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RECOMMENDATIONS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR)

Guidelines for the Diagnosis and Treatment of Community-Acquired Pneumonia. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)

SEPAR Working Group on Community-Acquired Pneumonia.
Tuberculosis and Respiratory Infections (TIR) Assembly*

The emergence in recent years of new microbiological techniques that have considerably improved the possibilities of obtaining a higher diagnostic yield in community acquired pneumonia (CAP) and the discovery of antimicrobial agents offering new treatment options have made necessary the revision and modification of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) guidelines on the diagnosis and treatment of CAP. The purpose is to bring them into line with current scientific evidence.

These guidelines deal exclusively with CAP in immunocompetent adults (patients 18 years or older). They do not address the management of this disease in children, patients with cancer, immunodepressed patients in general, patients discharged from hospital within the preceding 10 days, or institutionalized patients. In our opinion all these types of patients, and patients with upper respiratory tract infections not involving the lung, require different treatment and therefore fall outside the scope of these guidelines.

The recommendations are organized into 4 sections: epidemiology, diagnosis, predictive rules, and treatment. The literature was reviewed for each one of these topics, and an initial draft was drawn up on this basis. This draft was then discussed and edited at meetings attended by all the members of the panel until consensus was reached on the final joint document. The recommendations of this consensus document have been graded into 3 classes according to level of evidence: *level I* (well-designed prospective trials that are randomized and have appropriate methodology); *level II* (well-designed prospective studies, with controls but without randomization); and *level III* (retrospective studies of cases and expert opinion). Before final approval, the consensus document was reviewed critically by a panel of reviewers who had not attended the earlier meetings.

In order to facilitate easy comprehension and quick reading of these recommendations, the text has been supplemented by numerous tables and a summary (located at the end of the text). The summary and tables highlight what are, in our opinion, the most important aspects of the diagnosis, treatment, and prevention of CAP.

Epidemiology

Although it is difficult to estimate its incidence accurately, CAP is a common disease. In Europe, incidence ranges from 5 to 11 cases per 1000 population per year.[1,2] Two population-based studies of patients aged over 14 in Spain found annual incidence rates ranging from 1.6 to 1.8 episodes per 1000 population, with a predominance of episodes in older men and in winter (level II evidence).[3,4]

The percentage of CAP patients who are hospitalized is very variable, ranging from 22% to 61%.[3,5] This variability is caused by a variety of factors, including differences in admission criteria, the possibilities of receiving treatment in a hospital emergency department, the percentage of patients coming from nursing or retirement homes, and the availability of hospital beds. One Spanish study reported that 9% of patients hospitalized for CAP were admitted to the intensive care unit (ICU).[3]

A meta-analysis of 127 studies comprising 33 148 patients revealed an overall mortality of 14%, ranging from 2% in ambulatory patients to 37% in patients treated in the ICU.[6]

Etiology

An etiological diagnosis is made in 40% to 60% of CAP cases, depending on the number of techniques employed. In cases of mild pneumonia, a condition generally managed outside of the hospital, it is rarely

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necessary to establish etiology. The distribution of pathogens responsible for CAP by clinical setting is discussed below.

Outpatient CAP (Group 1)

Table 1 shows the frequency of the most common pathogens in ambulatory and hospitalized patients in Europe.[7] A total of 41 studies (12 Spanish) were analyzed. Nine of these dealt specifically with outpatient CAP (level II evidence). Spanish studies carried out using mainly serological diagnostic methods found, as would be expected, a predominance of atypical microorganisms.[8,9]

In a recent study of the correlation between the etiology of cases of pneumonia and the classes of Fine's prediction rule, 69% of the pathogens found in class I patients were atypical, with *Mycoplasma pneumoniae* being the most common (level II evidence). In class II and III cases, however, typical pathogens accounted for 55% and *Streptococcus pneumoniae* was the most common.[10]

On the basis of the data currently available, therefore, the most common causative pathogens in cases of CAP treated outside the hospital are *S pneumoniae* and *M pneumoniae.*

Hospitalized CAP (Group 2)

Etiology is established in between 40% and 60% of patients hospitalized for CAP (level II evidence),[7,11-15] and *S pneumoniae* is the predominant pathogen. When new techniques were used to establish etiology, it was found that at least a third of the CAP cases that had not been diagnosed by conventional methods were pneumococcal in origin.[16-18] The prevalence of atypical pathogens (excluding *Legionella* organisms) depends on the effort invested in identifying them. In the case series cited above, atypical pathogens (mainly *M pneumoniae*) are identified as the causative agents in 20% to 35% of cases. Some 5% to 10% of CAP cases are caused by *Haemophilus influenzae* and gram-negative bacilli, while *Staphylococcus aureus* is less common. Aspiration pneumonia accounts for 5% of CAP cases.[15] Cases of infection with *Legionella* species occur sporadically all year round, with epidemics occurring more frequently in the summer months. While the incidence of *Legionella* species is highest in the Mediterranean area, important outbreaks have been observed in other parts of Spain, such as Alcalá de Henares. In a recent Spanish study, a virus was detected in 18% of patients with CAP and was the sole pathogen in half of these cases (level II evidence).[19] More than 1 pathogen may be isolated in any type of pneumonia. The most common mixed etiologies are combinations of "typical" and "atypical" pathogens, although the significance of this finding is unclear. Etiology should be defined as mixed when reliable methods reveal the concurrent presence of more than 1 pathogen. In general, results found in the Spanish literature are similar to the European findings shown in Table 1.

TABLE 1
Etiology of CAP in Europe[7]

Organism	Community, %	Hospital, %	Intensive Care Unit, %
Streptococcus pneumoniae	19	26	22
Haemophilus influenzae	3	4	5
Legionella species	2	4	8
Staphylococcus aureus	0.2	1	8
Gram-negative enteric bacteria	0.4	3	7
Atypical pathogens*	22	18	3
Viruses	12	11	5
No pathogen identified	60	44	42

*Atypical pathogens: *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Chlamydia psittaci,* and *Coxiella burnetii.*

Cases of CAP Admitted to the ICU (Group 3)

In most of the European studies published over the last decade and particularly in Spain (Table 1), *S pneumoniae* and *Legionella* organisms were responsible for 50% of cases of severe CAP (level II evidence).[20-24] Gram-negative bacilli were the third most common pathogens in all case series, and the possibility of tuberculosis should also be considered in Spain, especially when there is hemoptysis and no other microorganisms are isolated.[22] Finally, consideration should be given to the possibility that disease may be caused by opportunist pathogens, such as *Pneumocystis jiroveci* in association with human immunodeficiency virus (HIV) infection or *Aspergillus* species in patients with chronic obstructive pulmonary disease (COPD) receiving corticosteroid therapy.

The severity of the patient's illness conditions the type of pathogens expected and the yield of the diagnostic methods used. The percentage of unidentified pathogens is significantly lower in intubated compared to nonintubated patients (33% vs 53%); moreover, there is a significantly higher incidence among intubated patients of both *Pseudomonas aeruginosa* (15% vs 7%) and *Legionella pneumophila* (6.6% vs 1%) (level III evidence).[25]

Etiology and Host-Related Factors

Older Patients

In a prospective multicenter study in Spain of CAP patients aged over 65, etiology was identified in 40% of patients (level II evidence), and the pathogens most often isolated were as follows: *S pneumoniae* (49%), *H influenzae* (14%), and *L pneumophila* (8%).[26] In another Spanish study of 1475 adults with CAP, *S pneumoniae* was isolated in 23% of the 305 patients over 80 years old, while *L pneumophila* was the causative pathogen in

only 1% of this subset of very elderly patients, a significantly lower percentage than the 8% found in the cohort of younger patients (level II evidence).[27] Although the etiology of pneumonia acquired in Spanish retirement and nursing homes has not been analyzed, the causative pathogens isolated in such settings in the United States of America differ from those found in cases of pneumonia contracted in the home. A notable example in residential care settings is the high frequency of *S aureus* (28%) (level II evidence).[28] However, these findings were not confirmed by the only study carried out with a control group in the United Kingdom (level II evidence).[29]

COPD

The main pathogens isolated in a Spanish multicenter study of patients with COPD hospitalized for CAP were *S pneumoniae, Chlamydophila pneumoniae,* and *H influenzae* (level II).[30] In patients with severe COPD, especially in the presence of bronchiectasis, *P aeruginosa* should also be considered (level II evidence).[31]

Other Predisposing Conditions

Congestive heart failure is a risk factor for CAP and viral infections.[19] Diabetes mellitus favors bacteremic pneumococcal pneumonia[32] and CAP caused by *S aureus* (level II evidence).[33]

Alcohol Consumption

Alcoholism is an independent risk factor for CAP and for severe presentation.[34] It is difficult to associate a particular CAP etiology with alcoholism because comorbidities are common. Aspiration pneumonia is common in alcoholic patients (level II evidence).

Aspiration

Bronchopulmonary aspiration of the oropharyngeal contents is associated with any condition or circumstance that depresses the patient's level of consciousness—stroke, degenerative diseases, head injuries, drug intoxication, and general anesthesia—and with any circumstance that alters the anatomy of the laryngopharyngeal region, such as intubation or the presence of tumors.[35] Etiology is usually polymicrobial, with a predominance of anaerobic microorganisms (level II evidence).[13]

HIV Infection

Bacterial pneumonia, and in particular disease caused by *S pneumoniae*, is the most common infection in both HIV-positive patients and patients with acquired immunodeficiency syndrome although, as mentioned above, other pathogens less commonly found in CAP are also frequently seen in seropositive patients (level II evidence).

Smoking

Smoking is associated with an increased risk for CAP irrespective of etiology. Smokers are 4 times more likely than nonsmokers to contract an invasive pneumococcal disease (level II evidence).[36] The association between smoking and CAP caused by *C pneumoniae*[13] or *Legionella* infection is also marked (level II evidence).[37]

Corticosteroid Therapy

The risk of respiratory infection in patients receiving long-term corticosteroid therapy is related to the dose used and the patient's underlying disease. Accumulations of 700 mg of prednisone and doses of more than 10 mg/day increase the patient's risk of infection. One Spanish study identified *Aspergillus* species and *S aureus* as the pathogens most often isolated in patients taking corticosteroids (level II evidence).[38]

Environmental Factors and Occupational Exposure

In certain cases, factors related to the host (hobbies, travel) and to occupational exposure may point to a specific etiology. This information can be helpful in orienting decisions on the diagnostic methods that should be used and in selecting the most appropriate empiric treatment (Tables 2 and 3) (level III evidence).

Epidemiological Characteristics Peculiar to Spain

L pneumophila

An increase in the incidence of CAP caused by *Legionella* infection has been reported in Spain, particularly in the Mediterranean area. Although most cases have been isolated, outbreaks affecting large numbers of people have occurred, particularly in the summer months. The most common sources of infection are aerosols generated by cooling towers and hot-water installations (level I evidence).[37,39]

Coxiella burnetii

Although it was traditionally considered that *C burnetii* was only common in the northern part of Spain,[12,40] this bacteria also plays an important role in the etiology of CAP in other regions (level II evidence).[4,8]

Chlamydophila psittaci

Psittacosis is a zoonosis caused by inhalation of organic waste products (feces, urine, or feathers) or respiratory secretions containing *C psittaci*. Although a disease traditionally associated with exotic and farm birds, psittacosis can also be transmitted by other animals. This means that its incidence in areas where there is agricultural activity is probably somewhat higher than usually believed. While in other countries epidemics have been described among farm workers and veterinarians, the only outbreaks reported in Spain have occurred within families and have affected only a small number of patients and taken a variety of clinical forms.[41]

Clinical Signs and Symptoms

The syndromic diagnosis of CAP is based on the presence of the signs and symptoms of acute infection in

TABLE 2
Etiology of CAP by Environmental Factors

Factor	Microorganism
Exposure to air conditioning, hotel or hospital stays	*Legionella pneumophila*
Nursing or retirement home residence	*Streptococcus pneumoniae,* enterobacteria, *Haemophilus influenzae, Staphylococcus aureus,* anaerobic microorganisms, *Chlamydophila pneumoniae, Mycobacterium tuberculosis, Pseudomonas aeruginosa*
Influenza epidemic in the community	Influenza virus, *S pneumoniae, S aureus, H influenzae*
Prison residence	*S pneumoniae, M tuberculosis*
Exposure to parenteral drugs	*S aureus,* anaerobic microorganisms, *M tuberculosis, Pneumocystis jiroveci*
Travel to Southeast Asia	*Burkholderia pseudomallei,* coronavirus (cause of severe acute respiratory syndrome)
Travel to the Southwest of the United States of America	*Coccidioides immitis*

TABLE 3
Etiology of CAP by Occupational Exposure

Occupation/ Workplace	Disease/ Microorganism	Source of Exposure
Slaughterhouses	Brucellosis	Calves, goats, pigs
	Psittacosis	Chickens, turkeys
	Q fever	Calves, sheep, goats
	Tuberculosis	Calves infected with *Mycobacterium bovis*
Farms	Brucellosis	Calves, goats, pigs
	Q fever	Calves, sheep, goats
	Psittacosis	Ducks, turkeys
	Tularemia	Rabbits, squirrels
	Pasteurellosis	Dogs, cats
Agricultural workers	Leptospirosis	Rodents
Health sector	Influenza	Sick people, workers
	Respiratory syncytial virus	Sick people, workers
	Tuberculosis	Sick people, workers
	Chickenpox	Sick people, workers
Hunting	Plague	Infected rodents
	Tularemia	Wild animals, ticks, deer flies
Army	Chickenpox	Infected fellow soldiers
	Mycoplasma species	Infected fellow soldiers
	Tuberculosis	Infected fellow soldiers
	Tularemia	Wild animals, ticks, deer flies
Pet shops	Psittacosis	Parrots, budgerigars
Veterinary surgeries	Brucellosis	Pets
	Pasteurellosis	Colonized cats
	Plague	Infected animals
	Psittacosis	Infected birds
	Q fever	Pets
	Tuberculosis	Calves infected with *M bovis*
		Primates infected with *Mycobacterium tuberculosis*
Textile industry	Carbuncle	Imported wool infected with spores
	Q fever	Wool, skins infected with *Coxiella burnetii*

conjunction with a recent appearance on a radiograph of a pulmonary infiltrate unexplained by other processes (level III evidence). In view of the variable clinical presentation of CAP, physicians should be conversant with the epidemiology of the geographical area where they work.[42] It can also be useful, particularly in healthy young adult patients, to differentiate between typical and atypical clinical presentations. The typical clinical presentation is characterized by an abrupt onset of less than 48 hours, chills, fever in excess of 37.8°C, productive cough, purulent sputum, and pleuritic chest pain. The most notable features of the atypical clinical picture are an unproductive cough, vague chest discomfort, and nonpulmonary signs and symptoms (joint pain, headache, altered consciousness, and gastrointestinal disorders such as vomiting and diarrhea). Other findings sometimes associated with CAP are leukocytosis (≥12 000/μL) or leukopenia (≤4000/μL), respiratory sounds consistent with a diagnosis of pulmonary consolidation (which has a sensitivity of less than 40% when found in isolation),[43] and a new radiographic infiltrate. Two other features that should be borne in mind are the discrepancy between the clinical and radiographic course of the disease characteristic of some atypical pneumonias and the frequent presence of hyponatremia, hypophosphatemia, and hematuria in pneumonias caused by *Legionella* species.[44-46] Mental confusion and worsening of the underlying disease is not uncommon in older patients, even when there is no fever.

Laboratory Tests

A complete blood count and routine biochemistry, as well as pulse oximetry or arterial blood gases (particularly recommended for patients with underlying heart or lung disease) should be performed for all pneumonia patients who come to a hospital. These tests serve to assess the severity of the disease and the possible need for hospitalization (level III evidence).[42]

Chest Radiograph

Since the clinical signs and symptoms of CAP are not specific, chest radiographs must be obtained for the following reasons: to confirm the diagnosis; to provide information on the location and extent of disease; to explore the possibility of complications (such as pleural effusion or cavitation); to detect underlying pulmonary disease or alternative diagnoses; and to monitor the progression or resolution of the disease.[47] The limitations of this imaging technique are that it cannot discriminate between pneumonia and other, non-infectious inflammatory infiltrates and that it does not detect small infiltrates that can be seen with more sensitive methods, such as computed tomography. Routine posteroanterior and lateral chest radiographs are universally recommended for patients with suspected pneumonia (level II evidence),[42,43,48] and should be obtained both for patients assessed outside of

the hospital setting and for those assessed in the hospital (irrespective of whether or not they are admitted), particularly when no clinical improvement is observed after 48 hours of empiric treatment (level III evidence).[49]

No single radiographic pattern identifies the etiology of the pneumonia or even differentiates between groups of pathogens (level II evidence).[50] The classic patterns (lobar pneumonia, bronchial pneumonia, and interstitial pneumonia) are not exclusively associated with any etiologic agent, although the identification of such patterns can be useful in some cases (level III evidence).[47,51] Bilateral involvement, the involvement of more than 2 lobes, and the existence of pleural effusion are indicators of severity (level III evidence), particularly bilateral pleural effusion, whether caused by the pneumonia itself or by associated heart failure (level II evidence).[6,52,53] Since radiographic cure almost always lags behind clinical cure and may sometimes take more than 8 weeks longer,[47] systematic radiography before discharge from hospital is not necessary, but radiographic confirmation of cure is still essential.

Etiologic Diagnosis (Table 4)

It is impossible to establish a firm etiologic diagnosis on the basis of clinical and radiographic findings (level II evidence). Even when appropriate diagnostic techniques are used in the hospital setting, etiologic diagnosis is only established in some 50% of cases.[42] No prospective studies have been undertaken to identify what tests should be used to determine etiology in CAP patients.[43] Furthermore, the absence of any proof that identification of the responsible pathogen influences prognosis has given rise to differences of opinion about the need to establish etiology. It has, however, been suggested that early etiologic diagnosis correlates with more rapid improvement after start of treatment,[54] and that inappropriate antibiotic therapy is associated with a poor prognosis.[21,55] Consequently, the more serious the CAP, the more diagnostic techniques should be used, while only a few or none of such techniques are necessary in mild cases (level III evidence).[42,43,45,48,49,56,57] However, start of antimicrobial treatment should never be delayed in order to obtain a reliable sample.[43] Diagnostic techniques should also be used in patients who do not respond to empiric treatment and in cases of slowly resolving CAP (level III evidence).[58]

Bacteria isolated in respiratory samples may represent colonization (unless they are inevitably pathogenic organisms, such as *L pneumophila* or *Mycobacterium tuberculosis*). Therefore, in order to obtain a firm etiologic diagnosis it is very often necessary to isolate the microorganism, or to detect its antigens or specific fragments of its genome, in uncontaminated samples such as blood, urine, pleural fluid, or lung tissue, or else to detect significant quantities of specific antibodies in serum. A probable diagnosis can be reached using quantified respiratory isolates or under certain conditions (level II evidence). The microbiological techniques potentially of use in the etiologic diagnosis of CAP can be classified as noninvasive and invasive.

TABLE 4
Minimum Necessary Techniques for the Diagnosis of CAP*

CAP patients managed outside the hospital	
No diagnostic technique (other than chest radiograph PA and L)	
Hospitalized CAP patients	
2 blood cultures (before start of antibiotic therapy) for aerobic and anaerobic microorganisms	
Urinary antigen assay for *S pneumoniae* and *Legionella* species	
Pleural fluid (if ≥10 mm on the lateral decubitus view): Gram stain, culture, anaerobic microorganisms. Pneumococcal antigen, if possible	
Patients with CAP admitted to the ICU	
Gram stain and sputum culture (before start of antibiotic treatment) Sputum culture in medium suitable for *Legionella* species	
2 blood cultures (before start of antibiotic therapy) for aerobic and anaerobic microorganisms	
Urinary antigen assay for *S pneumoniae* and *Legionella* organisms	
Pleural fluid (if >10 mm on the lateral decubitus view): Gram stain, culture, anaerobic microorganisms. Pneumococcal antigen assay, if possible	
Flexible bronchoscopy with telescoping catheter and protected specimen brush and/or BAL, or else: quantitative culture of tracheal aspirate (in recently intubated patients)	
Alternative: transthoracic fine needle aspiration (in nonintubated patients)	
Nonresponding CAP	
Sputum	Gram stain and conventional bacteria culture DIF for *Legionella* species Giemsa stain Normal and modified Ziehl stain Stain for fungi
Blood cultures	2 serial cultures
Urine	Antigen testing for pneumococci and *Legionella* species
BAL	Gram stain and intracellular bacteria Bacterial cultures and colony counts Normal and modified Ziehl stain Giemsa stain Stain for fungi DIF for *Legionella* species
Protected specimen brush	Gram stain Bacterial cultures and colony counts Normal and modified Ziehl-Neelsen stain Giemsa stain Stain for fungi DIF for *Legionella* species
Transthoracic fine needle aspiration (in nonintubated patients)	Gram stain Bacterial cultures and colony counts Normal and modified Ziehl-Neelsen stain Giemsa stain Stain for fungi DIF for *Legionella* species
Pleura	Anaerobic culture Aerobic culture Pneumococcal antigen Pneumococcal and mycobacterial PCR Normal and modified Ziehl-Neelsen stain
Nasopharyngeal exudate	PCR for virus and atypical microorganisms

*CAP indicates community-acquired pneumonia: PA, posteroanterior; L, lateral; ICU, intensive care unit; BAL, bronchoalveolar lavage; DIF, direct immunofluorescent assay; and PCR, polymerase chain reaction.

Noninvasive Diagnostic Techniques

Sputum

There is no clear consensus concerning the microbiological techniques that should be used to process sputum samples in CAP (Gram stain, aerobic culture, and culture on buffered charcoal-yeast extract for *Legionella* organisms). It is difficult to obtain adequate samples that are not highly contaminated by oral secretions (with fewer than 10 squamous cells and more than 25 polymorphonuclear cells per 100 power field, Murray's levels IV and V). In a prospective case series of hospitalized CAP patients, only 39% of the sputum samples fulfilled these criteria.[59] No authors have reported differences between the Fine risk classes in yield from sputum.[60] Gram stain and aerobic culture should be carried out on recently collected reliable sputum samples in all patients hospitalized for CAP (level II evidence). Sputum samples should be transported and processed rapidly, if possible in under 30 minutes and before antibiotic treatment is started, particularly if the presence of a resistant or atypical microorganism is suspected (level II evidence). Gram stain findings may guide therapy (level III evidence), and cultures, when the results correlate with those of the Gram stain, can be useful in determining the possible resistance of the pathogen to antimicrobial agents. Sputum culture in a medium suitable for *Legionella* organisms is recommended during epidemic outbreaks even when urine samples test positive for *Legionella* antigens because cultures facilitate diagnosis of infection by serogroups other than 1 and by *Legionella* species other than *L pneumophila* and can be used to identify links between clinical and environmental strains by way of molecular markers. Induced sputum samples are of value for detecting *M tuberculosis* and *P jiroveci* in patients who are unable to expectorate, and should be used when the epidemiologic context or immune status of the patients make such testing advisable (level I evidence).[43,48] Direct immunofluorescent assay of respiratory secretions may also be used to diagnose CAP caused by *Legionella* species, although the sensitivity of this test is under 50% in patients with adequate expectoration. Since this test uses serotype-specific antibodies, its diagnostic yield will depend on the species of *Legionella* and the serotypes used.

Blood Cultures

The practice of performing blood cultures in the ambulatory management of CAP is unjustified owing to their low diagnostic yield,[61] and their cost-effectiveness in patients hospitalized for CAP remains questionable.[62] At this time it is prudent to recommend, particularly in serious cases, that 2 serial blood cultures be performed on all patients admitted with CAP. If positive, the results of these tests will be of etiologic and prognostic value (level II evidence).[42,43,48,49,57,63] In an attempt to rationalize the use of blood cultures in CAP, a recent study proposed that the decision on whether or not blood cultures should be obtained could be based on the patient's risk of developing bacteremia.[64]

Pneumococcal Urinary Antigen Tests

Urinary antigen testing is a rapid immunochromatographic technique. There is some controversy about the concentration of the urine used in this test, but it appears that the moderate loss of sensitivity (66%) associated with the use of direct urine is compensated by the simplification and rapidity of the technique, while specificity remains close to 100%.[18] In Spain, it is considered reasonable to determine the urinary pneumococcal antigen in unconcentrated urine in cases of CAP that require hospitalization (level II evidence). False positives have been reported in patients with nonpneumococcal infections caused by *Streptococcus* organisms. In some cases, positivity persisted for some weeks after resolution of the CAP.[65] Since the results of pneumococcal urinary antigen testing complement those of sputum Gram staining in patients capable of expectorating adequately, the use of both of these techniques is recommended.[66]

Urinary Antigen Assay for Legionella *species*

Immunochromatographic urinary antigen assay has become the gold standard method for diagnosing Legionnaires' disease[67]; In this case, proper concentration and thermal treatment of the urine are essential if adequate sensitivity is to be obtained, despite the 2 to 3 hour processing time involved (level II evidence). Ultracentrifugation of the urine is probably a valid alternative because it can be done much more quickly without any loss of either sensitivity or specificity (level II evidence).[68] Urine should be tested for *Legionella* antigens in all of the following cases: hospitalized patients with enigmatic pneumonia after sputum Gram stain or pneumococcal urinary antigen assay, patients fulfilling the criteria for severe pneumonia, patients whose condition has failed to respond to treatment with beta-lactam antibiotics, and all cases that coincide with a suspected epidemic outbreak of Legionnaires' disease in the community.[43]

Pleural Fluid

The yield of aerobic and anaerobic culture and Gram stain of pleural fluid is low. Nevertheless, thoracocentesis is recommended when pleural effusion is associated with CAP because undetected empyema is one of the factors that predict treatment failure within 48 to 72 hours of hospital admission in such cases.[69] Testing pleural fluid samples for antigens may yield some additional diagnoses over and above those obtained by routine methods (level III evidence). The pneumococcal antigen has been successfully detected in pleural fluid using the immunochromatographic membrane assay (BINAX) but the use of this test is not yet standardized.

Serology

Serological testing is usually used in the differential diagnosis of pneumonias caused by intracellular agents. In view of its limited clinical utility, routine use of this

technique is not recommended (level III evidence) outside of exceptional circumstances, such as a suspected outbreak of Legionnaires' disease or tularemic pneumonia in the community, or epidemiological studies. The sensitivity and specificity of immunoglobulin-M detection are not sufficiently high to recommend the routine use of this technique.[70] Even with respect to the more classical serological studies based on the measurement of immunoglobulin-G, reasonable doubts have been raised concerning the specificity of this test for certain agents, such as *C pneumoniae* and *Legionella* species.[71]

Polymerase Chain Reaction in Noninvasive Samples

Polymerase chain reaction techniques, which identify the pathogens that cause CAP by way of fragments of DNA obtained from biological samples (sputum, blood, pleural fluid, or urine) fall outside routine clinical practice in most Spanish hospitals, and the assessment of their predictive value, both positive and negative, is problematic.[72] The routine use of such techniques is, therefore, not recommended. A better understanding of these techniques should, however, be sought in hospitals with the technical infrastructure and resources to carry them out.[16]

Invasive Techniques

The use of invasive techniques is only indicated in the most severe cases of CAP involving patients whose condition deteriorates rapidly or fails to respond to initial empiric antibiotic treatment (Table 4),[42,43,48,49] although some studies suggest that an etiologic diagnosis does not improve the prognosis of patients with severe CAP.[23,73] Invasive diagnostic techniques include transtracheal aspiration, transthoracic fine needle aspiration, and techniques involving fiberoptic bronchoscopy, such as the telescoping catheter with protected specimen brush and bronchoalveolar lavage (BAL). All of these procedures must be carried out by expert personnel (level III evidence).

Non-Bronchoscopic Techniques

Transtracheal aspiration is no longer used. Uncontaminated specimens of the lung parenchyma can be obtained by transthoracic fine needle aspiration. This technique is highly specific (90%), whereas its sensitivity varies greatly between case series (34%-82%) even when the procedure is performed by experts. Sensitivity improves significantly when the culture of these samples is complemented by antigen detection or gene amplification techniques (level II evidence).[74] Although polymerase chain reaction is a more sensitive technique than latex agglutination, the latter is more often used because it is more cost-effective, quicker, and simpler, and it provides useful information to support the decision concerning initial treatment (level II evidence).[74,75] Transthoracic fine needle aspiration may be considered in cases of abscessed CAP and in patients who do not respond treatment. The 2 most serious complications associated with this technique are pneumothorax (2%-5%) and hemoptysis (2%-5%). Open lung biopsy is the most invasive technique, and its use is exceptional because it rarely provides relevant information in immunocompetent patients with CAP.

Bronchoscopic Techniques

Numerous studies have shown that bronchoscopic techniques can provide useful microbiological information not only in ventilator-associated pneumonia but also in CAP.[76] The highest sensitivity is obtained with quantitative cultures of BAL and the best specificity with quantitative cultures of protected specimen brushes.

The cutoff point used to differentiate between colonization and infection in protected specimen brushings was 10^3 colony forming units per milliliter. The sensitivity of the protected brush method varies (54%-85%) and its specificity is quite high (over 85%), but both parameters are influenced by prior antibiotic therapy, such that performing the test 12 hours after initiation of antibiotic therapy may have a negative influence on the number of microorganisms isolated and the percentage of positive results obtained with this technique (level II evidence).[77]

In BAL, the cutoff point for the diagnosis of bacterial pneumonia is 10^4 colony forming units per milliliter; the results obtained with this technique correlate highly with diagnosis based on protected brush catheter specimens and histologic examination of the lung.[78] Because the presence of 5% or more intracellular microorganisms is predictive of positive results in quantitative cultures, it is a very specific marker of bacterial infection. Consequently, the use of this technique is recommended whenever BAL is performed.[78]

BAL appears to be the diagnostic technique of choice in cases of slowly evolving CAP because it facilitates the diagnosis of unsuspected infections with a greater degree of probability than other techniques.[58] In cases of CAP that do not respond to empiric antibiotic treatment, samples should be obtained using the protected specimen brush and BAL before modifying treatment so as not to obfuscate the presence of unusual, resistant or persistent pathogens.

Prediction Rules and the Admission Decision

The severity of CAP is initially assessed on the basis of prognostic factors to decide the most appropriate care setting—outpatient treatment, hospitalization, or ICU—and to identify the most appropriate empiric antibiotic treatment. A series of risk factors associated with increased morbidity and mortality were identified using a classic meta-analysis. These factors can be grouped as follows: *a)* patient-dependent factors, such as age and comorbidity; and *b)* factors related to the CAP episode, such as clinical, analytical, and radiographic findings.[6] Since no single prognostic factor is capable of predicting death with sufficient

TABLE 5
Risk Stratification (Fine's Rule)

Scoring of Each Variable to Predict Early Death	
Characteristic	**Score**
Age: Men Number of Years	
Women Number of Years –10	
Nursing home resident	+10
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cardiovascular disease	+10
Renal disease	+10
Altered mental status	+20
Respiratory rate ≥30/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35ºC or ≥40ºC	+15
Pulse rate ≥125/min	+10
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg/dL	+20
Sodium <130 mmol/L	+20
Glucose ≥250 mg/dL	+10
Hematocrit <30%	+10
PaO_2 <60 mm Hg	+10
Pleural effusion	+10

Fine Risk Class	Score	Death at 30 Days%
Class I	If <50 years and not suffering from cancer, heart failure, cerebrovascular, liver or kidney disease	0.1
Class II	<70	0.6
Class III	71-90	0.9-2.8
Class IV	91-130	8.2-9.3
Class V	>130	27-29.2

sensitivity or specificity, multivariate analysis is used. Such analysis makes it possible to identify independent risk factors with predictive value.[79]

In the past decade, various authors have devised prediction rules for estimating the risk of death in patients with CAP. These rules were developed to deal with the 2 objectives fundamental to the management of patients with CAP: *a)* to identify patients at low risk for death, who may be suitable for outpatient treatment; and *b)* to recognize patients at high risk for death, who must be hospitalized.[80]

Using models based on multivariate statistical analysis, Fine et al[81] developed a prediction rule that stratifies patients into 5 classes with respect to the risk of death (Fine risk class or pneumonia severity index). This rule was derived from data on 14199 patients with CAP included in a series of studies in the United States of America, and it was independently validated in a different cohort of patients (the Pneumonia Patient Outcomes Research Team study). Fine's rule predicts mortality by assigning points to each case based on 20 variables. Patients are stratified into 5 classes on the basis of the resulting score (Table 5): classes I to III (patients at low risk of death, 0.1%-2.8%), Class IV (risk of death between 8.2%-9.3%), and class V (high risk of death, 27%-31%). Because it identifies patients with a risk of death under 3% (classes I-III), this rule has become a tool used to decide when outpatient treatment is appropriate. Patients who fall into classes I and II receive outpatient treatment, patients in class III require brief inpatient observation, and patients classified as class IV and V are hospitalized.[81]

When applied to different populations, this rule has been shown to predict the risk of death very accurately, particularly in patients over 65 years old, although its ability to predict hospitalization is weaker. One of the foremost limitations of Fine's rule is that the score is based on 20 variables, some of which can only be obtained using analytical techniques solely available in hospitals. Another disadvantage is that it may underestimate the severity of disease in young patients. Moreover, this rule does not take into account social factors or the patient's personal circumstances, which may be important when deciding whether hospitalization is necessary or not.

Prospective studies undertaken to verify the usefulness of Fine's rule in the admission decision have shown that its use reduces the proportion of admissions in the low risk classes, but increases the proportion of readmissions at 4 weeks.[82,83]

The reasons for hospitalization of patients who fall into the low risk classes are numerous. One observational study concluded that Fine's pneumonia severity index has a low positive predictive value as an indicator for inappropriate hospitalization because it does not adequately detect the severity of comorbid diseases and the patient's social circumstances in the case of nonsevere CAP[84] (of the patients in the lower risk classes in whom admission was justified, 43% required hospitalization owing to social factors, 18% owing to their inability to take oral medication, 14% because of prior treatment failure, and 9% owing to suspected sepsis). In Spain, respiratory insufficiency and pleural complications have been reported as common motives for hospital admission and for longer hospital stays in patients with CAP who fall into the lower Fine risk classes.[15,85] After validation of Fine's prediction rule, a proposal was made to include additional factors in order to improve its predictive value with respect to hospital admission.[86] It has, in fact, been reported that up to 27% of patients admitted to ICUs with CAP have a low-risk pneumonia severity index (I-III).[87]

The British Thoracic Society developed a predictive rule, called CURB-65, based on 4 variables and the patient's age, which was subsequently further simplified. The name CURB-65 is an acronym of the 5 variables: confusion, urea (>7 mmol/L), respiratory rate (≥30/min), blood pressure (diastolic ≤60 mm Hg or systolic ≤90), and age (≥65 years).[88] Derived from a cohort study of 1068 patients, CURB-65 accurately stratifies patients with respect to the risk of death. The British Thoracic Society guidelines recommend that the patient's level of confusion be evaluated using a test comprising 10 questions or, more simply, by evaluating the outward signs of disorientation in person, place, or time. The final CURB-65 score, which ranges between 0 and 5, is

calculated by adding 1 point for each variable present. The risk of death associated with each score in the derivation cohort was as follows: 0 = 0.7%, 1 = 2.1%, 2 = 9.2%, 3 = 14.5%, and 4 = 40%. Hospitalization is recommended when a patient scores 1 or higher, especially in the presence of other indicators of severity, such as hypoxemia or multilobar pneumonia. The same study validated a simplified rule excluding the urea value for use in the primary care setting (called CRB-65). The scoring in CRB-65 ranges from 0 to 4, and the risk of death associated with each score was as follows: 0 = 1.2%, 1 to 2 = 8.5%, and 3 to 4 = 31%.[88]

Since, on the basis of the information currently available, no predictive rule delivers conclusive predictive values establishing risk of death, the physician's clinical judgment must take precedence in the hospitalization decision, and this decision should be taken on a case-by-case basis. In general, Fine's pneumonia severity index is considered to be more useful for detecting patients at low risk for death, and the CURB-65 rule for detecting patients at high risk.

The most recent guidelines issued by the Infectious Diseases Society of America define a 3-step process for deciding the initial site of treatment for patients with CAP.[43] The first step is to assess any preexisting conditions that might compromise the safety of home care, including respiratory insufficiency, social or psychiatric problems, substance abuse, and inability to take oral medications. The second step, after such conditions have been ruled out, is to calculate the Fine risk class. The third step involves clinical judgment in order to individualize the application of the Fine risk class on a case-by-case basis. Today, the new options that have emerged for the care of patients with CAP should also be evaluated, including home hospitalization, day hospitals, and admission to an observation unit. No studies have been undertaken specifically to evaluate these options.

The adoption of standardized criteria for the referral of patients with CAP to the ICU is difficult and depends on various factors. The considerable variation between hospitals in the percentage of patients with CAP admitted to the ICU (8.8%-26%) highlights the difficulty of standardizing such criteria.[87] Clinical assessment of severity is difficult, there is a tendency to underestimate severity,[80] and no clear definition of severe CAP exists. The criteria for use of mechanical ventilation are more homogeneous and reflect the severity of the patient's condition rather than any variability between hospitals.[87]

SEPAR's initial guidelines considered admission to the ICU in the presence of 1 or more of the following 6 complications: severe respiratory insufficiency, hemodynamic instability, renal failure requiring dialysis, disseminated intravascular coagulation, meningitis, or coma (level III evidence).[45] The earlier guidelines of the American and British Thoracic Societies and Fine's pneumonia severity index propose various criteria for admission to the ICU, but their ability to discriminate is low.[89] In order to improve these criteria one study proposed using a rule based on 5 factors classified as 2 major criteria (need for mechanical ventilation and presence of septic shock) and 3 minor criteria (systolic pressure <90 mm Hg, multilobar involvement, and ratio of PaO_2 to the fraction of inspired oxygen <250). The presence of 1 major or 2 or 3 minor criteria would be an indication for referral to the ICU. This modification increased specificity to 94% while maintaining sensitivity at 78%.[90] While the predictive value of this formula is still relatively low,[87] it is an improvement over the results obtained with the earlier American and British guidelines and the pneumonia severity index. The British CURB-65 severity score can also be used to decide on admission to the ICU when the score is greater than 3. Its validation in cases of severe CAP, defined as the presence of 2 or more of the clinical features reflected in the acronym, has a sensitivity of 82% and a specificity of 73% for the prediction of death or need for intensive care.[91,92]

The impact of comorbid diseases in cases of CAP treated in the ICU is poorly understood. It has been reported that the presence of neoplastic, neurological, or cardiac disease may be the cause of death in up to 47% of patients with severe CAP.[93] COPD only has a significant impact on mortality in severe CAP when it is associated with home oxygen therapy. However, other factors, such as the extent of the lung injury, nonpulmonary organ system failure, immunosuppression, and very advanced age, do have a significant impact.[94]

In cases of severe CAP, the availability of intermediate care units and the use of noninvasive mechanical ventilation may influence the decision on initial site of care because they represent more economical therapeutic options associated with lower levels of nosocomial infection.

Treatment of CAP

Antimicrobial treatment for patients with CAP is prescribed empirically after evaluation of the severity of the case, the most likely etiology, and the prevalence of resistant strains among the microorganisms most commonly found in our area.[95] Taking these factors into account, the clinician chooses the most appropriate empiric treatment targeting the microorganisms most probably involved (level II and III evidence). According to the most recent studies, some 35% to 50% of strains of *S pneumoniae* in Spain have reduced resistance to penicillin, while high-level resistance has decreased. The presence of the following factors is indicative of an increased risk of pneumococci with reduced sensitivity to beta-lactam antibiotics: age over 65 years, chronic lung disease, alcoholism, immunodeficiency, multiple comorbidity, contact with children in crèches, hospitalization, and treatment with beta-lactam antibiotics in the preceding 3 months. The prevalence of macrolide resistance is between 25% and 40% in Spain.[42,96,97] Two types of macrolide resistance have been

described: high-level resistance (minimum inhibitory dose of erythromycin 16 µg/mL or higher) caused by alterations to the ribosomal RNA, affecting all macrolides, and insensitive to dose increases; and low-level resistance (minimum inhibitory dose of between 1 and 8 µg/mL) mediated by an increase in the activity of the cytoplasmic efflux pump and confined to 14- and 15-membered macrolides. This low-level macrolide resistance is less common in Spain and can be overcome by dose increases.[42,96,97] Numerous factors that indicate possible pneumococcal resistance to fluoroquinolones have been described: the presence of COPD, nosocomial infection, residence in a nursing or retirement home, and prior treatment with fluoroquinolones.[98-100] Empiric monotherapy with fluoroquinolones should be avoided in immunodeficient patients who have been treated with these antibiotics in the preceding 4 months.[101]

Given the lack of any randomized trials of large numbers of patients with CAP treated with the different antibiotics available, there is scant evidence on which to base recommendations concerning antimicrobial treatment. In all cases, antibiotic therapy must be started early, not more than 4 hours after CAP is diagnosed. This strategy reduces both mortality and the length of stay in hospital (level II evidence).[43,102,103] In addition, the patient's clinical condition must be reassessed within 24 to 48 hours of initiating antibiotic treatment.

Group 1 patients have mild CAP and can therefore be treated as outpatients. The clinical picture in group 1 patients is not severe, and the main focus of antimicrobial treatment should be to treat the pneumococcus. Given the increase in the prevalence of strains of *S pneumoniae* with reduced sensitivity to penicillin and the macrolides and the need in many cases to cover atypical pathogens (in young patients, certain epidemic situations, and cases where the clinical signs and symptoms are highly suggestive), the recommended treatment for patients in this group is telithromycin 800 mg/day or else one of the new fluoroquinolones, such as levofloxacin 500 mg/day or moxifloxacin 400 mg/day, taken orally. Another possible option is high doses of oral amoxicillin (at least 1 g every 8 hours)—a regimen effective against most pneumococcal strains having reduced sensitivity to beta-lactam antibiotics—plus a macrolide, such as oral azithromycin 500 mg daily or oral clarithromycin 500 mg every 12 hours. In view of the high incidence of macrolide-resistant pneumococci in Spain and the predominant mechanism of resistance, monotherapy with macrolides should not be prescribed.

A subset of group 1 patients are suitable for outpatient management despite having concurrent chronic diseases or other risk factors for atypical etiology *(H influenzae,* enterobacteria). In such cases, the first line treatment is single-drug therapy with an oral fluoroquinolone providing effective pneumococcal cover (levofloxacin or moxifloxacin). Amoxicillin-clavulanic acid could be used as an alternative treatment, always bearing in mind its lack of activity against atypical microorganisms.

Group 2 patients are those who have been hospitalized for clinical reasons. In this group, *S pneumoniae* is still the most common causative pathogen, but there is a high probability that the patient will have factors associated with an increased risk of antibiotic-resistant pneumococci or enteric gram-negative bacilli (prior cardiopulmonary disease or other associated diseases, antibiotic therapy during the preceding 3 months). Atypical pathogens including *Legionella* organisms may be involved in approximately 20% of pneumonias in which the etiology is established. In these circumstances, therefore, initial empiric treatment should include 1 of the following regimens: a third-generation cephalosporin (cefotaxime 1 g/6 h or ceftriaxone 1-2 g/24 h, administered intravenously); or amoxicillin-clavulanic acid 1000/200 mg/8 h in combination with a macrolide, both administered intravenously. The combination of a macrolide with amoxicillin clavulanic acid 2000/125 mg/12 h can be used to treat many patients. If the urinary antigen test for *L pneumophila* is negative, the macrolide may be omitted and the patient treated with beta-lactam antibiotics alone. However, it has been suggested that the combination of a beta-lactam with a macrolide is more effective than monotherapy with a beta-lactam alone because it reduces mortality in patients with CAP, especially those with bacteremia.[104-106] This is a controversial hypothesis, and randomized studies are

TABLE 6
Empiric Antibiotic Treatment of Community-Acquired Pneumonia

Group 1
Telithromycin: 7-10 days
Moxifloxacin or levofloxacin 7-10 days*
Alternative: amoxicillin + macrolides (amoxicillin 10 days; azithromycin 3-5 days or clarithromycin 10 days) (all administered orally)
Group 2
Combined therapy: third-generation cephalosporins (cefotaxime or ceftriaxone) or amoxicillin-clavulanic acid + a macrolide (azithromycin or clarithromycin):
Monotherapy: levofloxacin
All administered intravenously at outset
Duration of treatment: 10 to 14 days
Group 3
High intravenous doses of a non-antipseudomonal cephalosporin (cefotaxime, ceftriaxone) + a macrolide (intravenous azithromycin or clarithromycin) or intravenous levofloxacin
Duration of treatment: 10 to 14 days
Suspected aspiration
Intravenous amoxicillin-clavulanic acid (2 g dose of amoxicillin) 14 days
Alternative: moxifloxacin, ertapenem, or clindamycin + third-generation cephalosporin
In cases with cavitation, treatment should be maintained until radiographic resolution has been confirmed
Suspected *Pseudomonas aeruginosa*
Intravenous piperacillin-tazobactam, cefepime, or carbapenem (imipenem or meropenem) + intravenous ciprofloxacin or levofloxacin, or else + an aminoglycoside: intravenous tobramycin or amikacin
Duration of treatment: 14 days

*In patients with comorbid diseases or recent antibiotic therapy.

TABLE 7
Doses and Routes of Administration for Antibiotic Treatment in Community-Acquired Pneumonia*

Drug	Administration	Dose
Amikacin	IV	15 mg/kg/24 h
Amoxicillin-clavulanic acid	Oral	875/125 mg/8 h
Amoxicillin-clavulanic acid	Oral	2000/125 mg/12 h
Amoxicillin-clavulanic acid	IV	1000-2000/200 mg/8 h
Azithromycin	Oral-IV	500 mg/24 h
Cefepime	IV	2 g/12 h
Cefotaxime	IV	1-2 g/8 h
Ceftriaxone	IV	1-2 g/24 h
Cefuroxime axetil	Oral	500 mg/8 h
Ciprofloxacin	Oral	500-750 mg/12 h
Ciprofloxacin	IV	400 mg/8-12 h†
Clarithromycin	Oral	1000 mg/24 h
Clarithromycin	IV	500 mg/12 h
Clindamycin	Oral	300 mg/8 h
Clindamycin	IV	600 mg/8 h
Ertapenem	IV	1 g/24 h
Imipenem	IV	1 g/8 h
Levofloxacin	Oral	500 mg/24 h‡
Levofloxacin	IV	500 mg/12 or 24 h§
Meropenem	IV	1 g/8 h
Moxifloxacin	Oral	400 mg/24 h
Piperacillin-tazobactam	IV	4-0.5 g/6-8 h
Telithromycin	Oral	800 mg/24 h
Tobramycin	IV	6 mg/kg/24 h

*IV indicates intravenous.
†When infection is caused by an organism with a minimum inhibitory concentration of >0.5 mg/L, the antibiotic should be administered every 8 hours to prevent the selection of resistant strains.
‡Initial dose 1000 mg.
§750 mg vials will soon be commercially available in Spain: doses of 750 mg/24 h.

necessary to clarify the situation (level II evidence). Another, equally valid, treatment option could be to use an antipneumococcal fluoroquinolone, such as levofloxacin or moxifloxacin (level II evidence).[107-109] The fact that this regimen has been reported to be associated with a lower risk of treatment failure justifies its use in cases of this kind.[110]

Patients who present with very severe CAP and require admission to the ICU (group 3) are a more selected and homogeneous group. They should be treated with high doses of a third-generation cephalosporin (cefotaxime 2 g/6-8 h or ceftriaxone 2 g/24 h, administered intravenously), always in combination with a macrolide (clarithromycin 500 mg/12 h or azithromycin 500 mg/day, administered intravenously) or an antipneumococcal fluoroquinolone (intravenous levofloxacin 500 mg/day).

In cases with risk factors for infection with *P aeruginosa* (broad-spectrum antibiotic therapy for more than 7 days in the preceding month, the presence of bronchiectasis, malnutrition, or diseases and treatments associated with neutrophil dysfunction),[31] the patient must be treated with combined therapy including effective coverage against *P aeruginosa*, *Legionella* species, and potentially resistant *S pneumoniae*. This can be achieved with a fourth-generation cephalosporin (cefepime 1-2 g/12 h), piperacillin-tazobactam (4000/500 mg/8 h), imipenem or meropenem (0.5-1 g/68 h) in combination with a fluoroquinolone (ciprofloxacin 400 mg/8 h or levofloxacin 500 mg/12 h), all administered intravenously. Some authors suggest that the carbapenem-fluoroquinolone combination should be avoided because of the potential risk of acquired cross-resistance.[111] The combination of a beta-lactam with an aminoglycoside (preferably tobramycin or amikacin) is another alternative; in this regimen, the synergistic effect of the 2 antibiotics compensates for the poor pulmonary penetration of the aminoglycosides.

When infection with anaerobic microorganisms is suspected (necrosis or cavitation on chest radiography or suspected aspiration), amoxicillin-clavulanic acid should be administered (with high doses of amoxicillin, 2 g). The other alternatives are clindamycin plus a third-generation cephalosporin or else single-drug therapy with ertapenem or moxifloxacin. If admission to the ICU is necessary, the cephalosporin should be replaced by a combination of piperacillin and tazobactam.

Tables 6 and 7 show the recommended doses and treatment regimens.

An early switch from initial parenteral treatment to oral treatment (switch therapy) in the antimicrobial treatment of patients with CAP can play an important role in reducing mean length of stay in hospital and cost of treatment, without compromising the patients' safety. When switch therapy is indicated, the minimum duration of empiric parenteral antimicrobial therapy should be 2 to 4 days, the time required to stabilize the patient's condition in most cases.[112-114] The criteria for using switch therapy are ability to take oral medication, absence of fever (<37.8°C), improvement or resolution of the signs and symptoms of pneumonia, hemodynamic stability, and absence of mental confusion or unstable comorbidities, septic metastasis, or other active infections (level II evidence).[112,113,115] Patients may be discharged from hospital 24 hours after they are clinically stable.

The optimum duration of antibiotic treatment is difficult to establish. Cases of CAP are usually treated for 10 to 14 days, although shorter regimens (5 to 7 days) have been tried with the new antibiotics that have a longer mean half-life in an attempt to achieve similar clinical and bacteriologic results with a lower drug consumption. This would favor improved patient adherence and facilitate the reduction of resistance (level III evidence).[116,117] Given the lack of studies recommending shorter treatments, the duration of antibiotic therapy should be between 10 and 14 days in hospitalized patients and between 7 and 10 days in ambulatory patients.[118] In general, duration of treatment is also conditioned by the severity of the patient's condition, the presence of underlying disease or bacteremia, the course of the disease, and the causative pathogen. It should never be less than 14 days in cases of CAP caused by *L pneumophila*, *S aureus*, or *P aeruginosa*, and may extend to up to 4 weeks in patients with pulmonary cavitation and suspected infection with anaerobic microorganisms (level II evidence).[112]

The general measures that should be undertaken in all patients with CAP include rest, abundant liquids to maintain correct hydration levels, antipyretic medication to reduce fever, and analgesics if there is chest pain. Other support measures that may be necessary in patients with severe CAP include oxygen therapy (to maintain arterial oxygen saturation at ≥90% and PaO_2 at ≥60 mm Hg), mechanical ventilation in the event of acute respiratory insufficiency, and replacement of liquids and/or pressor amines to maintain proper blood pressure.

In severe cases of CAP, noninvasive mechanical ventilation has been shown to improve respiratory insufficiency and to reduce the rate of orotracheal intubation and the length of stay in the ICU, although this therapeutic benefit only occurred in the subgroup of patients with COPD (level I evidence).[119] Other studies have found that, although noninvasive mechanical ventilation initially improves oxygenation in severe CAP, subsequent intubation is required in 66% of patients (level III evidence).[120]

In view of the large number of complications and the poor prognosis associated with orotracheal intubation in patients with COPD who have severe CAP, noninvasive mechanical ventilation should be tried initially. In patients with severe CAP who develop hypoxemic respiratory insufficiency, noninvasive mechanical ventilation is associated with a significant reduction in the need for endotracheal intubation and mortality at 30 days when compared to initial oxygen therapy delivering high inspired fractions of oxygen. An initial therapeutic test with noninvasive mechanical ventilation with strict monitoring of failure indicators is, therefore, recommended.[121,122] High risk patients should be carefully assessed on admission using any of the prediction rules, and should be reevaluated frequently to ensure early detection of any deterioration in clinical or oximetric parameters. The need to increase the fraction of inspired oxygen, any alteration in the patient's mental state, and respiratory or metabolic acidosis are all indicators of the need for intensive care in such patients.

Nonresolving CAP

Between 10% and 25% of patients with CAP do not respond to treatment. This group includes cases where improvement in the general clinical picture is delayed or does not occur as well as patients whose condition continues to deteriorate despite antimicrobial treatment.[55] The causes of this lack of response are diverse (Table 8).[123,124]

The case must be reevaluated if a patient does not respond to treatment including a thorough revision of the medical history. A new bacteriologic study should be performed using noninvasive and even invasive techniques (via flexible bronchoscope), and this should be complemented by other techniques, such as chest computed tomography, which may play a key role in determining what changes should be made in antibiotic treatment (level III evidence).

TABLE 8
Causes of Failure to Respond to Empiric Treatment in Community Acquired Pneumonia

Inappropriate or ineffective treatment
Pathogens not covered by or resistant to antimicrobial treatment*
Uncommon pathogens (fungi, parasites, mycobacteria)
Inappropriate duration, dosage, or route of administration
Patient nonadherence to treatment
Alteration in defense mechanisms
Local. Recurrent pneumonia†
Systemic immunodeficiency
Presence of complications
Empyema
Distant septic foci‡
Phlebitis or catheter infections
Drug fever
Nosocomial pneumonia
Other noninfectious complications§
Incorrect diagnosis‖
Pulmonary embolism. Pulmonary infarct
Lung cancer or metastases
Acute pulmonary edema
Pulmonary hemorrhage
Eosinophilic pneumonia
Hypersensitivity pneumonitis
Acute interstitial pneumonitis
Pulmonary vasculitis
Cryptogenic organizing pneumonia
Pulmonary sequestration
Foreign body

*Consider atypical microorganisms if these are not covered. Many of the regimens proposed do not provide adequate cover for Staphylococcus aureus. In some regions, the incidence of beta-lactamase producing strains of Haemophilus influenzae can be over 30%. Other pathogens may develop resistance in the course of treatment.
†Recurrent pneumonia is defined as pneumonia that recurs after an asymptomatic period and after radiographic resolution. It mainly affects patients with COPD, bronchiectasis, heart disease, cystic fibrosis, and immunodeficiency. If the pneumonia always affects the same lobe, the presence of a bronchial obstruction should be investigated.
‡Meningitis, septic arthritis, pericarditis, endocarditis.
§Renal failure, heart failure, acute respiratory distress syndrome, etc.
‖Differential diagnosis.

Prevention of CAP

CAP can be prevented by combating the pathogens that cause the disease (the prototype of this strategy being specific vaccination against *S pneumoniae*) and by trying to eliminate the risk factors that favor its occurrence (by way of influenza vaccination and antismoking campaigns).

Pneumococcal Vaccination

Two kinds of pneumococcal vaccinations are currently in use: *a)* the 23-valent polysaccharide vaccination, which contains purified capsular polysaccharide antigens of the 23 serotypes that cause 85% to 96% of pneumococcal infections in children and adults[125] and is effective in preventing invasive pneumococcal infection (bacteremia, meningitis, and infection of any sterile site) caused by these 23 serotypes; and *b)* the heptavalent conjugate vaccine, which protects against the 7 serotypes that cause most cases of otitis media, pneumonia, and meningitis in children.

Antipneumococcal vaccination provokes a humoral response that decreases 5 to 10 years after vaccination. Its administration causes mild local reactions in 50% of cases and fever very occasionally.

Criteria for Using the 23-Valent Polysaccharide Vaccination

1. Age over 65 years
2. People aged between 2 and 65 years:
– Chronic pulmonary or cardiac disease
– Diabetes mellitus
– Alcoholism, chronic liver disease
– Functional or anatomic asplenia

3. Immunodeficient patients aged 2 years and over:
– HIV infection
– Congenital immunodeficiency
– Nephrotic syndrome and renal failure
– Immunosuppressant therapy (including transplant patients)

Criteria for Using the Conjugate Vaccination

1. Age: under 23 months
2. People between 24 and 59 years old:
– Sickle cell anemia, congenital or acquired asplenia, splenic dysfunction
– HIV Infection
– Situations of immunosuppression:
– Congenital immunodeficiency
– Nephrotic syndrome and renal failure
– Immunosuppressant therapy (including transplant patients)
– Chronic diseases (cardiac, pulmonary, and diabetes mellitus)

The 23-valent polysaccharide vaccination should not be administered to patients with acute pneumococcal infection, and neither is it recommended during pregnancy or breast-feeding. It is less effective in patients with a deficient immune system, although some scientific associations recommend its use in such cases, and even advise revaccination after 5 years. People over 65 should be administered a second dose of vaccine if they received their primary vaccination during the previous 5 years and were under 65 years old at that time, although a second dose within 3 years of primary vaccination is formally contraindicated because of the possibility that severe reactions could occur because of the high circulating levels of antibodies (level III evidence). Revaccination is not recommended under other circumstances except in the case of patients aged over 10 with asplenia. The antipneumococcal vaccination can be administered concurrently with other vaccinations, such as the influenza vaccination, but a different site should be used (level I evidence).[126,127]

Influenza Vaccination

In Spain, the influenza epidemic occurs during the winter months. It affects 1% to 5% of the population and 40% to 50% of people over 65. Vaccination against influenza has been shown to be effective in preventing or attenuating viral disease in both older and younger people. Its efficacy depends on the similarity between the circulating virus sequence and that of the vaccination administered, and it can prevent the disease in 70% to 90% of healthy people under 65.[128,129] Although its efficacy is lower in older people and patients with chronic debilitating diseases, the vaccination can still attenuate disease caused by the influenza virus in such patients, reducing the incidence of lower respiratory tract infections and of the complications and mortality associated with influenza infection.

Recommendations for Priority Influenza Vaccination[130]

1. Population at high risk for complications:
– Age: ≥65 years
– Adults and children with pulmonary or cardiovascular diseases including asthma
– Residents of closed institutions
– Adults and children monitored or hospitalized during the previous year because of chronic metabolic diseases (including diabetes mellitus), renal failure, hemoglobinopathies, or deficient immune status (including immunodeficiency caused by drugs or HIV)
– Children and adolescents (6 months-18 years) treated for extended periods with acetylsalicylic acid (in order to prevent the development of Reye's syndrome).
– Pregnant women who will be in their second or third trimester during the influenza season
– Children between 6 and 23 months

2. Population at risk of transmitting influenza to people at high risk:
– Health-care personnel in contact with patients
– People working in geriatric nursing homes and people taking care of patients with chronic diseases
– People working in residential facilities and shelters with people at high risk
– Workers providing home help to people at high risk.
– Individuals (including children) who live with people at high risk
– People living with children aged under 24 months

3. People who provide special services to the community or are in direct contact with the population:
– Shop assistants and cashiers in public establishments
– Tour guides
– Students

There are 2 kinds of influenza vaccinations. The inactivated vaccine, which contains dead viruses, is administered by intramuscular injection and can be used in all persons over 6 months old, including both the healthy population and people suffering from chronic diseases. The attenuated vaccine, which contains live viruses capable of reproduction, is administered intranasally, is more expensive, and has only been approved for the healthy population aged between 5 and 49 years including people in direct contact with the

high-risk population. This attenuated vaccine should not be administered to people with a history of Guillain-Barré syndrome, or to children or adolescents receiving long term treatment with acetylsalicylic acid, pregnant women, or people allergic to egg protein.

Concern about possible adverse events has limited the use of the influenza vaccination in some patients, although the inactivated vaccine does not contain live viruses and cannot, therefore, cause influenza infection. The local reactions are slight, usually only lasting about 24 hours. However, fever, malaise and myalgia may occur between 6 and 12 hours after vaccination.[131] On rare occasions, immediate allergic reactions have occurred in patients with hypersensitivity to eggs. The most feared adverse event, Guillain-Barré syndrome, was only associated with the vaccination given in 1976.[132]

Antismoking Campaigns

Smoking is the principal risk factor for invasive disease caused by *S pneumoniae* in young people.[36] Furthermore, it increases the risk of CAP and the incidence and severity of pneumonias caused by chickenpox and *Legionella* organisms.[37,133] The risk of developing CAP decreases by 50% in the 5 years after a smoker gives up the habit (level I evidence).

Summary of the Recommendations

Epidemiology

The incidence in Spain of CAP in adults is between 1.6 and 1.8 episodes per 1000 population per year. It is more predominant in the winter months, and tends to be more common in older males (level II evidence).

The percentage of patients with CAP who are hospitalized is very variable (22%-61%). Approximately 9% of CAP patients are admitted to the ICU.

Overall mortality attributable to CAP has been estimated to be around 14%, varying between 37% of the patients admitted to the ICU and 2% of those treated as outpatients.

The etiology of the CAP episode is established in 40% to 60% of cases.

The most common causative agent in patients managed outside the hospital (group 1) is *S pneumoniae,* followed by *M pneumoniae* (Table 1).

S pneumoniae is also the most common pathogen in patients hospitalized with CAP (group 2), although *M pneumoniae, H influenzae*, gram-negative bacilli, and *Legionella* species are also common in this group (Table 1).

In most patients with CAP admitted to the ICU (group 3), the causative microorganisms are *S pneumoniae* and *Legionella* species. Gram-negative bacilli are also common pathogens in this group (level II evidence) (Table 1).

S pneumoniae is the most common causative agent of CAP in people over 65 in Spain, followed at a considerable distance by *H influenzae* and *L pneumophila* (level II evidence).

In cases of CAP affecting patients with COPD, the pathogens most often isolated are *S pneumoniae, C pneumoniae,* and *H influenzae* (level II evidence). *P aeruginosa* should also be considered (level II evidence) in patients with severe COPD and comorbid bronchiectasis .

Smokers are 4 times more likely to suffer from an invasive pneumococcal disease than nonsmokers.

Diagnosis

The syndromic diagnosis of CAP is based on the presence of the signs and symptoms of an acute infection associated with a recent pulmonary radiographic infiltrate unexplained by other processes (level III evidence).

A complete blood count, routine biochemistry, and pulse oximetry or arterial blood gas analysis should be performed for all patients with pneumonia who come to a hospital in order to assess severity and evaluate the need for hospitalization (level III evidence).

Posteroanterior and lateral chest radiographs should be obtained for hospitalized patients with CAP and ambulatory patients when no clinical improvement is observed after 48 hours of empiric treatment (level III evidence).

Bilateral or multilobar (>2 lobes) radiographic involvement and pleural effusion are indicators of severe disease (level III evidence).

Radiographic cure often lags behind clinical cure and may sometimes take more than 8 weeks longer. While it is not necessary to obtain chest radiographs before discharging the patient from hospital, it is essential to obtain radiographic confirmation of cure.

Etiologic Diagnosis (Table 4)

In general, the more severe the case of CAP, the more techniques should be used to obtain an etiologic diagnosis. Few or no tests are necessary in cases of mild CAP (level III evidence). Start of antimicrobial therapy should never be delayed in order to obtain a reliable sample for etiologic diagnosis.

Gram stain and culture of recent sputum (under 30 minutes old) is recommended for all patients hospitalized with CAP, especially if the presence of a resistant or atypical microorganism is suspected (level II evidence).

In severe cases of CAP, 2 serial blood cultures should be performed. If positive, the results of these tests will be of etiologic and prognostic value (level II evidence).

It is considered reasonable to test for pneumococcal urinary antigens in cases of CAP requiring hospitalization (level II evidence).

Urine should be tested for *Legionella* organisms in the following cases: hospitalized patients with enigmatic CAP after sputum Gram stain and/or pneumococcal urinary antigen assay, patients fulfilling severity criteria, those who do not respond to beta-lactam antibiotic therapy, and all cases coinciding with a suspected epidemic outbreak of Legionnaires' disease in the community.

Serological testing or polymerase chain reaction of specimens obtained using noninvasive methods is not recommended in routine clinical practice (level III evidence).

The use of invasive techniques to obtain an etiologic diagnosis in CAP is only indicated in patients whose condition deteriorates rapidly or fails to respond to initial empiric antibiotic treatment.

Prediction Rules and the Admission Decision

Fine's rule is more useful for detecting patients with CAP at low risk for death.

Recommendations on the Site-of-Care Decision (Outpatient or Hospital Care)

1. Rule out the presence of any conditions that indicate severity or could represent an obstacle to home treatment, including instability of associated diseases, hemodynamic instability, respiratory insufficiency, pleural effusion, and inability to take oral medications. Evaluate the social circumstances and any social problems, such as substance abuse or psychiatric problems, that might compromise adherence to treatment (level II evidence).

2. Calculate a predictive score. Patients classified as Fine group I or II may be sent home. Hospitalization for observation should be considered in patients classified as Fine group III. Patients classified as Fine group IV or V should be admitted to hospital. In non-hospital clinical settings, the CRB-65 rule should be used to determine the need for hospitalization—a score of more than 1 (level II evidence).

Criteria for Admission to the ICU

1. Septic shock or need for mechanical ventilation (level III evidence).

2. The presence of 2 of the following criteria: systolic blood pressure <90 mm Hg, ratio of PaO_2 to the fraction of inspired oxygen <250 (level II evidence).

3. Score >3 on the CURB-65 scale (level II evidence).

Treatment

Initial antibiotic therapy for patients with CAP is established empirically after assessing severity, most likely etiology, and the prevalence of the most common microorganisms in the geographical area.

The incidence in Spain of *S pneumoniae* with decreased sensitivity to penicillin is between 35% and 50%; high-level resistance has decreased. Macrolide resistance ranges from 25% to 40%, is predominantly high-level resistance, affects all the macrolides, and is unresponsive to dose increases.

Antibiotic treatment should be started as early as possible (within 4 hours of CAP diagnosis) because this strategy has been shown to reduce mortality and length of stay in hospital (level II evidence).

The patient's clinical condition should be reevaluated 24 to 48 hours after start of antibiotic therapy.

In patients with CAP managed outside the hospital, the fundamental aim of antibiotic treatment should be to treat *S pneumoniae* (Tables 6 and 7). This outpatient group includes a subgroup of patients with chronic comorbid diseases or other risk factors for atypical pathogens. Such patients require specific treatment (Tables 6 and 7).

In patients hospitalized with CAP, *S pneumoniae* must be treated because it is the most common pathogen, but physicians should also bear in mind the higher risk among hospitalized patients of having CAP caused by resistant pneumococci, gram-negative enteric bacilli, and atypical pathogens including *Legionella* species (Tables 6 and 7).

Patients with CAP requiring admission to the ICU should be treated with high doses of a third-generation cephalosporin plus a macrolide or an antipneumococcal fluoroquinolone (Tables 6 and 7).

CAP patients with risk factors for infection by *P aeruginosa* should be treated with a combined therapy effective against this pathogen that also provides coverage against resistant pneumococci and *Legionella* species.

Switch therapy plays an important role in the effort to reduce mean length of stay in hospital and overall cost of treatment without compromising patient safety. The minimum duration of empiric parenteral antimicrobial treatment should be from 2 to 4 days. Patients may be discharged from hospital some 24 hours after they are clinically stable.

Optimum total duration of antibiotic treatment is difficult to establish. In general, it should be maintained for between 7 and 10 days in patients with CAP managed outside the hospital, and from 10 to 14 days in hospitalized patients. Patients with CAP caused by *L pneumophila, S aureus,* or *P aeruginosa* should be treated for at least 14 days, and those who present with pulmonary cavitation and suspected infection with anaerobic microorganisms may require treatment for several weeks (level II evidence).

General measures for the management of CAP include correct hydration, analgesics, antipyretics, support measures such as oxygen therapy and mechanical ventilation in cases of severe respiratory insufficiency, and replacement of fluids and/or pressor amines to maintain adequate blood pressure.

In cases of severe respiratory failure in patients with COPD and severe CAP, noninvasive mechanical ventilation should be tried initially (level I evidence).

When respiratory failure occurs in patients with severe CAP who do not have COPD, noninvasive mechanical ventilation should be started and the evolution of the patient's condition should be monitored closely (level I evidence).

The causes of nonresponding CAP are numerous (Table 8).

Vaccination against influenza has been shown to be effective in preventing or attenuating viral disease in both older and younger people.

The 23-valent antipneumococcal vaccination is effective in preventing invasive pneumococcal disease:

bacteremia, meningitis, or infection of any sterile site. The heptavalent pneumococcal conjugate vaccine protects patients against the 7 serotypes that cause most cases of otitis media, pneumonia, and meningitis in children.

Stopping smoking reduces the risk of CAP by 50% in the 5 years after quitting (level I evidence).

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