Philippine Clinical Practice Guidelines

Community-Acquired Pneumonia Clinical Practice Guidelines

Diagnosis, Empiric Management and Prevention of Community-Acquired Pneumonia in Immunocompetent Adults

2016 Update

Treatment

Joint Statement of
PSMID • PCCP • PAFP • PCR

COMMUNITY-ACQUIRED PNEUMONIA

INTRODUCTION

Internationally, community-acquired pneumonia (CAP) remains the leading cause of death from an infectious disease. It is the sixth leading cause of death overall and is a major cause of morbidity and mortality. Since the last publication of Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia (CAP) in Immunocompetent Adults in 2010, several changes had emerged:

- Multiple international societies had published and revised their guidelines of the management of patients with CAP.
- New organisms had emerged and development of resistance had increased over time among respiratory pathogens.
- The influx and efflux of antimicrobial agents used in the treatment had likewise posed a threat to the rapid rise of antimicrobial resistance. The use, misuse, abuse and overuse had also shaken the market of antimicrobial agents.

It is for these reasons that a long overdue update on the management of CAP is needed. There is a need to standardize care by providing management strategies based on best available evidences. The evidences may be the same; however, regional differences, causative agents, antibiotic resistance rates, drug licensing, healthcare structure and available resources may vary. Recommendations made by one national organization may therefore not be applicable to other countries

TREATMENT

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

- Patients should receive initial therapy as soon as possible after the diagnosis is established.

Antibiotics, the mainstay for the treatment of pneumonia, should be initiated as soon as a diagnosis of CAP is made. The 2004 PCPG for CAP recommended a maximum four-hour window

from diagnosis to antimicrobial initiation. This recommendation was based on studies that 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, however, found an internal inconsistency in outcomes between the group that received antibiotics within the first two hours and the group which received antibiotics two to four hours after diagnosis. Although therapy within 4 hours of arrival to the hospital has been associated with reduced mortalities in some studies, undue emphasis on early therapy could lead to unnecessary use of antibiotics and associated complications. For these reasons, the present guideline maintains its position to not recommend a specific time interval between diagnosis and antibiotic administration for patients.

Reference:

1. *Bordon J, et al. Early administration of the first antimicrobials should be considered a marker of optimal care of patients with community-acquired pneumonia rather than a predictor of outcomes. International Journal of Infectious Diseases 17 (2013) e293–e298.*

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4. *Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia (CAP) in Immunocompetent Adults : 2004 Update.*

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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. Use of extended macrolides may also be considered

- For low-risk CAP with stable comorbid illness, β-lactam with β-lactamase inhibitor combinations (BLIC) or second generation cephalosporins 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.

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

- 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 an IV respiratory fluoroquinolone is recommended as an initial antimicrobial treatment.

- 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 OR a combination of an IV antipneumococcal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) and an IV ciprofloxacin or high dose IV levofloxacin.

TABLE 1. EMPIRIC ANTIMICROBIAL THERAPY FOR CAP WITH USUAL RECOMMENDED DOSAGES IN 50-60 KG ADULTS WITH NORMAL LIVER AND RENAL FUNCTIONS

RISK STRATIFICATION	POTENTENTIAL PATHOGEN	EMPIRIC THERAPY
Low-risk CAP Stable Vital signs RR<30/minute PR<125/min SBP> 90 mm Hg DBP > 60 mm Hg Temp >36ºC or <40ºC No altered mental state of acute onset No suspected aspiration No or stable c o-morbid conditions Chest X ray – localized infiltrates - No evidence of pleural effusion	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* Enteric Gram-negative bacilli (among those with co-morbid illness)	**Without co-morbid illness** Amoxicillin 1 gm TID OR Extended macrolides[a]: Azithromycin 500 mg OD OR Clarithromycin 500 mg BID **With stable co-morbid illness** β-lactam/β-lactamase inhibitor combination (BLIC)[b] OR 2nd gen oral cephalosporin[c] +/- extended macrolides[a] Co-amoxiclav 1 gm BID OR Sultamicillin 750 mg BID OR Cefuroxime axetil 500 mg BID +/- Azithromycin 500 mg OD OR Clarithromycin 500 mg BID
Moderate-risk CAP Unstable Vital Signs: RR ≥ 30/min PR ≥ 125/min Temp ≤ 36ºC or ≥ 40ºC SBP<90 mmHg DBP ≤60 mmHg Altered mental state of acute onset Suspected aspiration Unstable/Decompensated comorbid condition -uncontrolled diabetes mellitus, -active malignancies -neurologic disease in evolution, -congestive heart failure (CHF) Class II-IV -unstable coronary artery disease	*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[d] (BLIC, cephalosporin) + extended macrolides[a] or respiratory fluoroquinolones[e] (PO) Ampicillin-Sulbactam 1.5 gm q6h IV OR Cefuroxime 1.5 g q8h IV OR Ceftriaxone 2 g OD + Azithromycin 500 mg OD PO OR Clarithromycin 500 mg BID PO OR Levofloxacin 500 mg OD PO OR Moxifloxacin 400 mg OD PO

-renal failure on dialysis -uncompensated COPD -decompensated liver disease		If aspiration pneumonia is suspected and, a regimen containing ampicillin-sulbactam and/or moxifloxacin is used, there is no need to add another antibiotic for additional anaerobic coverage. If another combination is used may add clindamycin to the regimen to cover microaerophilic streptococci. Clindamycin 600 mg q8h IV OR Ampicillin-Sulbactam 3 g q6h IV OR Moxifloxacin 400 mg OD PO
High-risk CAP Any of the clinical feature of Moderate risk CAP plus any of the following: Severe Sepsis and Septic Shock OR Need for Mechanical Ventilation	*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[d] + IV extended macrolides[a] or IV respiratory fluoroquinolones[c] Ceftriaxone 2 gm OD OR Ertapenem 1 gm OD + Azithromycin dihydrate 500 mg OD IV OR Levofloxacin 500 mg OD IV OR Moxifloxacin 400 mg OD IV ***Risk for P. aeruginosa*** IV antipneumococcal antipseudomonal β-lactam[f] (BLIC, cephalosporin or carbapenem) + IV extended macrolides[a] + aminoglycoside[g] Piperacillin-tazobactam 4.5 gm q6h OR Cefepime 2 gm q8-12h OR Meropenem 1 gm q8h + Azithromycin dihydrate 500 mg OD IV + Gentamicin 3 mg/kg OD OR Amikacin 15 mg/kg OD OR

		IV antipneumococcal antipseudomonal β-lactamf (BLIC, cephalosporin or carbapenem) + IV ciprofloxacin / high dose levofloxacin Piperacillin-tazobactam 4.5 gm q6h OR Cefepime 2 gms q8-12h OR Meropenem 1 gm q8h + Levofloxacin 750 mg OD IV OR Ciprofloxacin 400 mg q8-12h IV **If MRSA pneumonia is suspected, add** Vancomycin 15 mg/kg q8-12 h OR Linezolid 600 mg q12h IV OR Clindamycin 600 mg q8h IV

a Extended macrolides: azithromycin, clarithromycin
b Oral β-lactam/β-lactamase inhibitor combination (BLIC) – amoxicillin-clavulanic acid, sultamicillin
c. Oral second-generation cephalosporin: cefuroxime axetil
d. IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem): ampicillin-sulbactam, cefuroxime Na, ceftriaxone, ertapenem
e. Respiratory fluoroquinolones: levofloxacin, moxifloxacin
f. IV antipneumococcal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem): piperacillin-tazobactam, cefepime, imipenem-cilastatin, meropenem
g. Aminoglycosides: gentamicin, amikacin

References:

Low Risk CAP:

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Moderate Risk CAP:

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2. *Eliakim-Raz N et al. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults (Review) Cochrane Database Syst Rev 2012, Issue 9:CD004418. doi: 10: 1002/14651858. CD004418.pub4*

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<u>High Risk CAP</u>:

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2. *Adamantia L et al. Managing CAP in the ICU. Curr Infect Dis Rep. 2015 Nov;17(11):48.*

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Key Points to Remember

For Low Risk CAP

- The advantage of using some extended macrolides over *amoxicillin* on *Streptococcus pneumoniae* is the once-a-day dosaging of azalide. The 2014 reports 4.3% erythromycin resistance for *Streptococcus pneumoniae.*
- If the patient has history of allergy to β-lactam drugs (eg. amoxicillin), may opt to use an extended macrolide.
- The increase in the dosage recommendation of amoxicillin was based on the 2014 ARSP report that shows consistent level of resistance of *Streptococcus pneumoniae* to penicillin whether using meningeal breakpoints 10.3%.
- US Food and Drug Administration (FDA) warned the public that azithromycin can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias.

- Azithromycin use has been associated with increased risk of death among patients at high baseline risk, but not for younger and middle-aged adults

- Fluoroquinolone labels need much stronger warnings about the risks for serious adverse events, including tendinitis and tendon rupture, prolongation of the QT interval, and peripheral neuropathy, according to a joint panel of the US FDA Food and Drug Administration (FDA). Fluoroquinolone labeling currently has warnings about the risks for tendonitis, tendon rupture, central nervous system effects, peripheral neuropathy, myasthenia gravis exacerbation, QT prolongation and Torsades de Pointes, phototoxicity, and hypersensitivity.

- NON-USE OF FLUOROQUINOLONES (FQ) AS 1ST LINE THERAPY IN CAP. FQ is not recommended as first line treatment option for low risk CAP. It is recommended that they be reserved as potential second line agents for the treatment of pulmonary tuberculosis, particularly for multi-drug resistant tuberculosis.

- Ampicillin can be given orally or parenterally. Amoxicillin is preferable to ampicillin in the oral treatment of infection because of its improved oral bioavailability and less frequent dosage frequency. The activity of co-amoxiclav and ampicillin-sulbactam is dependent on its parent β-lactam. The incidence of diarrhea with amoxicillin is less than that of ampicillin, because of more complete absorption, however effective concentrations of orally administered amoxicillin are detectable in the plasma for twice as long as with ampicillin.

- In the event that β-lactam/β-lactamase inhibitor combination (BLIC) OR 2nd gen oral cephalosporin +/- extended macrolides were used and patient is nonresponsive, REASSESS the patient

- Use of oral third generation cephalosporin is recommended ONLY as step down drug from an IV third generation cephalosporin (e.g. IV ceftriaxone → cefpodoxime). Cefpodoxime is preferred over cefixime based on lower MIC against Pen-susceptible *Streptococcus pneumoniae*.

For Moderate-High Risk CAP

- The addition of sulbactam increases the bioavailability of oral ampicillin when the two drugs are administered in the form of the prodrug sultamicillin. Also, sulbactam does not interfere with the kinetics of intravenous ampicillin but increases the absorption of oral ampicillin. Water for injection is the normal solvent. Parenteral amoxicillin-clavulavic acid should be dissolved in 20 ml of solvent. This yields approximately 20.9 ml of solution for single-dose use. A transient pink coloration may or may not develop during reconstitution and the reconstituted solutions are normally colorless to yellow in color. It should be administered within 20 min of reconstitution.

- Reserve the use of carbapenems for risk of potentially resistant strains (e.g. ESBL producing enterobacteriaciae) - such as prior use of 3rd gen cephalosporins and fluoroquinolones.

- For non-PNDF (non-Philippine National Drug Formulary) based institutions, carbapenem choices include meropenem or imipenem.

- For hospitalized patients with severe CAP defined by any one of the following: (1) a requirement for intensive care unit (ICU) admission, (2) necrotizing or cavitary infiltrates, or (3) empyema, empirical therapy for MRSA is recommended pending sputum and/or blood culture results. If culture isolates revealed absence of MRSA, may discontinue the anti-MRSA therapy.

- In patients with active influenza or with history of influenza infection within 2 weeks of development of CAP, add Vancomycin 15 mg/kg q8-12h OR Linezolid 600 mg q12h IV to the CAP regimen.

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5. *Hampel B et al. Comparative pharmacokinetics of sulbactam/ampicillin and clavulanic acid/amoxicillin in Human volunteers. Drugs (suppl. 7) 1988; 35:29-33.*

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How can response to initial therapy be assessed?

- Temperature, respiratory rate, heart rate, blood pressure, sensorium, oxygen saturation and inspired oxygen concentration should be monitored to assess response to therapy.

- Response to therapy is expected within 24-72 hours of initiating treatment. Failure to improve after 72 hours of treatment is an indication to repeat the chest radiograph.

- Follow-up cultures of blood and sputum are not indicated for patients who are responding to treatment.

References

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3. *Blasi F et al. Early versus later response to treatment in patients with community-acquired pneumonia: analysis of the REACH study. Respiratory Research 2014, 15(6): 1-10.*

4. *Ramirez JA. Clinical stability and switch therapy in hospitalised patients with community-acquired pneumonia: are we there yet? Eur Respir J 2013; 41: 5–6.*

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.

TABLE 2. 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

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 3. ANTIBIOTIC DOSAGE OF ORAL AGENTS FOR STREAMLINING OR SWITCH THERAPY

ANTIBIOTIC	DOSAGE
Amoxicillin-clavulanic acid	625 mg TID or 1 gm BID
Azithromycin	500 mg OD
Cefixime	200 mg BID
Cefuroxime axetil	500 mg BID
Cefpodoxime proxetil	200 mgw BID
Levofloxacin	500 - 750mg OD
Moxifloxacin	400 mg OD
Sultamicillin	750 mg BID

Reference:

1. *Ramirez JA. Clinical stability and switch therapy in hospitalised patients with community-acquired pneumonia: are we there yet? Eur Respir J 2013; 41: 5–6*

How long is the duration of treatment for CAP?

- Duration of treatment is 5 to 7 days for low risk uncomplicated bacterial pneumonia. *(Strong recommendation, Moderate to Very Low Quality of Evidence NICE guidelines 2014)*

- Treatment duration for moderate risk bacterial pneumonia is 7-10 days *(Strong recommendation, Low Quality of Evidence, NICE guidelines 2014)*

- 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 28 days if with associated bacteremia.

- 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.

- A 5-day course of oral or IV therapy for low-risk CAP and a 10-day course of IV 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.

- Patients should be afebrile for 48 to 72 hours with no signs of clinical instability before discontinuation of treatment.

TABLE 4. DURATION OF ANTIBIOTIC USE BASED ON ETIOLOGY

ETIOLOGIC AGENT	DURATION OF THERAPY (DAYS)
Most bacterial pneumonias except enteric Gram-negative pathogens *S. aureus (MSSA and MRSA)*, and *P. aeruginos*a	5-7 days 3-5 (azalides) for *S. pneumoniae*
Enteric Gram-negative pathogens, *S. aureus (MSSA and MRSA)*, and *P. aeruginosa*	MSSA community-acquired pneumonia a. non-bacteremic - 7-14 days b. bacteremic - longer up to 21 days MRSA community-acquired pneumonia a. non-bacteremic - 7-21 days b. bacteremic - longer up to 28 days *Pseudomonas aeruginosa* a. non-bacteremic - 14-21 days b. bacteremic - longer up to 28 days
Mycoplasma and *Chlamydophila*	10 - 14 days
Legionella	14-21; 10 (azalides)

Reference:

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9. *Scalera NM, et al. Determining the duration of therapy for patients with community-acquired pneumonia. Curr Infect Dis Rep 2013;15:191-5.*

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What should be done for patients who are not improving after 72 hours of empiric antibiotic therapy?

- The lack of a response to seemingly appropriate treatment in a patient with CAP should lead to a complete reappraisal, rather than simply to selection of alternative antibiotics.

- 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 according to culture result.

- Follow-up chest radiograph is recommended to investigate for other conditions such as pneumothorax, cavitation and extension to previously uninvolved lobes, pleural effusion, pulmonary edema and ARDS. For an underlying mass, bronchiectasis, loculation , pulmonary abscesses, a CT scan would provide more information.

- Obtaining additional specimens for microbiologic testing should be considered.

TABLE 5. REASONS FOR A LACK OF RESPONSE TO TREATMENT OF CAP

Correct organism but inappropriate antibiotic choice or dose
Resistance of organism to selected antibiotic
Wrong dose (e.g., in a patient who is morbidly obese or has fluid overload)
Antibiotics not administered
Correct organism and correct antibiotic but infection is loculated (e.g., most commonly empyema)
Obstruction (e.g., lung cancer, foreign body)
Incorrect identification of causative organism
No identification of causative organism and empirical therapy directed toward wrong organism
Non-infectious cause
Drug-induced fever
Presence of an unrecognized, concurrent infection

References

1. *Musher DM et al . Community-Acquired Pneumonia N Engl J Med 2014;371:1619-28.*

2. *Welte T et al. Managing CAP patients at risk of clinical failure. Respiratory Medicine 2015;109:157-169,*

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 clinically stable and oral therapy is initiated.
- A repeat chest radiograph prior to hospital discharge is not needed in a patient who is clinically improving.
- 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.

Table 6. 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^{o}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

Reference:

1. *Aliberti S et al. Criteria for clinical stability in hospitalized patients with community-acquired pneumonia Eur Respir J 2013; 42: 742–749.*

2. *Robinson S et al. Patient Outcomes on Day 4 of Intravenous Antibiotic Therapy in Non Intensive Care Unit Hospitalized Adults With Community-Acquired Bacterial Pneumonia. Infectious Diseases in Clinical Practice November 2014; 22: 320-325.*

What other information should be explained and discussed with the patient?

Explain to patients with CAP that after starting treatment their symptoms are expected to steadily improve, although the rate of improvement will vary with the severity of the pneumonia. Most people can expect that by:

1 week: fever should have resolved

4 weeks: chest pain and sputum production should have substantially reduced

6 weeks: cough and breathlessness should have substantially reduced

3 months: most symptoms should have resolved but fatigue may still be present

6 months: most people will feel back to normal.

Reference

1. *Aliberti S Peyrani P Filardo G Mirsaeidi M Amir A Blasi F Ramirez JA . Association between time to clinical stability and outcomes after discharge in hospitalized patients with community-acquired pneumonia. Chest* 2011 *Aug 140 (2) 482-8.*

2. *El Moussaoui R et al. Long-term symptom recovery and health-related quality of life in patients with mild-to-moderate-severe community-acquired pneumonia. Chest. 2006; 130(4):1165-1172.*

3. *National Institute for Health and Care Excellence (NICE) Pneumonia - Diagnosis and management of Community and Hospital-acquired Pneumonia in Adults. December 2014.*

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