SPECIAL ARTICLE

# Update to the Latin American Thoracic Society (ALAT) Recommendations on Community-Acquired Pneumonia

ALAT Work Group*

## Introduction

The reasons for updating the Latin American Thoracic Society (ALAT) recommendations on community-acquired pneumonia have been explained in the preamble to the update of the recommendations on infectious exacerbation of chronic obstructive pulmonary disease (COPD). In addition to new information, the present text includes the original recommendations, making it unnecessary to refer to the previous version.

## Definition

Community-acquired pneumonia (CAP) is an infection that compromises the lung parenchyma and is caused by microorganisms acquired while the patient is not in a hospital environment. The severity of this disease is variable; in healthy individuals CAP can be so mild that it may even be confused with a cold, bronchitis, or a nonrespiratory infection; but it can also be a serious and life-threatening illness requiring admission to an intensive care unit.

The epidemiology and treatment of CAP has changed considerably in recent years with the isolation of new pathogens and the emergence of microorganisms that have developed resistance to traditional antimicrobial agents. Thanks to continuous research, new antibiotic agents that are useful in the treatment of CAP have been developed. These developments have made necessary the publication of revised guidelines for managing this very common and potentially serious condition.

An evidence-based approach was used to draw up these recommendations, after a review of all the most relevant studies published. The supporting evidence was classified on 3 levels: level I evidence, based on randomized, controlled clinical trials; level II evidence, based on well-designed controlled trials without randomization (including cohort studies, case series, and case control studies); and level III evidence, based on case reports and/or expert opinion. When the treatment recommendations are based on data concerning susceptibility in the absence of clinical observations, the evidence was classified as level III.

## Diagnosis

The 3 objectives of the complementary methods used to diagnose CAP are as follows: *a)* to ascertain whether and to what degree the lung parenchyma is affected (chest radiograph); *b)* to identify the etiologic agent (microbiological and serological tests), and *c)* to assess the patient's overall condition (standard laboratory workup). The number and type of investigations undertaken will depend on the seriousness of the patient's condition and the limitations of the of treatment setting. While it may sometimes be difficult to obtain a chest radiograph in certain care situations it is, nonetheless, important to stress that at least 1 posteroanterior radiograph should be obtained for the diagnosis of CAP. In addition to making possible a firm diagnosis of pneumonia, chest radiography can reveal the extension of the disease (a prognostic factor) and detect associated complications, such as parapneumonic effusion, abscesses, cavitation, neoplasms, and the presence of chronic lung injury.

Bacteriological examination of sputum includes Gram staining, cultures, and antibiograms. Sputum samples are only useful if they are of good quality. Except in the presence of an inflammatory reaction, samples should not be contaminated by oropharyngeal flora. An inflammatory reaction is indicated in the microscopic study by the presence of very few squamous cells and abundant neutrophils. Fewer than 10 squamous cells and

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more than 25 neutrophils per 10 power field are acceptable limits.[1] The validity of sputum cultures diminishes substantially in patients who have received prior antibiotic treatment.[2] In spite of these limitations, direct examination of sputum can be useful to orient initial treatment (level III evidence). In addition, when other techniques are used, sputum can play a valuable role in the detection of acid-alcohol resistant bacilli, *Legionella pneumophila*, fungi, *Pneumocystis carinii*, and viruses.

Sputum culture can reveal etiology in many cases. However, while a sputum sample is often the most useful specimen for this purpose, culture results are never available when a decision is taken regarding initial treatment. Currently, the practical importance of the sputum culture is due to the fact that it can be used to document the sensitivity of different pathogens to antibiotics (level III evidence).

The sensitivity of blood cultures for the isolation of the pathogen in CAP ranges between 0.5% and 20% depending on the severity of the patient's clinical condition.[3-7] Pleural fluid cultures and blood cultures are useful for confirming etiology because they are highly specific, and because the presence of a pathogen in these specimens is generally considered to constitute definitive proof that the microorganism isolated is the causative agent of the CAP. Blood culture should be performed for all patients coming to the emergency department or hospitalized with suspected infection by a microorganism resistant to standard antibiotics.

Invasive techniques for reaching a bacteriological diagnosis are necessary in some patients. The most commonly used invasive procedures involve bronchoscopy, including bronchoalveolar lavage, protected specimen brush and related techniques, and lung biopsy. Such techniques are only used in immunodepressed and other high-risk patients who have been admitted to an intensive care unit, and in patients who do not respond to conventional treatment and whose condition deteriorates, both clinically and radiographically.

Serological studies are useful for the diagnosis of certain types pneumonia caused by the following pathogens: viruses generally, *Mycoplasma pneumoniae, Chlamydia psittaci, Chlamydia pneumoniae, L pneumophila, Coxiella burnetii, Leptospira interrogans*, fungi, and hantavirus. They are, however, only useful for identifying the cause retrospectively. Detection of the urinary antigen of *Streptococcus pneumoniae* or *L pneumophila* can be very useful for obtaining a quick etiologic diagnosis. Moreover, it is a highly reliable technique. Other methods that are not yet widely used include polymerase chain reaction, which has been approved by the American Food and Drug Administration for the detection of *Mycobacterium tuberculosis*, but not of other respiratory pathogens.[8] Table 1 lists the diagnostic studies recommended for CAP patients according to severity of illness.[9]

The basic laboratory workup should include a complete blood count and tests for urea and glucose. Complementary tests (electrophoresis, liver function) may also be ordered. These laboratory tests are of little value in determining the etiology of a CAP, but they can help determine prognosis, and the results may affect a decision to hospitalize a patient or not. Complementary tests should be performed for patients with risk factors (level II evidence). Blood gases should be analyzed in patients who require intensive care and may also be required for the assessment of some less severely ill inpatients.

TABLE 1
**Diagnostic Approach to Community-Acquired Pneumonia[9]**

*1.* Patients without risk factors
Minimum option: posteroanterior chest radiograph
Maximum option: posteroanterior and lateral chest radiographs, white blood cell and differential counts, and bacteriological examination of sputum

*2.* Patients with risk factors
Minimum option: posteroanterior and lateral chest radiographs, and standard laboratory workup
Maximum option: same as above plus microbiological studies (sputum, blood cultures, pleural fluid)

*3.* Hospitalized patients
Minimum option: lateral and posteroanterior chest radiographs, basic laboratory workup, liver function tests, electrolytes, microbiological studies (sputum, blood cultures, pleural fluid)
Maximum option: the above plus arterial blood gases and serological studies

*4.* Patients in intensive care units
Minimum option: lateral and posteroanterior chest radiographs, basic laboratory workup, liver function tests, electrolytes, arterial blood gases, microbiological studies (sputum, blood cultures, pleural fluid)
Maximum option: the above plus bronchoscopic techniques and serological studies

## Epidemiology

CAP is a common and potentially serious infection associated with significant morbidity. The annual incidence of CAP among adults is between 1.6 and 13.4 cases per 1000 population. The incidence is higher among males and among the very young and old.[7,10-14] Data on incidence is difficult to obtain because different diagnostic criteria are used, and because CAP is not a reportable disease, so that many cases are not reported or recorded.

It is estimated that 258 people per 100 000 in the general population and 962 per 100 000 in the over-65 age group are hospitalized every year in the United States of America due to CAP.[15,16] A review of population studies indicates that the overall rate of hospitalization due to CAP is between 22% and 50%,[7,10,13] and that some 6% of these patients require care in an intensive care unit.[10]

Mortality among patients with CAP is an important

issue. Among outpatients with CAP, mortality is under 1%.[17] In a recent meta-analysis of inpatients with CAP, mortality was 13.7% overall, 17.6% among the elderly, and 19.6% among patients with bacteremic CAP.[18] Among patients requiring intensive care, overall mortality was 36.5%.[18] In Chile, pneumonia is the leading cause of death for a specific diagnosis in the adult population, ahead of acute myocardial infarction and cerebrovascular disease (according to the Chilean Ministry of Health, 1998). In the Chilean population, mortality and hospitalization rates related to CAP are higher among the very young and the elderly; this is similar to the situation reported in other countries. According to a recent prospective study of 463 immunocompetent adult patients hospitalized because of CAP, in-hospital mortality was around 8% overall; 2.6% among patients treated in the general wards, and 17.5% among those needing intensive care.[19] In Brazil, CAP was the fourth leading cause of death in 2000, and was more common among individuals aged under 1 and over 70, as reported by the Ministry of Health for that year.

The variations observed in mortality rates depending on etiology are also an important factor. Mortality varies between a maximum of 61%, in cases of CAP caused by *Pseudomonas*, and a minimum of 35% in cases caused by enteric bacteria, *Staphylococcus aureus*, and infections of mixed etiology. The mortality rate is under 15% for CAP caused by *L pneumophila* and *S pneumoniae* and under 10% in cases attributed to viruses and atypical pathogens.[18] These mortality rates make CAP the fifth leading cause of death in industrialized countries, after cardiovascular, neoplastic, and cerebrovascular disease, and COPD.[16]

CAP is also an important cause of morbidity because it gives rise to persistent symptoms and leads to absenteeism in the workplace. In a recent population study, although symptoms disappeared a mean 5.4 days after diagnosis, the mean time that elapsed before return to normal activity was 23 days. Radiographic resolution occurred within 30 days in nearly 90% of patients.[14] However, among comorbid patients and the elderly, symptoms attributable to the respiratory infection often persist for up to 1 to 2 months after the episode (level II evidence).

In light of the high frequency of CAP and the clinical and social repercussions of the disease, the creation and publication of guidelines aimed at improving the care of affected patients is fully justified.

## Microbiology of CAP

In considering the etiology of CAP, we must take into account the limitations of the diagnostic tests. Test shortcomings are evident in most studies, which report that the etiology is unknown in between 30% and 50% of patients. There is evidence that in most cases in which the etiologic agent is not identified, the causative pathogen is *S pneumoniae* (level II evidence).[20,21]

Most of the guidelines for the diagnosis and management of CAP published in recent years have been based on 4 factors that can influence the etiology of the disease: the need for hospitalization, the severity of the illness, the patient's age, and comorbidity.

### *CAP in Outpatients*

Most CAP patients can be treated as outpatients. Relatively few studies have focused on the etiology of CAP in them, however. In some studies,[22,23] only serological techniques were used, while in others,[8,24] the diagnosis of CAP was, in most cases, based on clinical criteria without radiographic confirmation. Finally, in other studies, the percentage of cases in which the etiology was unknown was as high as 74%.[25] Without losing sight of these limitations, we may conclude that pneumococcus accounts for between 7% and 36% of cases, *Haemophilus influenzae* for 8% to 12%, *S aureus* for around 1%, and *M pneumoniae* for between 0.5% and 37%. The remaining cases are pneumonias of undetermined origin (level II evidence). The incidence of *M pneumoniae* varies according to epidemic waves, which, at least in northern Europe, occur every 3 to 4 years; only sporadic cases are found outside of these epidemics.[26] Moreover, pneumonia caused by *Mycoplasma* is more common in younger people, and will therefore vary in frequency depending on the demographic characteristics of the series.

### *CAP in Patients Treated in a Hospital Setting*

Patients with CAP who must be hospitalized account for between 20% to 50% of cases.[7,14] Various prospective studies in the literature reveal *S pneumoniae* to be the causative pathogen in 30% to 40% of cases. *H influenzae* is also frequently involved (10%-12%). Other causative pathogens, such as Gram negative bacilli, *S aureus*, and respiratory viruses, are less common (level II evidence).[6,7,27-33]

The proportion of patients infected by more than one pathogen at a time (generally a combination of classical bacteria with "atypical" bacteria and viruses) varies from one study to another. This percentage ranges from under 10% in some studies to nearly 40% in others.[34] This finding highlights the need to prescribe broad-spectrum empirical treatment for hospitalized patients with CAP (level III evidence).

### *Severe CAP*

Intensive care is required by about 2% of patients with CAP, who may represent up to 10% of patients admitted to intensive care units. In general, the etiology of these severe cases of pneumonia is similar to that of the more moderate cases. *S pneumoniae* is still the most common causative pathogen (10%-36%). However, the number of cases attributed to *H influenzae* is greater in this group, making it the second leading cause in some recent studies.[35,36] Gram negative bacilli are associated with

CAP only in patients with chronic underlying diseases, such as COPD. *Pseudomonas aeruginosa* is found in patients with structural abnormalities of the lung (level III evidence).[3]

The frequency of pneumonias caused by the so called "atypical" organisms varies considerably from one study to another. Rates vary from 4%[36] to 14%,[3] mainly due to the involvement of *L pneumophila*. Only *S pneumoniae* (15%) has been found to be more common than *L pneumophila* as a causative agent, with *M pneumoniae* (6%) as the third leading cause. In more recent studies, *S pneumoniae* has continued to be the most frequent cause of severe CAP (24%), while *L pneumophila* was only responsible for 2% of cases.[37] One possible explanation for this finding, which has also been reported by other authors,[38,39] could be that the increased use of macrolides has very probably reduced the number of serious cases of CAP caused by *L pneumophila* (level III evidence). CAP caused by *L pneumophila* is not common in Latin America, and its incidence is undetermined, although in general, it is found only sporadically.[40] In a recent study carried out in Argentina, this pathogen was found in only 3 out of 92 CAP patients (3.3%). Two of these patients had become infected in Spain, and this leads us to suspect this pathogen in pneumonias in people who have travelled.[41] In Chile, Cabello et al[42] recently described serious pneumonia caused by *L pneumophila* in 8 patients, 2 of whom had recently been abroad. Approximately 5% of the adult population in Chile has serum antibodies against *L pneumophila*.[43] Finally, severe viral pneumonias are generally rare.

### *CAP Among the Elderly*

Analysis of the pathogens that cause CAP in elderly patients is essential for the selection of suitable empirical treatment, especially in light of the fact that over 90% of deaths from CAP occur in this population.[44] However, the increase in CAP-related morbidity and mortality among the elderly appears to be due not to age itself but rather to the interaction of diverse immunological and nutritional factors and chronic concomitant diseases.[15,44-46]

In an analysis of 11 studies involving patients over 65 with CAP, *S pneumoniae* was once again found to be the leading causative agent.[44] This pathogen is generally considered to be responsible for 40% to 60% of cases among elderly patients. Moreover, the number of bacteremias is greater (15%-25%) in these patients. *H influenzae*, Gram negative bacilli, respiratory viruses, and *S aureus* are all more common among the elderly than in younger individuals. On the other hand, a lower percentage of cases of CAP among the elderly are caused by *M pneumoniae* and other "atypical" pathogens (level II evidence). In a recent study of CAP in patients over 60, no particular etiological agent was predominant[47]; on the other hand, "atypical" pathogens, and in particular *M pneumoniae*, were found to predominate among younger patients.

Some studies have indicated that cases of CAP in elderly patients living in nursing homes have special microbiological characteristics, to the point that such cases could be considered comparable to nosocomial pneumonias. Sputum culture was the diagnostic method used in almost all studies in the literature, and the etiology was recorded as unknown in the majority of cases.[45] Most of the pathogens isolated are common microorganisms (*S pneumoniae*, *H influenzae*, *S aureus*); the frequency of Gram negative bacilli and "atypical" pathogens was low.

### *CAP Associated With Comorbidity*

The most common concurrent diseases found in CAP patients are cardiovascular and chronic neurological diseases and COPD.[19] However, because the airway is often colonized by significant bacterial isolates in COPD patients, it is particularly difficult to establish the etiology of the CAP even when highly specific and sophisticated techniques are used. A Spanish multicenter study on the etiology of CAP in patients with COPD did not find large differences between the COPD patients and the rest of the population hospitalized for CAP, although it did highlight the frequency of *C pneumoniae* and *L pneumophila*, which were only exceeded by *S pneumoniae*.[48] Smoking and alcohol consumption have also been associated with the presence of *C pneumoniae*, and hepatic comorbidity and alcoholism give rise to more frequent bacteremias, particular due to *S pneumoniae*.[47] Smoking is also a risk factor for CAP caused by *H influenzae* (level II evidence). Alcoholic patients seem to suffer more frequently from pneumonia caused by *Klebsiella pneumoniae*.[49] Finally, pneumonia caused by *P aeruginosa* is more common in patients with bronchiectasis and severe COPD (level III evidence). It is particularly important to note this fact both because of the high mortality associated with this pathogen, and because the empirical treatment regimens usually used for CAP are not effective against *Pseudomonas*.

### *New Pathogens*

Among the new causative agents for CAP that have emerged in recent years, *C pneumoniae* stands out. The incidence of this pathogen is estimated to be around 10% in most of the patient series reported in Europe, making it one of the most common causes of CAP.[10,14,31,50] *C pneumoniae* has been identified in 4.5% of the cases of CAP in Chile.[51] This microorganism is usually found in combination with other infections.[47,50] As the sole causative agent it is found more frequently in young patients with slowly evolving symptoms who have received antimicrobial treatment.[52] In general, the symptoms of this type of infection are mild and self-limiting. However, in recent studies *C pneumoniae* was the second leading cause of serious pneumonia, although frequently in association with other pathogens.[31,37]

Respiratory viruses are becoming increasingly more common as etiological agents of CAP. In a population

study, 25% of cases were caused by a respiratory virus, usually influenza, which was most often the sole etiological agent.[14] Some 80% of these patients required hospitalization, and 20% intensive care. It has now been recognized that hantavirus causes a pulmonary syndrome associated with high mortality rates throughout North and South America, from the southern tip of Chile and Argentina to Canada.[53-55]

The possible emergence of new CAP etiologies has recently been made clear by the epidemic outbreak of severe acute respiratory syndrome. This entity is an atypical form of pneumonia caused by a highly contagious coronavirus that first appeared in rural regions of China. The epidemic has spread rapidly across South East Asia[56] and, owing to air travel, has produced sporadic cases in Europe and some countries in the Americas, and a small epidemic in Toronto (Canada). The mortality of this form of CAP is 6.5%, and the risk factors for an unfavorable prognosis are diabetes and other comorbidities.[57]

*The Problem of Antibiotic Resistance*

Empirical antibiotic treatment of CAP should be active against the pathogens most commonly involved in its etiology and particularly against *S pneumoniae*. Of growing importance in the past decade has been the appearance of strains of *S pneumoniae* whose resistance to penicillin is not mediated by beta-lactamase. The penicillin resistance of *S pneumoniae* is a worldwide problem that has become more serious in recent years. In the USA the number of resistant strains rose from 3% in 1988 to more than 30% in recent years.[58,59] Researchers in Chile studied 75 strains of *S pneumoniae* isolated in respiratory samples taken from adult hospitalized patients. They found that 16% of strains were resistant to penicillin, 8%, to cefotaxime, and 1.3% to erythromycin.[60] They did not find any strains of *S pneumoniae* with a minimum inhibitory concentration (MIC) higher than 4 μg/mL for penicillin. The results obtained in another study involving 46 adult patients hospitalized for pneumococcal pneumonia were similar, except that 11% of strains were found to be resistant to erythromycin.[61] No strains isolated in either of these 2 studies had an MIC for penicillin of more than 2 μg/mL. The current definition of resistance stipulates that an MIC of 0.12 to 1 μg/mL represents an intermediate level of resistance, while strains with MICs of 2 μg/mL or more are considered to be highly resistant.[62] However, the controversy continues regarding the clinical importance of this *in vitro* resistance in the absence of meningitis. It would appear that infections with intermediate resistance respond to high doses of penicillin, and that resistance becomes a clinically important factor when the MIC values are over 4 μg/mL.[8]

TABLE 2
**Association Between Certain Clinical Aspects and a Greater Risk of Infection by Certain Pathogens**

| |
|---|
| *Pneumococcus resistant to penicillin and other antibiotics* |
| Age >65 years |
| Treatment with beta-lactams during the preceding 3 months |
| Alcoholism |
| Immunodepressant disease (including corticosteroid treatment) |
| Multiple comorbidity |
| Exposure to children in nurseries |
| Enteric Gram negative bacilli |
| Nursing home residence |
| Cardiopulmonary comorbidity |
| Multiple comorbidity |
| Recent antibiotic treatment |
| *Pseudomonas aeruginosa* |
| Bronchiectasis |
| Treatment with corticosteroids (>10 mg of prednisone per day for 1 month or more) |
| Broad spectrum antibiotic treatment for more than 7 days during the previous month |
| Malnutrition |

It is important to remember that the resistance of *S pneumoniae* varies from area to area; variations are found even within a single city and across different segments of the population.[63] Penicillin resistance also occasionally implies cross-resistance to macrolides, sulfamides, and cephalosporins, so that the activity of macrolides, such as clarithromycin and azithromycin, against the pneumococcus is often diminished in penicillin resistant strains.[64] Several studies have established the clinical features most often associated with antibiotic resistant respiratory pathogens. Some of these features are shown in Table 2.

This effect of cross resistance is not seen with other antibiotics, such as telithromycin and the quinolones.[65-67] The new fluoroquinolones that are active against pneumococcus, in particular moxifloxacin and gatifloxacin, are active even against highly penicillin-resistant strains.[66] These fluoroquinolones with greater activity against pneumococcus should be used because the development of resistance to levofloxacin during treatment of CAP with this antibiotic has been described and the result was clinical failure.[68] It is important to note that the problem of penicillin resistance has been growing continually over recent years. In light of this fact, there is some doubt about the use of certain antibiotics traditionally prescribed for CAP, such as beta-lactams, oral cephalosporins, and macrolides. Moreover, cefuroxime, ceftriaxone, and the beta-lactams, such as amoxicillin with and without beta-lactamase inhibitors, do not provide coverage for atypical microorganisms. The high resistance of *S pneumoniae* to co-trimoxazole and doxycycline in Latin America limit the prescription of these antibacterial agents.[69]

Telithromycin, the foremost representative of the ketolides, has good activity against all respiratory pathogens, including strains of pneumococci resistant to beta-lactams and macrolides.[65,70] Like the new fluoroquinolones, telithromycin is administered in a single daily oral dose. Its use is justified in patients with risk factors for resistant microorganisms as an alternative to quinolones in patients with mild or moderate CAP (level II evidence).[71] Its use is pending approval by health

TABLE 3
***In Vitro* Comparison of Different Antimicrobial Agents Active Against *Streptococcus pneumoniae* in Latin America***

| Antimicrobial Agents | Sensitivity, % |
|---|---|
| Penicillin | 71.4 |
| Amoxicillin | 85.5 |
| Amoxicillin-clavulanic acid | 85.5 |
| Cefuroxime | 81.2 |
| Cefotaxime | 88.9 |
| Co-trimoxazole | 58.1 |
| Azithromycin | 87.2 |
| Clarithromycin | 86.2 |
| Chloramphenicol | 94.0 |
| Tetracyclines | 74.4 |
| Levofloxacin† | 99.6 |
| Moxifloxacin† | 99.6 |
| Telithromycin† | 100 |

*Data from the Sentry program[54] (234 strains). Or, if asterisked (†), from the PROTEKT program[72] (514 strains) and from López et al.[73]

authorities in various countries, including the USA.

It is also important to implement policies for the rational use of antibiotics in order to limit the growth of resistance. Observed frequencies of resistance of *S pneumoniae* to various antibiotics in Latin American countries are shown in Table 3.

## Hospitalization and Severity Criteria

Hospital admission rates for adults with CAP are very variable, suggesting that there are no standardized protocols for the assessment of the morbidity and mortality risk in CAP patients. It is thought that physicians often overestimate the risk of morbidity and death in patients with CAP, and consequently hospitalize a large number of low-risk patients. The objective categorization of patients according to risk should help reduce this variability, and improve decisions about hospitalization and, consequently, the cost-effective management of the disease. Fine et al[74] developed a useful model for identifying low-risk patients by applying predictive rules in 2 steps. The validated results of the model indicate that patients at low risk of death who can be treated as outpatients can be adequately identified and assigned to 3 different risk groups (I, II, and III).

The discriminant rule developed by the British Thoracic Society[75] is useful for identifying high-risk patients. The rule confirms that a respiratory rate of more than 30 per minute, a diastolic pressure under 66 mm Hg, and a blood urea nitrogen concentration above 20 mg/dL are associated with a higher risk of death. A subsequent modification of these criteria added mental confusion as a predictor and observed that the presence of 2 factors was associated with a 36-fold increased risk of death.

It is important that clinical decisions concerning hospitalization be made on a case by case basis. Above all, physicians should avoid treating patients at risk on an outpatient basis, but it is also important to minimize the number of low-risk patients that are hospitalized unnecessarily. Based on a number of studies that have been carried out, a list has been drawn up of the risk factors that affect the need for hospitalization (Table 4).

TABLE 4
**Risk Factors Related to a Bad Prognosis in Patients With Community-Acquired Pneumonia**[3,6,7,18,24,25,31,36-38,48,74,75]

| |
|---|
| Requiring mechanical ventilation |
| Signs of sepsis |
| Systolic pressure <90 mm Hg |
| Diastolic pressure <60 mm Hg |
| Respiration rate >30/min |
| Confusion |
| Hypoxemia ($PaO_2$<60 mm Hg)* |
| Hypercapnia ($PaCO_2$>50 mm Hg)* |
| Suspected aspiration |
| Leukocytosis >40 000/μL or leukopenia <4000/μL |
| Urea >50 mg/dL |
| Anemia (hematocrit <32%) |
| Pleural effusion |
| Multilobar pneumonia |
| Pulmonary abscess |
| Radiographic progression |
| Peripheral septic focus |
| Hypothermia |
| Comorbidity requiring treatment |
| Unfavorable social factors |
| Oral treatment not possible |

*The partial pressure values for blood gases given refer to measurement at sea level. Pathological values vary according to altitude.

Most CAP patients have an appropriate clinical response within 3 days of start of treatment.[17] However, 10% of patients fail to respond to treatment.[76] In such cases we should reconsider the etiology, evaluate the possibility of a resistant causative agent, and consider complications and factors related to the host (Table 5).

Among possible causes we should consider include the following: "atypical" respiratory pathogens (*P carinii, Leptospira*, hantavirus, tuberculosis, and fungi), viral agents, noninfectious pulmonary infiltrates (such as pulmonary embolism), noninfectious inflammatory diseases (such as bronchiolitis obliterans organizing pneumonia), Wegener's granulomatosis, lupus pneumonitis, eosinophilic pneumonia, some forms of vasculitis, and neoplasms. Other candidates are processes secondary to drug consumption, such as amiodarone pulmonary toxicity.[77]

In the diagnostic reevaluation of these patients, bronchoscopy is a useful tool for clarifying the situation in some 50% of cases (level II evidence).[78,79] Using bronchoscopy, new samples should be obtained and a transbronchial biopsy performed when a noninfectious

TABLE 5
**Reappraisal When Treatment of Pneumonia Has Failed**

| |
|---|
| Consider alternative etiology: noninfectious pulmonary infiltrates |
| Possibility of resistant bacteria |
| Presence of focal suppuration |
| Inadequate concentration of antibiotic at the site of the infection |
| Nonadherence to treatment |
| Factors relating to the host: chronic obstructive lung disease, bronchiectasis, etc |

TABLE 6
**Etiology and Treatment of Community-Acquired Pneumonia in Outpatients According to Risk Factors for Different Bacterial Etiologies (Level II Evidence)***

| Characteristics | Treatment |
|---|---|
| No risk factors | Azithromycin or clarithromycin |
| Risk of PRSP | Moxifloxacin, levofloxacin or telithromycin |

*PRSP indicates penicillin resistant *Streptococcus pneumoniae*.

TABLE 7
**Etiology and Treatment of Community-Acquired Pneumonia in Patients Admitted to the General Wards (Level II Evidence)***

| Microorganisms | Treatment |
|---|---|
| *Streptococcus pneumoniae* and PRSP<br>*Haemophilus influenzae*<br>*Moraxella catarrhalis*<br>*Enterobacteriaceae*<br>*Mycoplasma pneumoniae*<br>*Chlamydia pneumoniae*<br>Anaerobic organisms | *1.* Moxifloxacin, gatifloxacin, levofloxacin, telithromycin<br>*2.* Ceftriaxone or cefotaxime + clarithromycin or azithromycin<br>*3.* Beta-lactamase inhibitor + clarithromycin or azithromycin IV |

*PRSP indicates penicillin resistant *Streptococcus pneumoniae*; IV, intravenous.

cause is suspected. Pneumonia that does not respond to treatment is a clear indication for referral to a specialized unit for assessment and in many cases for carrying out invasive diagnostic testing.

Another form of inappropriate response to treatment is late response (slow resolution), which takes the form of an inadequate radiographic improvement 30 days after start of treatment. This situation is generally seen in patients with weakened defense mechanisms, for example patients with concurrent diseases such as diabetes, heart failure, alcoholism, and cancer, among others.[80] Slow response may also occur in cases of pneumonia caused by atypical microorganisms, such as staphylococci and/or Gram negative bacteria.

## Treatment

Antibiotic treatment of CAP is empirical at the outset in most cases. Accumulated knowledge about the etiology of CAP in each particular geographical area and the susceptibility patterns of the most common pathogens against available antibiotics will define the most suitable choice of treatment for each case. The pharmacokinetic and pharmacodynamic characteristics of each antibiotic will determine its efficacy against respiratory infection. In the case of antibiotics that have a time-dependent bactericidal action and a minimal or moderate postantibiotic effect (beta-lactams, macrolides, and oxazolidinones), the most useful predictor of therapeutic efficacy is the period of time during which serum concentrations are higher than the MIC. The following variables have been found to be associated with antibacterial efficacy in the case of drugs that are classified as concentration-dependent and have a prolonged postantibiotic effect (aminoglycosides, fluoroquinolones, and ketolides): the area under the concentration-time curve of the antibiotic in relation to the MIC, also known as the area under the inhibitory curve (AUIC); and the maximum concentration/MIC ratio or inhibitory quotient. The AUIC represents both the time of exposure and the maximum concentration attained by the antimicrobial agent in the place of infection. It can, therefore, also be used to predict the effectiveness of time-dependent antibiotics with a prolonged elimination half-life and postantibiotic effect (azithromycin, tetracyclines, and streptogramins). A dose regimen that ensures high levels of the antibiotic not only at the focus of infection but also in areas that are normally colonized may impede or delay the phenomenon of resistance selection. This result is more easily achieved if antibiotics with concentration-dependent bactericidal effect are prescribed in such a way as to ensure an inhibitory quotient of between 8 and 10 or an AUIC greater than 100, except in the case of certain microorganisms, such as pneumococcus, for which an AUIC of more than 30 is sufficient. The objective of a dose regimen for antibiotics with time-dependent bactericidal effect should be to obtain serum concentrations that exceed the MIC of the pathogen for over 40% of the period between doses.[81]

These guidelines recommend a series of options for antibiotic treatment chosen on the basis of patient characteristics that identify those at greater risk for infections caused by certain pathogens, such as *H influenzae*, penicillin-resistant *S pneumoniae*, and anaerobic organisms (level II and III evidence).

Table 6 shows treatment regimens for CAP patients who can be treated on an outpatient basis. These regimens are suitable for empirical treatment of patients without risk factors for penicillin-resistant pneumococcal or enteric Gram negative bacteria (level I evidence). Two possible options are given. Amoxicillin may also be used when the likelihood of typical pneumonia is high. In cases with risk factors for penicillin resistant *S pneumoniae* or macrolides, the treatment of choice is fluoroquinolones or telithromycin (Table 6). When dealing with more serious cases of CAP in patients requiring hospitalization, the possible etiologies and recommended antibiotic treatment regimen vary (Table 7). Physicians should consider the possibility of infection by anaerobic bacteria in elderly patients with swallowing problems or low levels of awareness who may have aspirated pharyngeal or gastric content.

Intravenous therapy may not be necessary for hospitalized patients. Owing to the excellent pharmacokinetic properties of the new quinolones,[66,67] oral administration may be equally effective (level III evidence).

Finally, patients requiring intensive care because of the extreme seriousness of their condition should be treated using the empirical regimens shown in Table 8. In such

TABLE 8
**Etiology and Antibiotic Treatment of Severe Community-Acquired Pneumonia in Patients Admitted to the Intensive Care Unit (Levels II and III Evidence)***

| Microorganisms | Treatment |
|---|---|
| *Streptococcus pneumoniae* and PRSP<br>*Haemophilus influenzae*<br>*Moraxella catarrhalis*<br>*Enterobacteriaceae*<br>*Staphylococcus aureus* (MSSA and MRSA†)<br>*Legionella pneumophila*<br>*Moraxella pneumoniae*<br>*Chlamydia pneumoniae*<br>Anaerobic organisms | Moxifloxacin or gatifloxacin + ceftriaxone or cefotaxime |
| Suspected *Pseudomonas aeruginosa* | Ciprofloxacin + piperacillin/tazobactam, imipenem, meropenem, or cefepime |

*PRSP indicates penicillin resistant *S pneumoniae*; MSSA, methicillin-susceptible *S aureus,* and MRSA, methicillin-resistant *S aureus*.
†If the MSSA is confirmed, vancomycin, teicoplanin, or linezolid should be added.

cases, patients should be categorized according to whether they are at risk for CAP caused by *P aeruginosa*. Risk factors for CAP caused by *Pseudomonas* are as follows: a prior history of pneumonia caused by *Pseudomonas*; significant bronchiectasis; or severe COPD (level III evidence).

The most frequently used antibiotic dosage regimens are shown in Table 9. The duration of treatment is typically 7 to 14 days. However, shorter treatments are possible (5 days) using drugs with a long half life, such as azithromycin, and 7 to 10 days with the new fluoroquinolones and telithromycin.

A very new approach is to switch rapidly from intravenous to oral antibiotics (switch therapy). The choice of this regimen should be based on an appropriate clinical assessment and an understanding of the pharmacokinetic and pharmacodynamic properties of the indicated antimicrobial agents. This switch to oral administration has been shown to reduce the length of the hospital stay and is a cost effective option (level I evidence).[82] Some antimicrobial agents, such as the fluoroquinolones and linezolid, attain comparable blood concentrations whether they are administered orally or intravenously (level I evidence). Others, such as the beta-lactams, attain lower concentrations when administered orally, but still provide adequate and effective treatment (level I evidence).

Other new treatments include the use of longer intervals with short half life drugs and short treatments (5 to 7 days) with some antimicrobial drugs, such as azithromycin, telithromycin, and some new fluoroquinolones.[66,67,70]

## Prevention

Smoking increases the risk of CAP. Consequently, in smokers the first preventative measure should be to quit smoking (level II evidence).[83]

Other preventative measures, such as vaccines, should also be implemented (levels I and II evidence). The influenza vaccine is of particular interest, and should be administered every year following the World Health Organization recommendations and targeting the strains specified by this institution, since it has been demonstrated that this vaccine also reduces other infections of the lower airway.[84] Administration of the 23-valent pneumococcal vaccine is also recommended. This should be administered to people over 65 years of age, and to patients with chronic diseases who have increased susceptibility to pneumococcal infection, as recommended by international guidelines.[85,86]

## Implementation of CAP Guidelines in Hospitals

The aim of CAP recommendations is to modify local clinical practice in the direction of the ideal practice recommended in the guidelines. A 4-step process for implementing guidelines within a local area or region is required if this objective is to be met. The first of these 4 steps is the creation of a local document detailing the specific interventions considered to constitute the ideal

TABLE 9
**Antibiotic Dosage Regimens Usually Used for the Treatment of Respiratory Infections**

| Antibiotic | Dose | |
|---|---|---|
| | Oral | Intravenous |
| Clarithromycin OD | 500 mg/12 h once daily | 500 mg/day |
| Azithromycin | 500 mg the first day, then 250 mg/day | 500 mg/day |
| Telithromycin | 800 mg/day | |
| Moxifloxacin | 400 mg/day | 400 mg/day |
| Gatifloxacin | 400 mg/day | 400 mg/day |
| Levofloxacin | 500 mg/12h | 500 or 750 mg/day |
| Ciprofloxacin | 750 mg/12 h | 200-400 mg/12 h |
| Amoxicillin-clavulanic acid | 875/125 mg/12 h | 500/125 mg/8 h |
| Piperacillin-tazobactam | | 4.5 g/6-8 h |
| Imipenem | | 500 mg/6 h |
| Cefotaxime | | 1 g/8-12 h |
| Ceftriaxone | | 1-2 g/24 h |

approach to treating patients with CAP. The second step involves collecting and analyzing data concerning actual practice. These data will illustrate the divergence that exists between actual and ideal practice. The divergence from ideal practice should then be analyzed to assess why is it happening, and to decide whether or not the variation is justified. The third step includes the implementation of local interventions aimed at reducing the divergence from ideal practice. The final stage involves gathering and analyzing data concerning the results of interventions. Using this process it is possible to gauge whether the divergence from ideal care has been minimized or eliminated. It is important to document whether the distance between actual practice and the ideal approach has been reduced, since this would clearly demonstrate that the CAP guidelines had produced the desired effect.

To achieve the first objective an expert team from the local hospital should draw up guidelines for ideal care based on a careful review of the literature. Merely publishing the resulting guidelines may not produce any change in current practice if publication is not accompanied by a renewed effort to implement and promote guideline use. It is only during implementation that potential obstacles may appear. The following obstacles may emerge in the implementation of the second phase: *a)* lack of experience in measuring results; *b)* insufficient time and skills on the part of the person in charge of collecting and evaluating data, and *c)* lack of experience in evaluating variations in practice and defining their justification.

The following problems could arise during the third phase: *a)* lack of personnel with the appropriate skills to implement actions aimed at changing local practice, and *b)* lack of support from the authorities in implementing action aimed at correcting attitudes.

Finally, the following problems could occur in the fourth stage: *a)* lack of personnel to collect or quantify data, and *b)* lack of the information required to assess variations in practice over time.

The ultimate aim of CAP guidelines is to eliminate differences between actual practice and the ideal approach in every local hospital. In order to achieve this objective, the physicians and other health professionals involved must have a clear idea of how to implement the guidelines and correct problems in their application.

## Summary

CAP is a very common disease, especially among the very young and the elderly. In some Latin American countries it is one of the leading causes of hospitalization and death in adults. The emergence of new causative microorganisms and the development of antibiotic resistance on the part of common pathogens have made necessary a revision of the guidelines for dealing with this infection.

Pneumococcus is still the microorganism that most often causes CAP throughout different countries and risk groups. In some countries, prescription of the newly approved antibiotics, such as the new quinolones and the ketolides, is essential because of the resistance rate of pneumococcus to penicillin and macrolides. However, in areas where the resistance rate is still low, traditional antibiotics may still be used for treating outpatients with CAP.

The identification of risk factors associated with an unfavorable prognosis and infection with resistant or atypical microorganisms has improved the empirical treatment of CAP. These guidelines detail the principal risk factors described in the literature. This information is helpful in choosing the most appropriate antibiotic regimen. Other measures, such as the general improvement in living conditions, access to medical care, preventative measures, vaccination, and the in-service training of health care professionals, will all have a positive affect on the incidence and consequences of CAP.

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