 1-12.

24. Edelstein PH. Legionnaire's disease. Clin Infect Dis 1993; 16: 741-9.

25. Roig J, Aguilar X, Ruiz Z, Domingo C, Mesalles E, Manterola J, et al. Comparative study of Legionella pneumophila and other nosocomial-acquired pneumonias. Chest 1991; 99: 344-50.

26. Granados A, Podzamczer D, Guidol F, Manresa F. Pneumonia due to Legionella pneumophila and pneumococcal pneumonia: similarities and differences on presentation. Eur Respir J 1989; 2: 130-4.

27. Pedro-Bote ML, Sabria M. Legionellosis. Semin Resp Crit Care Med 2005; 625-34.

28. Masia M, Gutierrez F, Padilla S, et al. Clinical characteristics of pneumonia caused by atypical pathogens combining classic and novel predictors. Clin Microbiol Infect 2007; 13: 153-151.

29. Fields BS, Benson RF, Besser RE. Legionella and Legionnaires' disease: 25 years of investigation. Clin Microbiol Rev 2002; 15: 506-26.

Part Two: 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:

- Healthy individuals or those with stable co-morbid conditions, **and**
- Normal vital signs and physical examination findings, **and**
- 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 and 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.[2] 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 Chlamydophila*, 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 and, 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 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.[1]

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)

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 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 al.[8] 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.

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 multilobar 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 pneumonic 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.[5] 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

Chest Radiographic Findings	Odds Ratio	95% C.I.*
Multilobar radiographic pulmonary infiltrate	3.1	1.9 – 5.1
Bilateral pleural effusion	2.8	1.4 – 5.8

*Confidence Interval

References

1. Mandell LA, Wunderink RG, Anzueto A. et al. Infectious Diseases Society of America/ American Thoracic Society Consensus Guidelines on the Management of Community-acquired Pneumonia in Adults. Clinical Infectious Diseases 2007; 44: S27-72.

2. Thomas J. Marrie (editor). Community-acquired Pneumonia, 2001; Chapter 6 : Imaging Community-acquired Pneumonia by Gerry Schaller and Mark Logan; pp 56-57.

3. Pachon J, Prados MD, Capote F, et al. Severe Community-acquired Pneumonia: Etiology, prognosis, and treatment. Am Rev Respir Dis 1990; 142:369-73.

4. Lieberman D, Shvartzman P, Korsonsky I, Lieberman D. Diagnosis of ambulatory community-acquired pneumonia comparison of clinical assessment versus chest x-ray. Scand J Prim Health Care 2003; 21: 57-60.

5. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Practice Guidelines for the Management of Community-acquired Pneumonia in adults. Infectious Disease Society of America. Clin Infect Dis 2000; 31:347-82.

6. Niederman MS, Mandell LA, Anzueto A, et. al. American Thoracic Society Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163: 1730-1754.

7. Macfarlane JT. Lower respiratory tract infection and pneumonia in the community. Semin Respir Infect 1999; 14: 151-162.

8. O'Brien WT Sr. Rohweder DA, et al. Clinical indicators of radiographic findings in patients with suspected community-acquired pneumonia: who needs a chest x-ray? J Am Coll Radiol 2006 Sep;3(9):703-6.

9. Albaum N, Hill L, Murphy M, et al. Interobserver reliability of chest radiograph in community-acquired pneumonia. Chest 1996; 110: 343-350.

10. Torres A, Serra-Batlles J, Ferrer A, et al. Severe community-acquired pneumonia. Epidemiology and prognostic factors. Am Rev Respir Dis 1991; 144: 312-318.

11. Fine MJ, Smith DN, Singer DE. Hospitalization decision in patients with community-acquired pneumonia: a prospective cohort study. Am J Med 1990;89:713-21.

12. Dans PE, Charache P, Fahey M, Otter SE. Management of pneumonia in the prospective payment era: a need for more clinician and support service interaction. Arch Intern Med 1984; 144:1392-7.

13. Fine MJ, Smith MA, CarsonCA, et al. Prognosis and outcomes of patients with community-acquired pneumonia; a meta-analysis. JAMA 1996; 275(2): 134-140.

14. Marrie TJ, Durant J, Yates L. Community-acquired Pneumonia requiring hospitalization: 5-year prospective study. Rev Infect Dis 1989;11(4):586-99.

Part Three: 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)
- 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 outpatient, 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^{o}C or <40^{o}C, Systolic Blood Pressure (SBP) $\geq$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 outpatients 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.

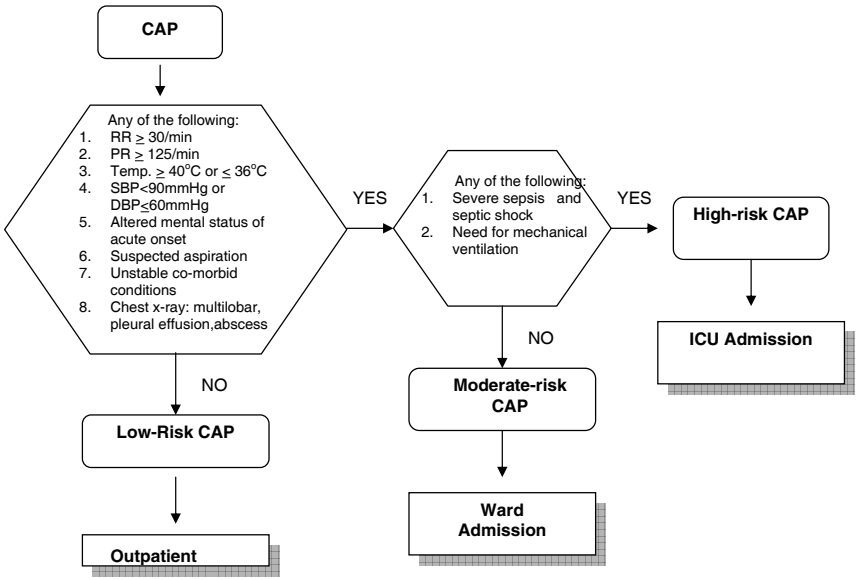
Table 4. Clinical Features of patients with CAP according to risk categories

Low-risk CAP	Moderate-risk CAP	High-risk CAP
Presence of:	Any of the following:	Any of the criteria under moderate- risk CAP category **plus**
Stable vital signs; RR <30 breaths/min • PR <125 beats/min • Temp >36 °C or <40 °C • SBP ≥90 mmHg • DBP >60 mmHg	Unstable vital signs: RR ≥30 breaths/min • PR ≥125 beats/min • Temp ≥40°C or ≤36°C • SBP <90 mmHg, • DBP ≤60 mmHg	Severe Sepsis and Septic shock
No altered mental state of acute onset No suspected aspiration No or stable comorbid conditions	altered mental state of acute onset Suspected aspiration Decompensated co-morbid condition	Need for mechanical ventilation
Chest X-ray: - localized infiltrates - no evidence of pleural effusion, abscess	Chest X-ray: - multilobar infiltrates - pleural effusion or abscess	

High-risk CAP: Patients with any 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**.

Figure 1 is an algorithm which may be used to guide physicians in the decision to hospitalize patients with CAP.

Figure 1. Algorithm for the management-oriented risk stratification of CAP among immunocompetent adults



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.[1,2,3]

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.[11-13] Several studies have shown a direct association between age and mortality[14] with an OR of 2.7; 95% CI 1.4-4.1 for age $\geq$65 years as an independent predictor of a complicated course.[15]

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.[16] A study by Halm et al[17] has also confirmed that selected low-risk elderly patients with pneumonia can be treated as outpatients with good results. A review by Ewig and Welte[6] 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 Brito[18] 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[12] et al 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 disease[19,20,21,22], diabetes mellitus[21,22], congestive heart failure[12,21,22], chronic renal failure, chronic liver disease[12], 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. [12] 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.[25-29]

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 following: 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 (20mg/dL), 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; O2 sat ≤93%; PaO_2/FiO_2 <333: if <age 50 or <60 mmHg; O2 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/mm3). [4]

Studies which found urea >7 mmol/l to be an independent predictor of mortality included a larger number of younger patients.[34-35] 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.[36] Leukopenia (WBC <4,000 cells/mm^3) resulting from CAP has consistently been associated with excess mortality as well 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. [37] 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 6 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.[40-43] Multivariate analysis showed that $PaO_2 \leq 60$ mmHg (OR=7.95; 95%CI:3.4-27.5), $PaCO_2 \geq 45$ mmHg (OR=4.6; CI:2.3-15.1); RR$\geq$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.[46] Even in CAP due to different etiologies, the frequency of severe sepsis may exceed 50%. [44] Septic shock is a known risk factor for mortality from pneumococcal infection.[47-50] 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.[2,4]

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 guidelines; the physician's aversion to risk; and prior or anticipated failure of outpatient treatment. Important medical and psychosoicial 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 preference, 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, trigerring 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.[39]

References

1. Mandell L. Severe CAP and the IDSA/ATS CAP Guidelines Prediction Rule: Validated or Not; CID 2009: 48: 386-8.

2. Liapikao A et al. Severe CAP: Validation of the IDSA/ATS CAP Guidelines to Predict an ICU admission; CID 2009: 48: 377-85.

3. Angus DC, Marrie TJ, Obrosky DS et al. Severe CAP: use of intensive care services and evaluation of the American and British Thoracic Society Diagnostic Criteria. Am J Respir Crit Care Med 2002; 166: 717-23.

4. Mandell LA, Wunderink RG Anzueto A et al. IDSA/ATS Consensus Guidelines on the Management of CAP in Adults. CID 2007: 44 (Suppl 2) 27-72.

5. Seymann G , Barger K, Choo S et al. Clinical Judgment versus Pneumonia Severity Index in Making the Admission Decision. J Emerg Med 2007, 261-8.

6. Ewig S and Welte T. CRB- 65 for the assessment of Pneumonia severity: Who could ask for more? Thorax. Aug 2008 63(8): 665-6.

7. Cuaresma AR, Panaligan M. Validation of CRB-65 scoring system in the management of CAP among patients admitted to USTH (unpublished)

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

9. Calavera ER. Validation of CURB-65 as a clinical prediction tool in Assessing Severity of CAP at the UERMMC. (unpublished)

10. Tabaloc MJ. Medical Outcomes and Process of Care of Adult Patients with CAP by Pneumonia PORT, Chong Hua Hospital, July 2003-June 2004. (unpublished)

11. Myint PK, Kamath AV, Vowler SL et al. Severerity Assessment criteria recommended by the BTS for CAP and older patients. Should SOAR (SBP, Oxygenation, age and RR) criteria be used in older people? A compilation study of 2 prospective cohorts. Age and Ageing 2006; 35: 286-91.

12. Kothe H, Bauer T, Marrie R et al. Outcome of CAP: influence of age, residence status & antimicrobial treatment. Eur Repir J 2008 Jul; 32(1): 139-46.

13. Brito V, Niederman M.S., How can we improve the management and outcome of pneumonia in the elderly? Eur Respir J 2008; 32; 12-4.

14. Marrie TJ, Durant H and Yates L. CAP requiring hospitalization: 5 year prospective study. Rev Infect Dis 1989; 11(4): 586-99.

15. Fine MJ. Hospitalization decisions in patients with CAP: a prospective cohort study. Am J Med 1990; 89:713-21.

16. Fine MJ, Auble TE, Yealy DM et al. A Prediction Rule to Identify low-risk patients with CAP. N Engl J Med 1997; 336: 243-50.

17. Halm EA, Atlas SJ Borowsky LH et al. Understanding physician adherence with a pneumonia practice guideline: effects of patient, system and physician factors. Arch Int Med 2000; 160: 98-104.

18. Niederman MS and Brito V. Pneumonia in the Older Patient. Clin Chest Med 2007; 28: 751-71.

19. Rello J, Rodriguez A, Torres A et al. Implications of COPD in patients admitted to the ICU by CAP. Eur Respir J 2006; 27:1210-16.

20. Molinos L, Clemente MG, Miranda B et al. CAP in patients with and without COPD. J Infect 2009. Mar 14

21. Arnold FW, Ramirez JA, McDonald LC et al. Hospitlaization for CAP: the PSI versus Clinical Judgement. Chest 2003; 124:121-4.

22. Marras TK, Gutierrez C, Chan CK. Applying Prediction Rule to Identify low-risk patients with CAP.Chest 2000; 118:1339-43.

23. The American Thoracic Society. Guidelines for the Initial Management of Adults with CAP: Diagnosis, Assessment of Severity; and Initial Antimicrobial Therapy. Am J Respir Dis 1993; 13:1418-26.

24. Minohue MF, Coley CM, Fine MJ et al. Patients hospitalized after initial outpatient treatment for CAP. Ann Emerg Med 1998; 21(3): 276-80.

25. Marrie TJ, Durant H, Yates L. CAP requiring hospitalization: 5 year prospective study. Rev Infect Dis 1989; 11: 586-99.

26. Torres A, Serra J, ferrer A et al. Severe CAP: etiology, epidemiology & prognostic factors. Am Rev Respir Dis 1991; 144: 312-8.

27. Moine P, Vercken JP, Chevret S et al. Severe CAP: etiology, epidemiology & prognostic factors. Chest 1994; 105:1487-95.

28. Shariatzadeh MR, Huang JQ, Marrie TJ. Differences in features of aspiration Pneumonia according to site of acquisition: community or continuing care facility. J Am Geriatrc Soc 2006; 54:296-302.

29. Shigemitsu H, Afshar K. Aspiration Pneumonias: Underdiagnosed and Undertreated. Curr Opin Pulm Med 2007; 133): 192-8.

30. Lim WS, Van der Eerden M, Laing R et al. Defining CAP severity on presentation to Hospital: an International and Validation study. Thorax 2003; 58: 377-82.

31. Chalmers JD, Singanayagam A, Hill AT. Systolic BP is superior to other Haemodynamic predictors of outcome in CAP. Thorax 2008; 63: 698-702.

32. Metlay JP, Fine M. Testing Strategies in the Initial Management of patients with CAP. Ann Int Med 2003; 138 (2): 109-18.

33. Charles P, Wolfe R, Whitby M t al. SMART-COP: A Tool for Predicting the Need for Intensive Respiratory or vasopressor Support in CAP; CID 2008; 47: 375-84.

34. The BTS and the Public Health Lab Service. CAP in Adults in British Hospitals in 1982-83: a survey of aetiology, mortality, prognostic factors and outcome. QJ med 1987; 62: 195-220.

35. Farr BM, Sloman AJ, Fisch MJ, Predicting death in patients hospitalized for CAP. Ann Int Med 1991; 115: 428-36.

36. Janssens JP, Gauthey L, Hermann F et al. CAP in older patients. J Am Geriatrc Soc 1996; 44: 539-44.

37. Rello J, Rodriguez A, Lisboa T et al. PIRO score for CAP: A new prediction rule for assessment of severity in ICU patients with CAP. Crit Care Med 2009; 37: 456-62.

38. Espana P, Capelastegui A, Gorordo I et al. Development and Validation of a Prediction Rule for Severe CAP. A J Respir Crit Care Med 2006; 174: 1249-56.

39. Niederman M. Making Sense of Scoring Systems in CAP. Respirology 2009. 14:327-35.

40. Sin DD, Man SF, Marrie TJ. Arterial Carbon Dioxide Tension on admission as a marker of in-hospital mortality in CAP. Am J Med 2005 Feb; 118 (2):145-50.

41. Lee J, Ryu Y, Chun E, et al. Outcomes and Prognostic Factors for Severe CAP that requires mechanical ventilation. The Korean J of Internal Medicine; 2007:22: 157-64.

42. Ray P, Birolleau S, Lefort Y et al. Acute Respiratory Failure in the elderly: etiology, emergency diagnosis and Prognosis. Crit Care 2006; 10 (3)/R 82

43. Confalonieri M, Potena A, Carbone G et al. Acute Respiratory Failure with Severe CAP. Am J respire Crit Care Med 1999; 160:1585-91.

44. Ewig S, Ruiz M, Mensa J et al. Severe CAP: assessment of severity criteria. A J Respir Crit Care Med 1998; 158: 1102-8.

45. ATS: Guidelines for the management of Adults with CAP: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163: 1730-54.

46. Dellinger RP, Levy M, Carlet J, et al. Surviving Sepsis Campaign: International Guidelines for management of Severe Sepsis and Septic Shock 2008: Intensive Care Med 2008; 34:17-60.

47. Dremsinov T, Clermont G, Kellum J et al. Severe sepsis in CAP: when does it happen, & do SIRS criteria help predict course? Chest 2006; 129; 968-78.

48. Yoshimoto A, Nakamura H, Fujimora M et al. Severe CAP in an ICU: risk factors for mortality. Intern Med 2005; 44: 710-6.

49. Schaaf B, Kruse J, Rupp J et al. Sepsis severity predicts outcome in community acquired pneumococcal pneumonia Eur Respir J 2007 Sept; 30(3); 517-24; 2008 Feb; 31(2): 478-9.

50. White M, Mankan A, Lawless M et al. Mortality in Humans with Pneumonia and sepsis Is related to an Uncompensated Anti-Inflammatory response to Infection. Arch Int Med 2008; 168 (13): 1468-9.

51. Aujesky D, McCausland JB, Whittle J, Obrosky D, Yealy D, Fine M. reasons Why Emergency department providers Do Not rely on the PSI to determine the Initial Site of treatment for patients with Pneumonia. CID 2009; 49:e100-8.

52. Labarere J, Stone RA, Scott OD et al. Factors associated with the Hospitalization of low-risk patients with CAP in a cluster-randomized trial. J Gen Intern med 2006; 21:745-52.

53. Fine MJ, Hough LJ, Medsger AR et al. The Hospital Admission Decision for patients with CAP. Results from the pneumonia Patient Outcomes research Team cohort study. Arch Int Med 1997; 157: 36-44.

54. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK<feagan BG. A controlled trial of a critical pathway for treatment of CAP. CAPITAL Study Investigators. CAP Intervention trial assessing Levofloxacin. JAMA 2000; 283:749-55.

55. The British Thoracic Society Guidelines for the management of CAP in Adults, Update 2009.

Part Four: Microbiologic Studies

11. What microbiologic studies are necessary in CAP?

- In low-risk CAP, microbiologic studies are optional. (Grade B)
- In moderate-risk 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 *Leginella pneumophila* are recommended in hospitalized patients with CAP. (Grade B)
- Invasive procedures (i.e., transtracheal, transthoracic biopsy, bronchoalveolar lavage, and protected brush specimen) to obtain specimens for special microbiologic studies for atypical pathogens (e.g., mycobacteria and other microorganisms that will not grow on routine culture) are options for non-resolving pneumonia, immunocompromised patients and patients in whom no adequate respiratory specimens can be sent despite sputum induction and routine diagnostic testing. (Grade B)

Since clinical signs and symptoms including radiologic findings are not specific for the microbial etiology of CAP, an etiologic agent should always be sought. The conditions which can alter response to standard antibiotic management are the presence of: 1) a bacterial etiology not covered by the empiric antibiotic 2) drug resistance and 3) etiologies other than bacteria (e.g., *Mycobacterium tuberculosis*, fungi, and viruses).

Low-risk CAP (with or without comorbid conditions): The most common etiologic agents are bacterial *(S. pneumoniae, H. influenzae)* and atypical pathogens *(M. pneumoniae, C. pneumoniae)*[1-3]. Since the bacterial etiology is predictable and the mortality risk is low, sputum 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 in which 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*). [4-7] In these patients, two 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 5 to 30% [8]. 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* be 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 to 15%) and the poor quality of samples in respiratory specimens[9].

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 pathogen is 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%)[10].

In Asian studies in which 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% [11]. Another study showed an overall prevalence of 23.5 % in Asian countries [12].

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%)[13].

This data shows that atypical pathogens can be found as etiologic agents in all risk classes of CAP (Table 5).

Table 5. Incidence of atypical pathogens

Region	Overall (%)	*M. pneumoniae* (%)	*C. pneumoniae* (%)	*L. pneumophila* (%)
In and out-patient				
Asia/African [10]	20	12	5	6
Asia [11]	25.2	11	13.4	1.1
In-patient				
Philippines [12]	23.5	12.2	4.7	6.6
Philippines [13]	43	14.2	12.8	27

Diagnostic tests for atypical pathogens: The most common methods for diagnosis include serology [a fourfold increase in IgG or IgM titers or an initially high initial IgG or IgM titer], culture, and PCR of respiratory specimens. For *L. pneumophila*, urine antigen test (UAT) to detect serotype 1 and direct fluorescent antibody test (DFA) of respiratory specimens are additional tests that are recommended.

However, the limitations of these tests include unavailability, the length of time to get the results [at least 2 weeks for serologic tests with initial low IgM titer], and cost. Thus, the tests tend to be useful only in the epidemiologic identification of the disease.

In Asian countries, it is of note that only 7 out of the 648 urine specimens collected for Legionella UAT (1.1%) were positive[11]. The prevailing serotype in Asia may not be serotype 1 which is the only serotype the UAT detects.

Emerging etiologies (human pandemic influenza A [H1N1] 2009, SARS): New and emerging causes of pneumonia (e.g., human pandemic influenza A [H1N1], SARS) should be sought during outbreaks or when there are epidemiologic clues that point to their presence. Rapid influenza diagnostic tests (RIDTs) in respiratory clinical specimens have low overall sensitivity in detecting human pandemic influenza A [H1N1] (40-69%). If the presence of human

pandemic influenza A [H1N1] is suspected in patients with moderate and high-risk pneumonia, a definitive determination with rRT-PCR should be conducted. The sensitivity test for rRT-PCR is 95.4 – 100%[14].

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 airway; thus, they are considered definite etiologic agents of pneumonia when isolated from respiratory secretions. [15]

Probable etiology: Pathogens demonstrated by smear or isolated from cultures 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 on expectorated sputum of good quality (i.e., 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 on Gram-stained sputum could theoretically select the appropriate monotherapy approximately 94% of the time.[16] 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 from 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 the *S. pneumoniae* UAT compared against the standard for diagnosis (blood, sputum and pleural fluid cultures) ranged from 82 to 88% (95% CI 74-95). The specificity was 96 to 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 6. Diagnostic tests for *M pneumoniae, C pneumoniae, L pneumophila*

Test	Sensitivity	Specificity
Diagnostic tests for *M. pneumoniae* [22]		
Respiratory or tissue culture	>90	50-90
Serology (complement Fixation, ELISA)	75-80	80-90
PCR	95	95-99
Diagnostic tests for *C. pneumoniae* [22,23]		
Respiratory or tissue culture	50-90	>90
Serology (microimmunofluorescence)	50-90	>85
PCR	>90	>90
Diagnostic tests for *L. pneumophila* [22,24]		
Sputum culture	75-99	100
Serology	40-75	95
Urine antigen test	60-70	99
PCR	>90	>90
Direct fluorescent antibody test	25-75	>90

References

1. Marrie TJ, Paulin-Costello M, Beecroft MD, Hernan Z. Etiology of community-acquired pneumonia treated in an ambulatory setting. Respir Med 2005 Jan;99(1):60-5.

2. Reechaipichitkui W, Lulitanond V, Sawanyawisuth K et al. Etiologies and treatment outcomes for out-patients with community-acquired pneumonia at Srinagarind Hospital, Khon Kaen, Thailand. Southeasr Asian J Trop Med Public Health. 2005 Sep;36(5):1261-7.

3. Holm A, Nexoe J, Bistrup LA et al. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. Br J Gen Pract 2007 Jul; 57 (540):547-54.

4. Song JW, Park SC, Choi Y et al. Atypical Pathogens as etiologic agents in hospitalized patients with community-acquired pneumonia in Korea: A prospective multi-center study. J Korean Med Sci 2006;21:602-7.

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

6. San Diego DC, Galvez BB, Balanag VM, Naval S. Philippine clinical practice guidelines of high risk CAP: a surveillance study (unpublished)

7. Bernas GA, Galvez BB. Community-acquired pneumonia: etiology, clinical profile and outcome. Phil J of Chest Dis 1997;5(1):31-9.

8. Stout JE, Yu V. Legionellosis. New England J Med 1997;337:682-687.

9. Mandell LA, Wunderink RG, Anzueto A. et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical Infectious Diseases 2007; 44: S27-72.

10. Arnold FW, Summersgill JT, Lajoie AS et al. A worldwide perspective of atypical pathogens in community acquired pneumonia. Am J Respir Crit Care; 2007: 175:1086-1093.

11. Jae-Hoon Soong, Won Sup Oh, Cheol-In Kang et al. Epidemiology and clinical outcomes of community acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. Int J Antimicrobial Agents 31 (2008) 107-114.

12. Ngeow YF, Suwanjutha S, Chantarojanasriri T et al. An Asian study on the prevalence of atypical respiratory pathogens in community acquired pneumonia. J Infect Dis. 2005; 9 (3): 144-53.

13. Ecarma RM. Alejandria M and Saniel M Prevalence and predictors of atypical pathogens in hospitalized patients with community-acquired pneumonia in the Philippines, 2002. (unpublished).

14. MMWR Morb Mortal Wkly Rep. 2009 Aug 7;58(30):826-9.

15. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Disease Society of America. Clin Infect Dis 2000; 31:347-82.

16. Murray P, Washington J. Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin Proc. 1975;50:339-444.

17. Boerner D, Zwadyk P. The value of sputum Gram's stain in community-acquired pneumonia. JAMA, 1982;247 (5):642-645.

18. Smith MD, Derrington P, Evans R et al. Rapid diagnosis of bacteremic pneumococcal infections by using Binax NOW streptotoccus urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol 2003;41(7):2810-3.

19. Smith, MD, Shepard CL, Hogan A et al. Diagnosis of Streptococcus pneumoniae infections in adults with bactermia and community acquired pneumonia: clinical comparison of pneumococcal PCR and urinary antigen detection. J Clin Microbiol 2009;47(4):1046-9.

20. Thorsteinsson S, Musher D, Fagan T. The diagnostic value of sputum culture in acute pneumonia. JAMA 1975; 233(8):894-95.

21. Davidson M, Tempest B, Palmer D. Bacteriologic diagnosis of acute pneumonia. Comparison of sputum, transtracheal aspirates and lung aspirates. JAMA 1976; 235(2):158-63.

22. File TM, Tan JS, Pflouffe, JE. Lower respiratory tract infections: the role of atypical pathogens: Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila in respiratory infection. Infect Dis Clin N Am 1998 (12): 3.

23. Campbell LA, Kuo CC. Cultivation and laboratory maintenance of Chlamydia pneumoniae. Curr Protoc Microbiol. Curr Protoc Microbiol 2009. Chap 11.

24. Stout JE, Yu V. Legionellosis. New England J Med 1997;337:682-687.

Part Five: 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 PCPG[1] for CAP recommended a maximum four-hour window from diagnosis to antimicrobial initiation. This recommendation was based on studies which showed a reduced in-hospital mortality when antimicrobial therapy was initiated within the first four hours of admission and diagnosis of CAP. The 2007 IDSA ATS Guidelines[2], however, found an internal inconsistency between the group that received antibiotics within the first two 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 A)
- For low-risk CAP with stable comorbid illness, β-lactam with β-lactamase inhibitor combinations (BLIC) (Grade A) or second-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 third-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 either an IV extended macrolide or IV respiratory fluoroquinolone is recommended as an initial antimicrobial treatment. (Grade A)
- For high-risk CAP with risk for *P. aeruginosa*, a combination of an IV antipneumococcal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) with an extended macrolide and aminoglycoside (Grade A) OR a combination of an IV antipneumococcal, 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 pneumonia, despite extensive laboratory testing, the causative pathogen remains unknown in 40 to 70% of cases.[3] 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 to 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.[4] 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 etiology

Table 7. Empiric antimicrobial therapy for CAP

Risk Stratification	Potential Pathogen	Empiric Therapy
Low- risk CAP	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophila 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:** β-lactam/β-lactamase inhibitor combination (BLIC)[b] or second-generation oral cephalosporins[c] +/- extended macrolides Alternative: third-generation oral cephalosporin[d] +/- extended macrolide
Moderate-risk CAP	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* Enteric Gram-negative bacilli *Legionella pneumophila* Anaerobes (among those with risk of aspiration)	IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem)[e] + extended macrolide OR IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem)[e] + respiratory fluoroquinolones[f] (FQ)
High-risk CAP	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* Enteric Gram-negative bacilli *Legionella pneumophila* Anaerobes (among those with risk of aspiration) *Staphylococcus aureus* *Pseudomonas aeruginosa*	**No risk for P. aeruginosa:** IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem)[e] + IV extended macrolide or IV respiratory FQ **With risk for P. aeruginosa:** IV antipneumococcal antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem)[g] + IV extended macrolide + aminoglycoside[h] OR IV antipneumococcal antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem)[g] + IV ciprofloxacin/levofloxacin (high-dose)

[a] Extended macrolides: azithromycin dihydrate, clarithromycin
[b] Oral β-lactam/β-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-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem): amoxicillin-clavulanic acid, ampicillin-sulbactam, cefotiam, cefoxitin, cefuroxime Na, cefotaxime, ceftizoxime, ceftriaxone, ertapenem
[f] Respiratory fluoroquinolones: levofloxacin, moxifloxacin
[g] IV antipneumococcal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem): cefoperazone-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanic acid, cefipime, cefpirome, imipenem-cilastatin, meropenem
[h] Aminoglycosides: gentamicin, tobramycin, netilmicin, amikacin

of the pneumonia to be atypical organisms such as *Mycoplasma pneumoniae* and *Chlamydophila 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, sultamicillin,), 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 third-generation cephalosporin (i.e., cefdinir, 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 (i.e., levofloxacin, moxifloxacin) has added coverage 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 monotherapy 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-

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

Antibiotic	Dosage	Antibiotic	Dosage
Low-risk CAP (All antibiotics are taken orally.)			
β-lactams:		**Second-generation cephalosporin**	
Amoxicillin	500 mg TID	Cefaclor	500 mg TID or 750 mg BID
Macrolides		Cefuroxime axetil	500 mg BID
Azithromycin dihydrate	500 mg OD		
Clarithromycin	500 mg BID	**Third-generation cephalosporin**	
β-lactam with β-lactamase inhibitor combination (BLIC)		Cefdinir	300 mg BID
		Cefixime	200 mg BID
Amoxicillin-clavulanic acid	625 mg TID or 1 gm BID	Cefpodoxime proxetil	200 mg BID
Amoxicillin-sulbactam	1 gm TID		
Sultamicillin	750 mg BID		
Moderate-risk CAP			
Macrolides		**Second-generation cephalosporin**	
Azithromycin dihydrate, PO/IV	500 mg q24h	Cefotiam, IV	1 gm q8h
Clarithromycin, PO/IV	500 mg q12h	Cefoxitin, IV (with anaerobic activity)	1-2 gm q8h
Erythromycin, PO/ IV	0.5-1 gm q6h	Cefuroxime Na, IV	1.5 gm q8h
Antipneumococcal fluoroquinolones		**Third-generation cephalosporin**	
Levofloxacin PO/IV	500-750 mg q24h	Cefotaxime, IV	1-2 gm q8h
Moxifloxacin PO/IV	400 mg q24h	Ceftizoxime, IV (with anaerobic activity)	1-2 gm q8h
β-lactam with β-lactamase inhibitor combination (BLIC)		Ceftriaxone, IV	1-2 gm q24h
Amoxicillin-clavulanic acid, IV	1.2 gm q8h	**Carbapenem**	
Ampicillin-sulbactam, IV	1.5 gm q8h	Ertapenem, IV	1 gm q24h

High-risk CAP (All antibiotics are given intravenously.)			
Macrolides		**Non-antipseudomonal carbapenem**	
Azithromycin dihydrate	500 mg q24h	Ertapenem	1 gm q24h
Clarithromycin	500 mg q12h		
Erythromycin	0.5-1 gm q6h		
		Antipseudomonal, anti-pneumococcal β-lactams (BLIC, cephalosporin, carbapenem)	
Antipneumococcal fluoroquinolones			
Levofloxacin	750 mg q24h		
Moxifloxacin	400 mg q24h	Cefoperazone-sulbactam	1.5-3 gm q8-12h
		Piperacillin-tazobactam	2.25-4.5 gm q6-8h
Aminoglycosides		Ticarcillin-clavulanic acid	3.2 gm q6h
Amikacin	15 mg/kg q24h	Cefepime	2 gm q8-12h
Gentamicin	3 mg/kg q24h	Cefpirome	2 gm q12h
Netilmicin	7 mg/kg q24h	Imipenem-cilastatin	0.5-1 gm q6-8h
Tobramycin	3 mg/kg q24h	Meropenem	1-2 gm q8h
Non-antipseudomnonal BLIC		**Anti-pseudomonal fluoroquinolones**	
Amoxicillin-clavulanic acid	1.2 gm q6-8h	Ciprofloxacin	400 mg q12h
Ampicillin-sulbactam	1.5 gm q6-8h	Levofloxacin	750 mg q24h
Non-antipseudomonal third-generation cephalosporin		**Others:**	
Cefotaxime IV	1-2 gm q8h	Oxacillin (Staphylococcus)	1-2 gm q4-6h
Ceftizoxime IV (with anaerobic activity)	1-2 gm q8h	Clindamycin (Staphylococcus and anaerobes)	600 mg q6-8h
Ceftriaxone IV	1-2 gm q24h	Metronidazole (anaerobes)	500 mg q6-8h
		Linezolid (MRSA)	600 mg q12h
		Vancomycin (MRSA)	1 gm q12h

anti-pseudomonal β-lactams include cephalosporins such as cefuroxime sodium, ceftriaxone or cefotaxime. Cefoxitin, ceftizoxime or ertapenem are options that also have anaerobic activity. Agents that 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 antipneumococcal 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 multidrug-resistant tuberculosis. Frequent outpatient fluoroquinolone use for CAP was associated with fluoroquinolone-resistant tuberculosis.[5] 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: Empiric 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 that 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 >7.5mg/day[2]. For these patients, the recommended empiric therapy should include regimens with a parenteral antipneumococcal, antipseudomonal β-lactam plus a parenteral extended macrolide and aminoglycosides OR a combination of a parenteral antipneumococcal, antipseudomonal β-lactam plus either parenteral ciprofloxacin or high dose levofloxacin. Antipneumococcal, antipseudomonal cephalosporins include cefepime and cefpirome. Carbapenems 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, pneumatocoeles 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.[2]

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 because of its ability 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 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-gram suspension. This 2-gram suspension is administered as single dose preparation and is considered another option for better compliance among patients with 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 US as a single-dose one-day regimen for the treatment of adult patients with mild CAP or Acute bacterial sinusitis.[6] 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 crossover 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 for 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 other pathogens such as 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 preparartions 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 approved recently by US 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), methicillin-resistant *S. aureus* (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 COPD and asthma patients.

Doripenem. Doripenem is the newest of the carbapenems to be approved for the management of infections in the United States. Compared with other carbapenems, doripenem had the lowest MIC_{90}s 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 *Stenotrophomonas maltophilia* and has activity similar to the other carbapenems against other Gram-negative bacilli. Since doripenem is stable for up to eight 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 to 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 studies[14-18] demonstrated that *S. pneumoniae* remains a common pathogen in patients with CAP treated on outpatients. Similarly, the presence of atypical pathogens was also identified.[14-18] Extended macrolides and azalides provide coverage against these potential pathogens. Woodhead[19] as well as Mundy et al.[20] 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 i.e., co-amoxiclav, sultamicillin, amoxicillin-sulbactam, and 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]

Table 9. Resistance rates of *S. pneumoniae* and *H. influenzae in the Philippines* (ARSP, 2004-2008)

Resistance rates in percentage of S. pneumoniae (ARSP, 2004 – 2008)				
	Chloramphenicol	**Penicillin**	**Co-trimoxazole**	**Erythromycin**
2004	5	5.3	15.2	1.3
2005	4.4	11.3	16.5	5.4
2006	5.4	5.6	14	2.2
2007	5.2	0.9	18.5	1.9
2008	5.3	0	23.3	3.9

Resistance rates in percentage of H. influenzae (ARSP, 2004 – 2008)				
	Ampicillin	**Chloramphenicol**	**Co-trimoxazole**	**Azithromycin**
2004	0	0	25	1.2
2005	10.3	19.6	15.1	0
2006	9.3	14	15.9	0
2007	11.1	8	13.4	0
2008	10.3	15.4	22	0

The Antimicrobial Resistance Surveillance Program (ARSP)[27] of the Philippines' 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 co-trimoxazole 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 outpatient setting is advised. A study in the Philippines[28] 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 fluoroqunolones 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 Long et al. among patients with culture-proven pulmonary TB before a 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.[31-54] The Asia CAP study among hospitalized CAP patients noted atypical pathogens in 43% of isolates.[55] 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 β-actam 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 β-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 from the ARSP[27] (Table 10) showed an increasing rate of resistance of common Gram-negative bacilli against levofloxacin. Thus, among non-ICU patients, combination therapy is recommended for optimum coverage of potential Gram-negative bacilli using either a non-antipseudomonal β-lactam plus extended macrolides or a non-antipseudomonal β-lactam plus a respiratory fluoroquinolone .

Table 10. Levofloxacin (LVX) resistance pattern among Enterobacteriaceae (ARSP 2008)[27]

	Escherichia coli	***Enterobacter spp.***	***Klebsiella spp.***
Number of isolates	3,047	1,688	2,337
LVX number	667	571	538
LVX resistance rate (%)	22.3	25.0	14.3

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 rate with BL+M than with F with no difference in length of stay among PSI class V patients.[73] Likewise, in the study of Metersky among patients with bacteremic pneumonia, the use of macrolide in therapy was strongly associated with improved outcome and may have advantages over a fluoroquinolone combination.[74] 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. [75-80]

The recommended standard empirical regimen for severe

CAP should routinely cover the three most common pathogens that cause severe CAP, all of the atypical pathogens, and most of the relevant Enterobacteriaceae species. For patients with risk of infection by *P. aeruginosa*, broad-spectrum coverage against this high-risk pathogen is recommended. The use of an antipneumococcal, antipseudomonal β-lactam plus extended macrolides and aminoglycosides is recommended. Alternatively, the use of antipneumococcal antipseudomonal β-lactam with either ciprofloxacin or levofloxacin (750-mg dose) is also appropriate. Pseudomonal CAP requires combination treatment to prevent inappropriate initial therapy, just as pseudomonal nosocomial pneumonia does. [2,81-89]

New antibiotics and new preparations of previously available antibiotics have been made available for the treatment of CAP. A new formulation of an extended macrolide is available locally as azithromycin dihydrate 2-gram suspension. Pharmacokinetic study done on 64 patients with lung cancer undergoing open surgery for lung resection were randomized to receive either a single 2 gram dose of azithromycin extended-release (ER) or a single 500 mg dose of azithromycin immediate-release (IR). Within the first 24 hours, a single 2 gram azithromycin-ER dose produced dose-related increase in systemic exposure compared with a single 500 mg azithromycin-IR dose, which resulted in higher levels of azithromycin in epithelial lining fluid, alveolar macrophages and lung tissue. Both formulations had similar safety profiles. By achieving high azithromycin exposure early in the course of treatment without compromising tolerability, azithromycin-ER shows the potential for improved antibacterial efficacy compared with azithromycin-IR.[90] In clinical trials, a single dose of azithromycin-ER was no less effective than seven days treatment with levofloxacin or clarithromycin-ER in patients with CAP. Clinical cure rate at test-of-cure is 89.7% for azithromycin-ER vs 93.7% for levofloxacin and 92.6% for azithromycin-ER vs 94.7% for clarithromycin-ER. Bacteriological response rate at test-of-cure is 90.7% for azithromycin-ER vs 92.3% for levofloxacin and 91.8% for azithromycin-ER vs 90.5% for clarithromycin-ER.[91,92] As of this writing, no head-on study is available comparing the extended-release and immediate-release formulations of azithromycin.

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] In the same study, the anhydrous form of azithromycin seemed to be unstable since it converted to dihydrate during 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 the 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.[7]

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. catarrhali*s and other pathogens such as Gram-negative bacilli.[9] However, clinical data of parenteral amoxicillin-sulbactam for 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 that 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 the tigecycline group, although the discontinuation rates due to adverse events were low for both treatment groups.[93,94]

Doripenem is the newest of the carbapenems to be approved for the managemrent of infections in the United States. In phase III trials, doripenem is noninferior to imipenem (clinical cure rate of 68.3% for doripenem vs. 64.8% for imipenem) and piperacillin-tazobactam (clinical cure rate of 81.3% for doripenem vs 79.8% for piperacillin-tazobactam) for the treatment of nosocomial pneumonia and ventilator-associated pneumonia. It is also noninferior compared with meropenem in the treatment of complicated intra-abdominal infection (clinical cure rate of 83.9% for doripenem vs. 85.9% for 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 90.2%)[11]

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 afer 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)

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)

Table 11. Indications for streamlining of antibiotic therapy

Indications for streamlining of antibiotic therapy:
1. Resolution of fever for > 24 hours 2. Less cough and resolution of respiratory distress (normalization of respiratory rate) 3. Improving white blood cell count, no bacteremia. 4. Etiologic agent is not a high-risk (virulent/resistant) pathogen e.g. *Legionella, S. aureus* or Gram- negative enteric bacilli 5. No unstable comorbid condition or life-threatening complication such as myocardial infarction, congestive heart failure, complete heart block, new atrial fibrillation, supraventricular tachycardia, etc. 6. No sign of organ dysfunction such as hypotension, acute mental changes, BUN to creatinine ratio of >10:1, hypoxemia, and metabolic acidosis 7. Patient is clinically hydrated, taking oral fluids and is able to take oral medications

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.

Table 12. Antibiotic dosage of oral agents for streamlining or switch therapy*

Antibiotic	**Dosage**	**Antibiotic**	**Dosage**
Amoxicillin-clavulanic acid	625mg TID or 1 gm BID	Cefaclor	500 mg TID or 750 mg BID
Amoxicillin-sulbactam	1 gm TID	Cefuroxime axetil	500 mg BID
Sultamicillin	750 mg BID	Cefdinir	300 mg BID
Azithromycin dihydrate	500 mg OD	Cefixime	200 mg BID
Clarithromycin	500 mg BID	Cefpodoxime proxetil	200 mg BID
		Levofloxacin	500-750 mg OD
		Moxifloxacin	400 mg OD

**for adults weighing 50 to 60 kg with normal liver and renal function*

Table 13. Benefits of intravenous to oral sequential antibacterial therapy

Benefits for patients
• More convenient • Less local adverse effects related to intravenous administration, such as phlebitis • Earlier mobilization resulting in a lower risk for thrombosis • Reduced hospital stay resulting in a lower risk for cross or nosocomial infections
Pharmacoeconomic benefits
• Less infusion equipment, cannulas, and infusion bottles required • Less hospital waste to dispose of • Oral antibacterials less expensive than parenteral antibacterials • Reduced storage costs for parenteral therapy • Less hospital staff time required • Reduced length of hospital stay

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-risk and high-risk CAP or for those with suspected or confirmed Gram-negative, *S. aureus* or *P. aeruginos*a pneumonia, treatment should be prolonged to 14 to 21 days. (Grade B)
- A treatment regimen of 10 to 14 days is recommended for *Mycoplasma* and *Chlamydophila* pneumonia while *Legionella* pneumonia is treated for 14 to 21 days. (Grade B)
- A 5-day course of oral or IV therapy for low-risk CAP and a 10-day course for *Legionella* pneumonia is possible with new agents such as the azalides, which possess a long half-life and achieve high tissue levels that prolong its 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)

Table 14. Duration of antibiotic use based on etiology

Etiologic Agent	Duration of therapy (days)
• Most bacterial pneumonias except enteric Gram-negative pathogens, *S. aureus*, and *P. aeruginosa*	5-7; 3-5 (azalides) for *S. pneumoniae*
• Enteric Gram-negative pathogens, *S. aureus*, and *P. aeruginosa*	14
• *Mycoplasma* and *Chlamydophila*	10-14
• *Legionella*	14-21; 10 (azalides)

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 *M. 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 ARDS. (Grade B)
- Obtaining additional specimens for microbiologic testing should be considered. (Grade B)

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 that is 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
9. Nosocomial superinfection

In patients who are 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, then the antibiotic should be changed. If the dose is inadequate, the dose should be corrected and the drug continued.

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 in 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 to establish a new radiographic baseline and to exclude the possibility of malignancy associated with CAP, particularly in older smokers. (Grade B)

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, a 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 defervescense.[95] Fever associated with severe pneumonia has been observed to decline in 72 hours and to completely lyse in 5 days.[96] Leukocytosis usually resolves by day 4.[97] 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 $\leq$37.2 °C), heart rate of $\leq$100 beats/min, respiratory rate of $\leq$24 breaths/min, systolic blood pressure of $\geq$90 mmHg and oxygen saturation of $\geq$90% or arterial oxygen partial pressure of $\geq$60mmHg.[98] 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.[98]

Chest radiographic findings usually clear more slowly than clinical findings and multiple radiographs are generally not required.[99] Follow-up chest radiography should not be done too early as pneumonic 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.[100]

Observational studies have shown that host factors particularly age and presence or absence of comorbid illnesses 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.[101] Radiographs of patients less than 50 years old with pneumonia due to *S. pneumoniae* cleared by 4 weeks in only 60% of patients.[102,103] 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.[102,103,104] *L. pneumophila* infection may take substantially longer to clear; only 55% of such infections show complete resolution by 12 weeks.[105]

Delayed resolution of radiograph abnormalities was independently associated with multilobar 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 <28 days after hospital admission of patients with severe CAP did not seem to provide additional clinical value in those responding to initial therapy.[106]

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.[107] 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.[108-112]

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.[113] 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 MIC_{50} for many common pathogens responsible for CAP.[107,114,115] The improved bioavailability of the newer antibiotics allows oral preparations to rapidly achieve adequate serum levels in patients with a functioning gastrointestinal tract. [116] 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. [117,118]

Non-response or failure to improve. Two patterns of unacceptable response are seen in hospitalized patients.[119] 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* [120] 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.[121]

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

Independent risk factors for failure to improve that have been identified include multilobar involvement, cavitating 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.[122,123,124]

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.[125,126,127] 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 to 5 day course for low-risk CAP. [118-134] and a 10-day course for *Legionella* pneumonia in immunocompetent patients. In an open-label non-comparative trial of 25 hospitalized immunocompetent patients with *Legionella* pneumonia given 4 days of parenteral azithromycin followed by 4 days of oral azithromycin, 22 patients were clinically cured.[135] Well-designed randomized controlled trials to establish the optimal duration of CAP are lacking.

References

1. Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management and Prevention of Community-acquired Pneumonia in Immunocompetent Adults 2004 Update – Joint Statement of the Philippine Society for Microbiology and Infectious Diseases, Philippine College of Chest Physicians and Philippine Academy of Family Physicians.

2. Mandell LA et al. Infectious Diseases Society of America/American Thoracic Society

Consensus Guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27-72.

3. Restrepo MI and Anzueto A. Severe community-acquired pneumonia. Infections in the intensive care unit. Infect Dis Clin N Am 2009;23(3):504.

4. Taguinod-de los Reyes MC, Mendoza MT, Saniel MC. Open-labeled randomized controlled trial and economic evaluation of azithromycin in the outpatient treatment of community-acquired pneumonia in adults. Section of Infectious Disease, UP PGH, 1998 (unpublished).

5. Long R. et al. Empirical treatment of community-acquired pneumonia and the development of fluoroquinolone-resistant tuberculosis. Clin Infect Dis 2009;48:1354-60.

6. Harrison TS and Keam SJ. Azithromycin extended release – a review of its use in the treatment of acute bacterial sinusitis and community-acquired pneumonia in the US. Adis Drug Evaluation 2007;67(5):773-92.

7. Gandhi R, Pillaj O, Thilagavathi R, Gopalakrishnan B, Kaula CL, Panchagnulaa R. Characterization of azithromycin. Eur J Pharm Sci. 2002;16(3):175-84.

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 azitromax 500mg tablet (Pfizer Italiana S.p.A., Italy) in healthy volunteer. 2002. (Unpublished)

9. Acuna C and Rabasseda X. Amoxicillin-sulbactam: A Clinical and Therapeutic Review. Drugs of Today. 2001; 37(3): 193-210.

10. Galvez, BB. A multicenter randomized controlled trial comparing the efficacy and safety of oral preparations of amoxicillin (500mg) + sulbactam (500mg) vs amoxicillin (500mg) + clavulanate (125mg) in the treatment of low-risk community-acquired pneumonia in adult Filipino patients. 2009 (unpublished)

11. Matthews SJ, Lancaster JW. Doripenem monohydrate, a broad-spectrum carbapenem antibiotic. Clin Ther. 2009;31(1):42-63.

12. Paterson DL and DePestel DD. Doripenem. CID 2009;49:291-98

13. Moran GJ. New directions in antiinfective therapy for community-acquired pneumonia in the emergency department. Pharmacotherapy 2001;21(7s):95-99.

14. Marrie TJ, Paulin-Costello M, Beecroft MD, Hernan Z. Etiology of community-acquired pneumonia treated in an ambulatory setting. Respir Med 2005 Jan;99(1):60-5.

15. Moreno B R, Riquelme O R. Etiology of community-acquired pneumonia in immunocompetent adults. Rev Chilena Infectol 2005;22 Suppl 1:s18-25.

16. Holm A, Nexoe J, Bistrup LA et al. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. Br J Gen Pract 2007;57(540):547-54.

17. Almirall J, Boixeda R, Bolibar I et al. Differences in the etiology of community-acquired pneumonia according to site of care: a population-based study. Respire Med 2007 Oct; 101 (10): 2168-75.

18. Reechaipichitkui W, Lulitanond V, Sawanyawisuth K et al. Etiologies and treatment outcomes for out-patients with community-acquired pneumonia at Srinagarind Hospital, Khon Kaen, Thailand. Southeast Asian J Trop Med Public Health. 2005;36(5):1261-7.

19. Woodhead M. Prospective study of the etiology and outcome of pneumonia in the community. Lancet 1987:671-4.

20. Mundy LM, Oldah D, Auwaerten PG, et al. Implications for macrolide treatment in community-acquired pneumonia. Chest 1998;113(5):1201-6.

21. Niederman MS, Mandell LA, Anzueto A, et. al. American Thoracic Society guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163: 1730-1754.

22. British Thoracic Society Guidelines for the management of community-acquired pneumonia in adults. Thorax 2001;56 Suppl 4;1-64.

23. Calver, AD, Walsh NS, Quinn PF, et al. Dosing of amoxcillin/clavulanate given every 12 hours is as effective as dosing every 8 hours for treatment of lower respiratory tract infection. Clin Infect Dis 1997;24(4):570-4.

24. Higuera F, Hidalgo H, Feris J, Giguere G, Colins J. Comparison of oral cefuroxime axetil and oral amoxicillin/clavulanate in the treatment of community-acquired pneumonia. J Antimicrob Chemother 1996; 37(3):555-64.

25. Genne D, Siegrist H, Humair L, Janin B, de Torrente A. Clarithromycin versus amoxicillin-clavulanic acid in the treatment of community-acquired pneumonia. Eur J Clin Microbiol Infect Dis. 1997; 16(11):783-8.

26. Rovira E, Martinez E, Belda A, Gonzalvo F, Ripolles F, Pascual J. Treatment of community-acquired pneumonia in outpatients: randomized study of clarithromycin alone versus clarithromycin and cefuroxime. Respiration 1999; 66(5):413-8.

27. Carlos C. Antimicrobial Resistance Surveillance Program (ARSP) of the Department of Health (DOH), Philippines, 2004-2008.

28. Grimaldo ER, Tupasi TE, Rivera AB, et al. Increased resistance to ciprofloxacin and ofloxacin in MDR-MTB isolates from patients seen at a tertiary hospital in the Philippines. Int J Tuberc Lung Dis 2001;5(6):546-50.

29. Williams JH. Fluoroquinolones for respiratory infections: too valuable to overuse. Chest 2001;120(6):1771-5.

30. Ginsberg A, Hoper N, Parrish N, et al. Fluoroquinolone resistance in patients with newly diagnosed tuberculosis. Clin Infect Dis 2003;37:1448-52.

31. Ortiz MF, Comia CT. Adherence of the physicians at Mary Mediatrix Medical Center to the 2004 Philippine Guidelines on the Management of Patients Hospitalized for CAP. (unpublished)

32. San Diego DC, Galvez BB, Balanag VM, Naval S. Philippine clinical practice guidelines of high-risk community-acquired pneumonia: a surveillance study (unpublished)

33. Bernas GA, Galvez BB. Community-acquired pneumonia: etiology, clinical profile and outcome. Scientific proceedings (LCP). 1996;Jan-June;4(1).

34. Comia C and Mendoza, M. The adherence of physicians at the Philippine General Hospital to the 2004 Philippine Guidelines on the Management of Patients Hospitalized for Community-acquired Pneumonia. Philippine Journal of Microbiology and Infectious Diseases. 2006;35(3):5-17.

35. Ortiz M and Comia C. Adherence of the physicians at Mary Mediatrix Medical Center to the 2004 Philippine guidelines on the Management of Patients Hospitalized for Community-acquired Pneumonia (CAP)

36. Song, Jae-Hoon et al. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. International Journal of Antimicrobial Agents. 2008;31:107-114.

37. Charles PG, Whtiby M, Fuller AJ et al. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxyxycline or a macrolide is the most appropriate therapy. Clin Infect Dis 2008;46(10):1513-21.

38. Eliott JH, Anstey NM, Jacups SP et al. Community-acquired pneumonia in Northern Australia: low mortality in a tropical region using locally-developed treatment guidelines. Int J Infect Dis 2005;9(1):15-20.

39. Wilson PA, Ferguson J. Severe community-acquired pneumonia: an Australian perspective. Intern Med J 2005 Dec; 35(12):699-705.

40. Riquelme O R, Riquelme O M, Rioseco ML et al. Rev Med Chil. 2006;134(5):597-605.

41. Leesik H, Ani U, Juhani A Altraja A. Microbial pathogens of adult community-acquired pneumonia in Southern Estonia

42. Hohenthal U, Vainionpaa R, Meurman O et al. Aetiological diagnosis of community-acquired pneumonia: utility of rapid Microbiological methods with respect to disease severity. Scand J Infect Dis 2008;40(2):131-8.

43. Paganin F, Lilienthal F, Bourdin A et al. Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. Eur Respir J 2004 Nov; 24(5):779-85.

44. Takayanagi N, Hara K, Tokunaga D et al. Etiology and outcome of community-acquired pneumonia in relation to age and severity in hospitalized adult patients. Nihon Kokyuki Gakkai Zasshi. 2006;44(12):906-15.

45. Motomura K, Masaki H, Terada M et al. Usefulness of the Japanese Respiratory Society Guidelines for Community-acquired Pneumonia: a retrospective analysis of community-acquired pneumonia between 2000 and 2002 in a general hospital. Respirology. 2005;10(2):208-14.

46. Al-Ali MK, Batchoun RG, Al-Nour TM. etiology of community-acquired pneumonia in hospitalized patients in Jordan. Saudi Med J 2006;27(6):813-6.

47. Sohn JW, Park SC, Choi Y et al. Atypical pathogens as etiologic agents in hospitalized patients with community-acquired pneumonia in Korea: a prospective multi-center study. J Korean Med Sci 2006;21:602-7.

48. Behbehani N, Mahmood A, Mokaddas EM et al. Significance of atypical pathogens among community-acquired pneumonia adult patients admittied to a hospital in Kuwait. Med Pric Pract 2005 Jul-Aug;14(4):235-40.

49. Fernandez R, Suarez I, Rubinos G et al. Community-acquired pneumonia: aetiologic changes in a limited geographic area. an 11 year prospective study. Eur J Clin Microbiol Infect Dis. 2007 Jul;26 (7): 495-9.

50. Yen MY, Hu BS, Chen YS. A prospective etiologic study of community-acquired pneumonia in Taiwan. J Formos Med Assoc. 2005 Oct;104(10):724-30.

51. Lauderdale TL, Chang FY, Ben RJ et al. Etiology of community-acquired pneumonia among adult patients requiring hospitalization in Taiwan. Respir Med 2005 Sep; 99(9):1079-86.

52. Reechaipichitkui W, Lolitanond V, Tantiwong P et al. Etiologies and treatment outcomes in patients hospitalized with community-acquired pneumonia at Srinagarind Hospital, Khon Kaen, Thailand. Southeast Asian J Trop Med Public Health. 2005 Jan;36(1):156-61.

53. Reechaipichitkui W, Pisprasert V. Severe community-acquired pneumonia treated at Srinagarind Hospital, Khon Kaen, Thailand. Southeast Asian J Trop Med Public Health. 2004 Jun;35(2):430-3.

54. Howard LS, Sillis M, Pasteur MC et al. Microbiologic profile of community-acquired pneumonia in adults over the last 20 years. J Infect 2005 Feb;50(2):107-13.

55. Saniel MC, Alejandria MM, Ecarma RM et al. Prevalence of atypical pathogens in hospitalized patients with community acquired pneumonia in the Philippines, 2002. (unpublished).

56. Okimoto N, Kurihara T, Honda N, et al. Clinical effect of ampicillin with beta-lactamase inhibitor (sulbactam/ampicillin) on community-acquired pneumonia in the elderly. J Infect Chemother 2003 Jun;9(2):183-6.

57. Jauregui L, Minns P, Hageage G. A comparison of ampicillin/sulbactam versus cefotaxime in the therapy of lower respiratory tract infections in hospitalized patients. J Chemother. 1995;7(2):153-6.

58. Ortiz G. Lopez J, Friedland I, et al. A study evaluating the efficacy, safety and tolerability of ertapenem vs. ceftriaxone for the treatment of community-acquired pneumonia in adults. Clin Infect Dis 2002;34(8):1076-83.

59. Vetter N, Hernandez E, Rohlf J, et al. A prospective, randomized double-blind multicenter comparison of parenteral ertapenem & ceftriaxone for the treatment of hospitalized adults with community-acquired pneumonia. Clin Ther 2002;24(11):1770-85.

60. Frank E, Liu L, Kinasewitz G, et al. A multi-center open label, randomized comparison of levofloxacin and azithromycin plus ceftriaxone in hospitalized adults with moderate to severe community-acquired pneumonia. Clin Ther 2002;24(8):1292-308.

61. Siasoco B, Bobadilla J, Chavez J, Lazo S, Espallardo N. A randomized controlled trial comparing the effectiveness and safety of once daily levofloxacin versus ceftriaxone with or without erythromycin in the treatment of community-acquired pneumonia. Phil J Int Med 2000; 38:26-31.

62. File T, Segreti J, Dunbar L, et al. A Multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother 1997;41(9):1965-72.

63. Dresser LD. Cost-effectiveness of gatifloxacin vs ceftriaxone with a macrolide for the treatment of community-acquired pneumonia. Chest 2001;119(5):1439-48.

64. Sanchez F, Mensa J, Martinez E, et al. Is Azithromycin the first choice macrolide for treatment of community-acquired pneumonia? Clin Infect Dis 2003; 36(10):1239-45.

65. Pena A, Roa C, Makalintal N, et al. Safety and efficacy of IV and oral azithromycin in community-acquired pneumonia: results of an open, multi¬center study among Filipino patients. Phil J Int Med 2003;41:51-8.

66. Contopoulos DG, Joannidis J, Chaw P, Lau J. Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for lower respiratory tract infection. J Antimicrob Chemother. 2001;48(5):691-703; J Antimicrob Chemother 2002; 50(3):433-4.

67. Plouffe JF, Breiman RF, Fields BS, et al. Azithromycin in the treatment of Legionella pneumonia requiring hospitalization. Clin Infect Dis 2003;37(11):1475-80.

68. McCarty JM. Clarithromycin in the management of community-acquired pneumonia. Clin Ther. 2000 Mar; 22(3):281-94; discussion 265.

69. Feagan BG. A controlled trial of a critical pathway for treating community-acquired pneumonia: the CAPITAL study assessing levofloxacin. Pharmacotherapy. 2001; 21(7 Pt 2):89-94S.

70. Hurst M, Lamb H, Scott L, Figgitt D. Levofloxacin: an updated review of its use in the treatment of bacterial infections. Drugs 2002; 62(14):2127-67.

71. Dunbar L, Wunderink R, Habib M, et al. High-dose, short course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003; 37:752-60.

72. Erard V, Lamy O, Bochud PY, Bille J, Cometta A, Calandra T. Full course oral levofloxacin for treatment of hospitalized patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2004;23(2):82-8.

73. Lodise TP. Comparison of β-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. Antimicrobial Agents and Chemotherapy. 2007;51(11):3977-3982.

74. Metersky ML, Houck AMP and Bratzier DW. Antibiotics for bacteremic pneumonia. Chest 2007;131:466-473.

75. Mufson MA, Stanek RJ: Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978–1997.Am J Med 1999;107:34S-43S.

76. Waterer GW, Somes GW, Wunderink RG: Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia.Arch Intern Med 2001;161:1837-42.

77. Martinez JA, Horcajada JP, Almela M, Marco F, Soriano A, Garcia E, Marco MA, Torres A, Mensa J: Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003,36:389-95.

78. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ: Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. Ann Pharmacother 2000;34:446-52.

79. Brown RB, Iannini P, Gross P, Kunkel M: Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest 2003;123:1503-11.

80. Garcia Vazquez E, Mensa J, Martinez JA, Marcos MA, Puig J, Ortega M, Torres A: Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis 2005;24:190-95.

81. Lin JC, Yeh KM, Peng MY, Chang FY. Efficacy of cefepime versus ceftazidime in the treatment of adult pneumonia. J Microbiol Immunol Infect. 2001;34(2):131-7.

82. Shlaes DM, Baughman R, Boylen CT, et al. Piperacillin/tazobactam compared with ticarcillin/clavulanate in community-acquired bacterial lower respiratory tract infection. J Antimicrob Chemother 1994 ;34(4):565-77.

83. Speich R, Imhof E, Vogt M, Grossenbacher M, Zimmerli W. Efficacy, safety and tolerance of piperacillin/tazobactam compared to co-amoxiclav plus an aminoglycoside in the treatment of severe pneumonia. Eur J Clin Microbiol Infect Dis 1998;17(5):313-7.

84. Finch RG, Pemberton K, Gildon KM. Pneumonia: the impact of risk factors on the outcome of treatment with meropenem and ceftazidime. J Chemother 1998;1:35-46.

85. Romanelli G. Cravarreza P, Pozzi A, et al. Carbapenems in the treatment of severe community-acquired pneumonia in hospitalized elderly patients: a comparative study against standard therapy. J Chemother 2002; 14(6):609-17.

86. Ho A, Leung R, Lai CK, Chan TH, Chan CH. Hospitalized patients with community-acquired pneumonia in Hong Kong: a randomized study comparing imipenem/cilastin and ceftazidime. Respiration 1997;64(3):224-8; 64(4):303.

87. Bartoloni A, Strohmeyer M, Corti G, et al. Multicenter randomized trial comparing meropenem and imipenem/cilastin in the hospital treatment of community-acquired pneumonia. Drugs Exp Clin Res. 1999;25(6):243-52.

88. Beaucaire G, Leroy O, Beuscart C, Karp P, Chidiac C, Caillaux M. Clinical and bacteriological efficacy and practical aspects of amikacin given once daily for severe infections. J Antimicrob Chemother 1991; 27 Suppl C: 91-103.

89. Covi M, Velluti G. Comparison of the efficacy and safety of isepamicin and amikacin in the treatment of acute lower respiratory tract infections caused by Gram-negative organisms. J Chemother 1995;7 Suppl 2:137-42.

90. Lucchi M, Damle M, Fang A, de Caprariis PJ, Mussi A, Sanchez P, Pasqualetti G and Del Tacca M. Pharmacokinetics of azithromycin in serum, bronchial washings, alveolar macrophages and lung tissue following a single oral dose of extended or immediate release formulations of azithromycin. Journal of Antimicrobial Chemotherapy 2008; 61(4):884-91.

91. D'Ignazio JD, Camere MA, Lewis DE and Jorgensen D, Breen JD. Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired pneumonia in adults. Antimicrobial Agents and Chemotherapy. October 2005: 4035-41.

92. Drehobl MA, De Salvo MC, Lewis DE et al. Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. Chest 2005 Oct;128(4):2230-7.

93. Tanaseanu C et al. Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC Pulmonary Medicine 2009;9:44.

94. Tanaseanu C, Bergallo C, Teglia O, Jasovich A et al. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. Diagn Microbiol Infect Dis 2008 July;61(3):329-38.

95. Halm E, Fine M, Marrie T, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia. JAMA 1998;279:1452-7.

96. Pachon, J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community-acquired pneumonia: etiology, prognosis, and treatment. Am Rev Respir Dis 1990;142: 369-73.

97. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Disease Society of America. Clin Infect Dis 2000;31:347-82.

98. Menendez R, Torres A, Rodrıguez de Castro F, et al. Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. Clin Infect Dis 2004;39:1783–90.

99. Dans PE, Charache P, Fahey M, Otter SE. Management of pneumonia in the prospective payment era: a need for more clinician and support service intereaction. Arch Intern Med 1984;144:1392-7.

100. Marrie TJ, Durant J, Yates L. Community-acquired pneumonia requiring hospitalization: 5 year prospective study. Rev Infect Dis 1989;11:586-99.

101. Mittl RL, Schwab RI, Duchin JS, Goih JB, Albeida SM, Miller W. Radiographic resolution of community-acquired pneumonia. Am J Respir Crit Care Med 1994;149: 630-5.

102. Jay S, Waldemar J, Pierce A. The radiologic resolution of S. pneumoniae pneumonia. N Engl J Med 1975;293:798-801.

103. Macfarlane, JT, Miller AC, Roderick Smith WH, Morris AH, Rose DH. Comparative radiographic features of community-acquired legionnaires' disease, pneumococcal pneumonia, M. pneumoniae and psitacosis. Thorax 1984;39:28-33.

104. El Solh A, Aquilina A, Gunen H, Ramadan F. Radiographic resolution of community-acquired bacterial pneumonia in the elderly. J Am Geriatr Soc 2004;52:224-9.

105. Grayston JT. Chlamydia pneumonia strain TWAR pneumonia. Ann Rev Med 1992;43:317-23.

106. Bruns AHW, Oosterheert JJ, Prokop M, Lammers JJ, Hak E, Hoepelman AIM. Patterns of resolution of chest radiograph abnormalities in adults hospitalized with severe community-acquired pneumonia. Clin Infect Dis 2007;45:983-91.

107. Hitt CM, Nightingale CH, Quintiliani R, Nicolau DP. Streamlining antimicrobial therapy for lower respiratory tract infections. Clin Infect Dis 1997;24(Suppl 2): S213-7.

108. Vogel, F. IV/oral sequential therapy in patients hospitalized with community-acquired pneumonia: which patients, when and what agents? Drugs 2002;62(2):309-17.

109. Ramirez JA, Vargas S, Ritter G, et al. Early switch from IV to oral antibiotics and early hospital discharge: a prospective observation study of 200 consecutive patients with community acquired pneumonia. Arch Intern Med 1999;159:2449-54.

110. Milkovich G. IV to oral transition therapy in Community-Acquired Pneumonia: The INOVA Health System Experience. Pharmacotherapy 2001;21(7s):83-8.

111. Ramirez JA. Managing antiinfective therapy of community-acquired pneumonia in the hospital setting: focus on switch therapy. Pharmacotherapy 2001;21(7s):79-82.

112. Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. Arch Intern Med 2002; 162:1278-84.

113. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired Streptococcus pneumoniae pneumonia. Arch Intern Med 2001;161(6):848-50.

114. Finch R, Schurmann D, Collins O, et al. Randomized controlled trial of sequential IV and oral moxifloxacin compared with sequential IV and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. Antimicrob Agents Chemother 2002;46(6):1746-54.

115. Lode H, Grossman C, Choudhri S, et al. Sequential IV/PO moxifloxacin treatment of patients with severe community-acquired pneumonia. Respir Med 2003;97(10):1134-42.

116. Halm EA, Switzer G, Mittman B, Walsh M, Chang C, Fine M. What factors influence physicians' decisions to switch from IV to oral antibiotics for community-acquired pneumonia? J Gen Intern Med 2001:16:599-605.

117. Cockburn J, Gibberd RW, Reid AL, Sanson RW. Determinants of non-compliance with short-term antibiotic regimens. Br Med J 1987;295:814-18.

118. Oosterheert JJ, Bonten MJ, Schneider MM, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicenter randomized trial. BMJ 2006;333:1193.

119. Arancibia F, Ewig S, Martinez JA, et al. Antimicrobial treatment failures in patients with community-acquired pneumonia. Am J Respir Crit Care Med 2000; 162:154–60.

120. Bernas GA, Galvez BB. Community-acquired pneumonia: etiology, clinical profile and outcome. Phil J of Chest Dis 1997;5(1):31-9.

121. Finch RG, Woodhead MA. Practical considerations and guidelines for the management of community-acquired pneumonia. Drugs 1998;55(1):31-45.

122. Roson B, Carratala J, Fernandez-Sabe N, Tubau F, Manresa F, Gudiol F. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 2004;164:502–8.

123. Menendez R, Torres A, Zalacain R, et al. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. Thorax 2004; 59:960–5.

124. Genne D, et al. Analysis of factors associated with early failure in hospitalized patients with community-acquired pneumonia. European Journal of Microbiology and Infectious Diseases 2006;25:159-66.

125. Siegel R, Halpern N, Almenoff P, Lee A, Cashin R, Greene J. A prospective randomized study of inpatient IV antibiotics for community-acquired pneumonia: The optimal duration of therapy Chest 1996;110(4): 965-71.

126. Siegel R, Alicea M, Lee A, Blaiklock R. Community-acquired pneumonia: Determination of the optimal duration of therapy. Chest 1997;112(3) Suppl 3 5S-6S.

127. Siegel RE, Alicea M, Lee A, Blaiklock R. Comparison of 7 versus 10 days of antibiotic therapy for hospitalized patients with uncomplicated community-acquired pneumonia: a prospective, randomized, double blind study. Am J Ther 1999;6(4):217-22.

128. Myburgh J, Nagel GL, Perschel E. The efficacy and tolerance of a 3-day course of azithromycin in the treatment of community-acquired pneumonia. J Antimicrob Chemother 1993;31(Suppl E):163-70.

129. Zachariah J. A randomized, comparative study to evaluate the efficacy and tolerability of a 3 day course of azithromycin versus a 10 day course of co-amoxiclav as treatment for adult patients with lower respiratory tract infections. J Antimicrob Chemother 1996;37 Suppl C;103-13.

130. Rizzato G, Montemurro L, Fraioli P, et al. Efficacy of a 3-day course of azithromycin in moderately severe community-acquired pneumonia. Eur Respir J 1995; 8(3): 398-402.

131. O'Doherty B, Muller O. Randomized, multicenter study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of adults with mild to moderate CAP. Eur J Clin Microbiol Infect Dis 1998; 17:828-33.

132. Mandell L, File T. Short-Course Treatment of Community-Acquired Pneumonia. Clin Infect Dis 2003; 37:761-3.

133. File TM. Clinical efficacy of newer agents in short-duration therapy for community-acquired pneumonia. Clin Infect Dis 2004; 39(Suppl 3): S159-64.

134. El Moussaoui R, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: a randomized double blind study. BMJ 2006; 332: 1355.

135. Plouffe JF, et al. Azithromycin in the treatment of Legionella pneumonia requiring hospitalization. Clin Infect Dis 2003; 37:1475-80.

PART SIX: 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 mainstays of CAP prevention are pneumococcal and influenza vaccinations. Pneumococcus is the most common cause of bacterial CAP. Influenza predisposes individuals to bacterial CAP. During influenza outbreaks, pneumococcal vaccines may be useful in preventing secondary pneumococcal infections and reducing illness and death.[1] 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.[2]

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.[3-7]

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 United States.[3] In the Philippines, surveillance data of invasive isolates of *Streptococcus pneumoniae* among children with bacteremia/meningitis showed that 92% were vaccine types.[8]

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended for the high-risk groups[1] 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.[9] All persons who have existing indications for PPSV23 should continue to be vaccinated according to these current recommendations during the outbreak of novel influenza A(H1N1).[1]

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 expectancies in the country are lower. According to 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 Adult Filipinos," vaccination of PPSV23 is recommended for persons >50 years old.

PPSV23 is administered intramuscularly or subcutaneously as a single 0.5 mL dose. Routine revaccination of immunocompetent persons previously vaccinated with PPSV23 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 has been misinterpreted as suggesting revaccination every 5 years.[10]

Revaccination may be given to the following groups: (1) persons >65 years who received their first dose more than 5 years ago and before they reached age 65; (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) persons who received solid organ or bone marrow transplant.[5]

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-Barré Syndrome) have been associated with the administration of pneumococcal vaccine.[3]

There is no evidence that PPSV is harmful to either a pregnant woman or her fetus. Howver, as a precaution, women with conditions that put them at risk for pneumococcal disease should be vaccinated before becoming pregnant, if possible.[11]

Table 16. Recommendations for pneumococcal vaccination

Indications

- Persons aged >60 years of age
- Persons with chronic illnesses: chronic pulmonary diseases (chronic obstructive pulmonary disease, bronchiectasis, chronic pulmonary tuberculosis), cardiovascular (including congestive heart failure and cardiomyopathies), diabetes mellitus, chronic alcoholism, chronic liver disease, chronic renal failure or nephrotic syndrome, cerebrospinal fluid leaks, functional or anatomic asplenia
- Immunocompromised persons: HIV/AIDS, lymphoma, leukemia, multiple myeloma, generalized malignancy; those receiving immunosuppressive chemotherapy or corticosteroids, solid organ or bone marrow transplant
- Residents of nursing homes and other long-term care facilities
- Smokers or asthmatic persons aged 19 to 64 years

Adult Dose

- Single 0.5 ml dose given intramuscularly or subcutaneously

One-time revaccination may be given to the following[4] groups:

- Persons >65 years of age who received their first dose more than 5 years ago and before they reached age 65
- Persons <64 years of age who received the vaccine more than 5 years ago and who have the following: asplenia, HIV, leukemia, lymphoma, generalized malignancy, multiple myeloma, chronic renal failure or nephritic syndrome
- Persons receiving immunosuppressive therapy including corticosteroids
- Persons who received solid organ or bone marrow transplant

Precautions / Contraindications

- Immediate anaphylactic reaction to a previous dose of pneumococcal vaccine
- Allergy to a vaccine component : anaphylaxis to phenol or thimerosal
- Moderate to severe illness with or without a fever

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.[12,13] 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 for 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.[14] Vaccines prepared for a previous influenza season should not be administered to provide protection for any subsequent season.[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 humans 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 the 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 the WHO in February each year. For vaccines being made for the Southern Hemisphere, the recommendation is made by the WHO in September.

Each country then can use the recommendations made by the WHO to assist with national decisions about which viruses to use in influenza vaccines for their country.[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 the 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.[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.[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.[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 be given once a year 2 to 3 months before the start of the influenza season (preferably from February to June).[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 group 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.[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.[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.[18,19]

The previous 1976 swine influenza vaccine was associated with increased frequency of Guillain-Barré Syndrome. Evidence for a causal relation of Guillain-Barré Syndrome with subsequent vaccines prepared from other influenza viruses is unclear. The likelihood of coincidentally experiencing Guillain-Barré Syndrome after influenza vaccination is expected to be greater among persons with a history of Guillain-Barré Syndrome than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of Guillain-Barré 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-Barré Syndrome 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

Table 17. Recommendations for influenza vaccination

Indications
• All persons aged ≥50 yrs • Chronic Illness: chronic pulmonary (including asthma), chronic cardiovascular (except hypertension), renal, hepatic, neurological / neuromuscular, hematological or metabolic disorders (including diabetes mellitus) • Immunosuppression: HIV, malignancies, immunosuppressive drug, radiation therapy, organ or bone marrow transplantation • Pregnancy in the 2nd or 3rd trimester • Residents of nursing homes and other chronic care facilities • Health care personnel • Household contacts (including children) and caregivers of children aged <5 years and adults aged ≥50 years • Household contacts (including children) and caregivers of persons with medical conditions that put them at high risk for severe complications from influenza
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-Barré Syndrome

contraindication for use of either pneumococcal or influenza vaccine immediately after an episode of pneumonia.

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 bacteremic 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 (PPV) 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, 7,390 (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 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.[3] 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.[30]

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.[33] 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 suggesst that cigarette smoking is the major avoidable risk factor for acute pneumonia in adults.[34] 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.[36] 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.[37] 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/h1n1flou/guidance/ppsv_h1n1.htm

2. Mandell L. Wunderrink R., Anzueto A., et al. Infectious Diseases Society of America/ American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44: S27-72.

3. Centers for Disease Control and Prevention. Prevention of Pneumococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997;47 (No.RR-8).

4. Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR (ACIP), 2009. MMWR July 31, 2009; 58 (No. RR-8):1-52.

5. Philippine Society for Microbiology and Infectious Diseases and Philippine Foundation of Vaccination. Handbook on Adult Immunization for Filipinos. 2009

6. Council on Pulmonary Infections, Philippine College of Chest Physicians. Recommendations for Adult Vaccination Against Pulmonary Infections. 2003

7. Department of Health Technical Working Group for Influenza Prevention & Management. Guidelines on Prevention and Management of Influenza. DOH Administrative Order No. s. 2003

8. Capeding MRZ, Sombrero LT, Lucero MG, Saniel MC. Serotype distribution and antimicrobial resistance of invasive Streptococcus pneumoniae isolates in Filipino children. Jour Infect Dis 1994; 169:479-480.

9. ACIP Provisional Recommendations for Use of Pneumococcal Vaccines. www.cdc.gov/vaccines/recs/provisional/downloads/pneumo-oct-2008-508.pdf

10. Centers for Disease Control and Prevention..PneumococcalDisease. www.cdc.gov/travel/yellowBookCh4-Strep.aspx

11. Pneumococcal Polysaccharide Vaccine: What you need to know. www.cdc.gov/vaccines/pubs/vis/downloads/vis-ppv.pdf

12. Gross PA, Hermogenes AW, Sacks H, Lau J, Levandowski R. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of literature. Ann Intern Med 1995;123 (7):518-27.

13. Mullooly JP, Bennett MD, Hombrook MC, et al. Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintainance organization. Ann Intern Med 1994;121:947-52

14. Centers for Disease Control and Prevention. Questions and Answers: Selecting the Viruses in the Influenza (Flu) Vaccine. www.cdc.gov/flu/professionals/vaccination/virusqa.htm

15. Centers for Disease Control and Prevention. Use of Influenza A(H1N1) 2009 Monovalent Vaccine. Recommendations of thee Advisory Committee in Immunization Practices (ACIP), 2009. MMWR August 28, 2009 / 58(RR10);1-8.

16. Recommended composition of influenza virus vaccines for use in the southern hemisphere in the 2010 influenza season. www.who.int/entity/csr/disease/influenza/200909. RecommendationFAQ.pdf.

17. Chan V. Epidemiological Data on Influenza in the Philippines. First International Symposium on Adult Immunization in Asia: Prevention of Influenza and Pneumococcal Infections. Hanoi, Socialist Republic of Vietnam 1998 April 20, 22; 35-7.

18. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. Efficacy of influenza vaccination in elderly individuals: a randomized double-blind placebo-controlled trial. JAMA 1994;272:1661-5

19. Margolis KL, Nichol KL, Poland GA, Pluhar RF. Frequency of adverse reactions to influenza vaccine in the elderly: a randomized controlled trial. JAMA 1990;264:1139-41

20. Butler JC, Shapiro ED, Carlone GM. Pneumococcal Vaccines: History, current status and future directions. Am J Med. 1999; 107 (1A): 69S-76S.

21. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. NEJM 1991; 325:1453-1460.

22. Forrester BL, Jahnigan DW, LaForce FM. Inefficacy of pneumococcal vaccine in a high-risk population. Am J Med. 1987;83:425-430.

23. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. NEJM 2003; 348(18): 1747-1755.

24. Fisman DN, Abrutyn E, Spaude KA, et al. Prior Pneumococcal Vaccination Is Associated with Reduced Death, Complications, and Length of Stay among Hospitalized Adults with Community-Acquired Pneumonia. Clin Infect Dis 2006; 42:1093-101.

25. Johnstone J, Marrie TJ, Eurich DT, et al. Effect of Pneumococcal Vaccination in Hospitalized Adults With Community-Acquired Pneumonia. Arch Intern Med 2007;167(18):1938-1943.

26. Nichol KL, Baken L, Wuorenma J, Nelson A. The Health and Economic Benefits Associated With Pneumococcal Vaccination of Elderly Persons With Chronic Lung Disease. Arch Intern Med. 1999;159:2437-2442.

27. Moberley SA, Holden J, Tatham DP, Andrews RM, Vaccines for preventing pneumococcal infection in adults. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No: CD000422. DOI:10.1002/14651858.CD000422.pub2.

28. Wilde JA, Mcmillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC.. Effectiveness of vaccination against influenza in health care professionals. JAMA 1999;281(10):908-13.

29. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost benefit of influenza vaccination in healthy working adults: a randomized controlled trial. JAMA 2000;284:1655-63.

30. Ahmed F, Singleton JA, Franks AL. Influenza vaccination for healthy young adults. NEJM 2001; 345:1543-1547.

31. Jefferson TO, Rivetti D, Di Pierrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Review 2007, Issue 2. Art. No.:CD001269.DOI:10.1002/14651858. CD001269.pub3.

32. Herrera G. et al. Influenza vaccine effectiveness among 50-64 year-old persons during a season of poor antigenic match between vaccine and circulating influenza virus strains : Colorado, United States, 2003-2004. VACCINE, Vol 25, Issue 1, January 2, 2007, pages 154-160.

33. Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in the elderly. Cochrane Database of Systematic Review 2006, Issue 3. Art. No.; CD004876.DOI: 10.1002/14651858. CD004876. pub2.

34. Farr BM, Bartlett CI, Wadsworth J, Miller DL. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. British Thoracic Society Pneumonia Study Group. Respir Med. 2000 Oct;94 (10) : 954-63.

35. Nuorti JP, Butler JC, Farley MM, et al. and The Active Bacterial Core Surveillance Team. Cigarette Smoking and IPD. N Engl J Med 2000;342:681-9.

36. Baik I, Curhan GC, Rimm EB, et al. A Prospective Study of Age and Lifestyle Factors in Relation to Community-acquired Pneumonia in US Men and Women. Arch Intern Med 2000;160:3082-3088.

37. Almirall J, Bolibar I, Serra-Prat M, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. Eur Respir J 2008; 31: 1274-1284

APPENDICES

Appendix 1. Grading system for the strength of the recommendations and quality of evidence

Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation for or against use
Quality of evidence	
Level I	Evidence from ≥1 properly randomized trial
Level II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees

REFERENCE

Kish MA. Guide to development of practice guidelines. Clin Infect Dis 2001; 32:851–4.

Appendix 2. Modified Winthrop-University Hospital infectious disease division's point system for diagnosing Legionnaire's disease in Adults

Presentation	Clinical Features[a]	Point Score
Headache	Acute onset	+1
Mental confusion/encephalopathic	Not drug-induced	+4
Lethargy	Acute onset	+3
Ear pain	Acute onset	-3
Nonexudative pharyngitis/sore throat	Acute onset	-3
Hoarseness	Acute onset	-3
Sputum	Purulent	-2
Hemoptysis	Mild/Moderate	-3
Chest pain	Pleuritic	-2
Loose stools/watery diarrhea	Not drug-induced	+4
Abdominal pain	With/Without diarrhea	+5
Relative bradycardia[b]	Temperature > 102°F	+5
Lack of response to β-lactams	After 72 hours	+5
Renal insufficiency	Otherwise unexplained	+3
Myocarditis	Otherwise unexplained	-5
Splenomegaly	Otherwise unexplained	-5
Laboratory test results		
↑ PO2 with A-a gradient (>30)	Otherwise unexplained	-5
Hyponatremia	Otherwise unexplained	+1
Hypophosohatemia	Otherwise unexplained	+5
↑ ALT/AST (SGOT/SGPT) (mild/transient)	Otherwise unexplained	+3
↑ Ferritin (>2 x normal)	Otherwise unexplained	+5
↑ Total bilirubin	Otherwise unexplained	+1
↑ CPK / Aldolase	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
[a] Acute onset associated with pneumonia and otherwise unexplained
[b] If not on β blockers, diltiazem, verapamil; no arrhythmias or pacemaker rhythms

Refrences

1. Cunha, Burke A. Severe Legionella pneumonia: rapid presumptive diagnosis with Winnthrop-University hospital's weighted point score system (modified). Heart Lung 2008; 37: 311-320.
2. Cunha BA, editor. Pneumonia essentials. 2nd ed. Royal Oak Michigan: Physicians Press; 2008.