

## Brazilian guidelines for community-acquired pneumonia in immunocompetent adults – 2009\*

Diretrizes brasileiras para pneumonia adquirida na comunidade em adultos imunocompetentes – 2009

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### Abstract

Community-acquired pneumonia continues to be the acute infectious disease that has the greatest medical and social impact regarding morbidity and treatment costs. Children and the elderly are more susceptible to severe complications, thereby justifying the fact that the prevention measures adopted have focused on these age brackets. Despite the advances in the knowledge of etiology and physiopathology, as well as the improvement in preliminary clinical and therapeutic methods, various questions merit further investigation. This is due to the clinical, social, demographical and structural diversity, which cannot be fully predicted. Consequently, guidelines are published in order to compile the most recent knowledge in a systematic way and to promote the rational use of that knowledge in medical practice. Therefore, guidelines are not a rigid set of rules that must be followed, but first and foremost a tool to be used in a critical way, bearing in mind the variability of biological and human responses within their individual and social contexts. This document represents the conclusion of a detailed discussion among the members of the Scientific Board and Respiratory Infection Committee of the Brazilian Thoracic Association. The objective of the work group was to present relevant topics in order to update the previous guidelines. We attempted to avoid the repetition of consensual concepts. The principal objective of creating this document was to present a compilation of the recent advances published in the literature and, consequently, to contribute to improving the quality of the medical care provided to immunocompetent adult patients with community-acquired pneumonia.

**Keywords:** Pneumonia; Diagnosis; Epidemiology; Practice guideline; Primary prevention.

### Resumo

A pneumonia adquirida na comunidade mantém-se como a doença infecciosa aguda de maior impacto médico-social quanto à morbidade e a custos relacionados ao tratamento. Os grupos etários mais suscetíveis de complicações graves situam-se entre os extremos de idade, fato que tem justificado a adoção de medidas de prevenção dirigidas a esses estratos populacionais. Apesar do avanço no conhecimento no campo da etiologia e da fisiopatologia, assim como no aperfeiçoamento dos métodos propedêuticos e terapêuticos, inúmeros pontos merecem ainda investigação adicional. Isto se deve à diversidade clínica, social, demográfica e estrutural, que são tópicos que não podem ser previstos em sua totalidade. Dessa forma, a publicação de diretrizes visa agrupar de maneira sistematizada o conhecimento atualizado e propor sua aplicação racional na prática médica. Não se trata, portanto, de uma regra rígida a ser seguida, mas, antes, de uma ferramenta para ser utilizada de forma crítica, tendo em vista a variabilidade da resposta biológica e do ser humano, no seu contexto individual e social. Esta diretriz constitui o resultado de uma discussão ampla entre os membros do Conselho Científico e da Comissão de Infecções Respiratórias da Sociedade Brasileira de Pneumologia e Tisiologia. O grupo de trabalho propôs-se a apresentar tópicos considerados relevantes, visando a uma atualização da diretriz anterior. Evitou-se, tanto quanto possível, uma repetição dos conceitos considerados consensuais. O objetivo principal do documento é a apresentação organizada dos avanços proporcionados pela literatura recente e, desta forma, contribuir para a melhora da assistência ao paciente adulto imunocompetente portador de pneumonia adquirida na comunidade.

**Descritores:** Pneumonia; Diagnóstico; Epidemiologia; Guia de prática clínica; Prevenção primária.

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## Methodology of the guidelines

This is a review and update of the previous guidelines published in 2004 by the Brazilian Thoracic Association. The present document presents certain topics that had not been discussed previously, as well as recently published data, and focuses exclusively on community-acquired pneumonia (CAP) in immunocompetent patients.

At the end of each section of this update are the principal recommendations and respective levels of evidence, according to the current guidelines of the Brazilian Medical Association.

The participants of this edition of 2008 were divided into four work groups. In each group, an editor was responsible for distributing the topics among the members of the group.

- Group I: Definition, incidence, mortality, etiology, diagnostic criteria and radiological diagnosis
- Group II: Diagnostic and complementary tests, etiologic investigation, severity and locale of treatment
- Group III: Treatment, treatment failure and prevention
- Group IV: Severe CAP: adjuvant treatment

### *Levels of evidence*

The present guidelines were based on up-to-date evidence in the literature, classified according to the recommendations of the Brazilian Medical Association (Chart 1). The final work of each group was extensively discussed among the editors and participants of the work groups.

## Definition and clinical manifestations

Pneumonia is an acute infectious disease that is inflammatory, affects the air spaces and is caused by viruses, bacteria or fungi. The term CAP refers to pneumonia acquired outside the hospital environment or special health care units, or to pneumonia that manifests within the first 48 h after admission to a health care facility.<sup>(1)</sup> However, there is a special group of pneumonia patients (those who were hospitalized for 48 h or more in the 90 days preceding the disease; those residing in nursing homes or other health care facilities; those who received intravenous antibiotics, chemotherapy or scar treatment in

the 30 days preceding the disease; and those undergoing treatment in dialysis clinics) that are more appropriately classified as having hospital-acquired pneumonia.<sup>(2,3)</sup>

The diagnosis is based on the following: symptoms of acute lower respiratory tract infection (cough and one or more of the following symptoms: expectoration, shortness of breath and chest pain); focal findings on physical examination of the chest; and systemic manifestations (confusion, headache, sweating, chills, myalgia and temperatures higher than 37.8°C). These indications can be corroborated by a chest X-ray finding of new pulmonary opacity. Other clinical conditions can manifest in a similar manner, which can pose difficulties for primary and emergency care physicians in making a diagnosis of CAP. The clinical findings are only moderately accurate and do not allow a diagnosis of CAP to be confirmed or excluded with any degree of certainty. In addition, the heterogeneity of the physical examination conducted by primary and emergency care physicians, as well as the relative lack of experience of such health professionals in comparison with those who specialize in detecting radiological alterations, contributes to the difficulty in diagnosing CAP.<sup>(4,5)</sup>

## Incidence and mortality

Most of the studies of CAP conducted in Brazil have focused on the etiology and treatment of the disease, and official statistics are a valuable source of information regarding the occurrence of CAP.

According to the Hospital Information Service of the Unified Health Care System, pneumonia was the leading non-obstetric cause of disease-related hospitalization in Brazil in 2007, accounting for 733,209 hospitalizations. Among such hospitalizations, there was a predominance of males, as well as greater occurrence between the months of March and July.<sup>(6)</sup>

The rate of hospitalization for pneumonia has decreased over the last decade,<sup>(7)</sup> whereas the rate of in-hospital pneumonia-related mortality has increased, which might be due to various factors, such as hospitalization of patients with pneumonia that was more severe and the aging of the population. The highest rates of hospitalization for pneumonia are observed among

individuals less than 5 years of age and among those over 80 years of age, showing opposite temporal trends: a downward trend among the former and an upward trend among the latter.

Respiratory diseases constitute the fifth leading cause of death in Brazil. Pneumonia is the second most common respiratory disease, causing 35,903 deaths in 2005, 8.4% of which occurred among patients less than 5 years of age and 61% of which occurred among patients over 70 years of age. The pneumonia-related mortality rate increased in the period between 2001 and 2004. In 2005, however, it fell to levels below 20/100,000 population, according to the latest mortality statistics provided by the National Ministry of Health.

The pneumonia-related mortality rate differs among age groups. Over the last 5 years, the rate has increased significantly among patients over 70 years of age, reaching levels above 500/100,000 population among those over 80 years of age. The lowest rates are found in the 5-49 year age bracket (less than 10/100,000 population); among those less than 5 years of age, the mortality rate remains at approximately 17/100,000 population, showing a slight downward trend (Figure 1). These data are similar to those obtained in other Latin American countries such as Chile.<sup>(6)</sup>

**Relevant points**

- Hospitalizations for pneumonia showed a predominance of males and greater occurrence between the months of March and July (level II evidence).
- The rate of hospitalizations for pneumonia has been decreasing since the last decade (level II evidence).
- The rate of in-hospital mortality has increased, which might be due to various factors, such as hospitalization of patients with pneumonia that was more severe and the aging of the population (level IV evidence).
- The pneumonia-related mortality rate differs among age groups and, as in other Latin American countries, has increased over the last decade among patients over 70 years of age (level II evidence).

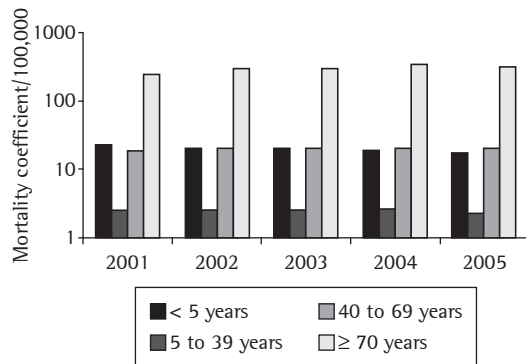
**Diagnostic and complementary tests**

**Radiological diagnosis**

The present guidelines reiterate the previous recommendation that anteroposterior and lateral chest X-rays be taken, because, in addition to being central to the diagnosis of CAP, this aids in

**Chart 1** - Levels of evidence of the recommendations according to the Brazilian Medical Association.

| Level of evidence | Evidence source                                  | Definition  |
|-------------------|--|---|
| I                 | Randomized controlled trials<br>Rich database    | Level I evidence is based on well-designed randomized controlled trials, which provide a consistent model of findings regarding the population to which the recommendation is addressed. Level I evidence requires a substantial number of studies, involving an adequate number of participants.   |
| II                | Randomized controlled trials<br>Limited database | Level II evidence is based on intervention studies, which include a limited number of patients, post hoc analyses or analyses of subgroups of randomized controlled trials, or meta-analyses of randomized controlled trials. In general, level II evidence is pertinent when there are few randomized trials, when the trials are limited in scope, when the trials are conducted among a population that differs from the recommended target population or when the results are somehow inconsistent. |
| III               | Nonrandomized trials<br>Observational studies    | Level III evidence is based on nonrandomized, uncontrolled trials or on observational studies.  |
| IV                | Consensus among the participants of the panel    | Evidence level IV is attributed only to cases in which some type of support was considered valuable but the literature on the topic has been deemed insufficient to warrant the attribution of any other level of evidence to such recommendation. The consensual panel is based on experience or clinical knowledge that does not fit the criteria listed above.   |



**Figure 1** - Age-specific mortality rates due to community-acquired pneumonia among different age groups, 2001-2005.

assessing severity, identifies multilobar involvement and might suggest alternative etiologies, such as abscess and TB. Chest X-rays can reveal concomitant conditions, e.g., bronchial obstruction or pleural effusion, as well as being useful in monitoring treatment response. However, the classification of CAP according to radiological patterns (lobar pneumonia, bronchopneumonia and interstitial pneumonia) is of limited use in predicting the causal agent: it cannot distinguish between the groups of agents (bacterial and nonbacterial).<sup>(9-15)</sup> Specific agents can cause different manifestations that can change or become more intense throughout the course of the disease, being frequently influenced by the immunological status.<sup>(13)</sup>

Chest X-ray is the imaging method of choice for the initial approach to CAP because its cost-effectiveness is excellent, the doses of radiation employed are low and the method is widely available.

Half of the cases diagnosed as CAP in Brazil in reality are not.<sup>(16)</sup> The greatest diagnostic difficulty lies in the interpretation of the chest X-rays by non-specialists.

Cavitation is suggestive of an anaerobic etiologic agent, *Staphylococcus aureus* and, occasionally, gram-negative bacilli. In such cases, screening for TB should always be performed. Swollen lobes causing bulging fissures is a nonspecific finding that reflects intense inflammatory reaction.<sup>(10)</sup>

A CT scan of the chest is useful in a number of situations: when a chest X-ray alone does not clearly show whether or not there is infiltrate;

when the clinical profile is unfavorable but chest X-ray is normal; when the objective is to detect complications such as loculated pleural effusion and encapsulated abscess in the airways; and when it is necessary to differentiate inflammatory infiltrate from lung masses.<sup>(17,18)</sup>

In cases of pleural effusion greater than 5 cm in the posterior mediastinum revealed by lateral chest X-ray in the orthostatic position, or in cases of loculated pleural effusion, thoracentesis should be performed in order to exclude the diagnoses of empyema and complicated parapneumonic effusion. Thoracentesis is strongly recommended in cases of pleural effusion that occupy more than 20% of the hemithorax.<sup>(19)</sup> Ultrasound is useful in cases of small pleural effusion or in suspected cases of loculated pleural effusion because it can determine the exact location of the effusion for subsequent drainage.<sup>(9,20)</sup>

Radiological progression after hospital admission might occur regardless of the etiology, and the therapeutic regimen should not be changed unless the clinical profile has shown no improvement.<sup>(10)</sup> Radiological resolution is relatively slow and occurs after clinical recovery. Complete resolution of radiological alterations occurs two weeks after the initial presentation in half of all cases and six weeks after the initial presentation in two thirds.<sup>(11)</sup> Advanced age, COPD, immunosuppression, alcoholism, diabetes and multilobar pneumonia are independently associated with slower resolution. Pneumonia caused by *Mycoplasma* sp. resolves more rapidly. Pneumonia caused by *Legionella* sp. resolves in a particularly slow manner. Residual lesions are found in 25% of the cases of *Legionella* sp. and bacteremic pneumococcal pneumonia.<sup>(10)</sup> Chest X-ray should be repeated six weeks after the onset of symptoms in smokers over 50 years of age (risk of bronchial carcinoma) and in cases in which the symptoms persist or physical examination reveals abnormal findings.<sup>(11,21)</sup>

## Recommendations

- Anteroposterior and lateral chest X-rays should be taken for the initial approach to patients suspected of having CAP (level III evidence).
- Chest X-ray is the only complementary test to which low-risk CAP outpatients should be submitted (level I evidence).

- The radiological patterns cannot be used to predict the causal agent or to distinguish between the groups of agents (level III evidence).
- A CT scan of the chest should be performed when there is doubt regarding the presence of inflammatory infiltrate; in order to detect complications; and in suspected cases of neoplasia (level III evidence).
- Significant pleural effusion ( $\geq 5$  cm, seen on lateral chest X-ray in the orthostatic position from the posterior ridge) should be drained.
- Ultrasound is useful in cases of small pleural effusion or in suspected cases of loculated pleural effusion (level III evidence).
- Chest X-ray should be repeated six weeks after the onset of symptoms in smokers over 50 years of age and in cases in which the symptoms persist or physical examination reveals abnormal findings.
- Persistence of radiological findings after six weeks requires additional investigation (level IV evidence).

### Peripheral oxygen saturation and arterial blood gas analysis

Peripheral oxygen saturation ( $SpO_2$ ) should be monitored routinely before recommending oxygen therapy. Arterial blood gas analysis should be conducted in cases of  $SpO_2 \leq 90\%$  on room air or in cases of severe pneumonia. Hypoxemia is an indication for supplemental oxygen and hospital admission.<sup>(22-24)</sup>

#### Recommendations

- The  $SpO_2$  should be monitored routinely before the initiation of oxygen therapy (level I evidence).

- Arterial blood gas analysis should be conducted in cases of  $SpO_2 \leq 90\%$  on room air or in cases of severe pneumonia (level I evidence).
- Hypoxemia is an indication for supplemental oxygen and hospital admission (level I evidence).

### Complementary tests

Urea levels higher than 65 mg/dL (corresponding to a value  $\geq 11$  mmol/L) constitute a strong marker of disease severity.<sup>(25-27)</sup> The blood workup shows low sensitivity and specificity, being useful as a criterion for severity and therapeutic response. Leukopenia ( $< 4,000$  leukocytes/mm<sup>3</sup>) denotes poor prognosis.<sup>(28,29)</sup> Glycemia, electrolyte and transaminase levels have no diagnostic value; they can, however, influence the decision of hospitalizing a patient by allowing the identification of concomitant diseases.<sup>(30,31)</sup>

#### C-reactive protein

As a marker of inflammatory activity, C-reactive protein has prognostic value in follow-up treatment. High C-reactive protein levels after 3-4 days of treatment and a  $< 50\%$  reduction in initial C-reactive protein levels suggest worse prognosis or complications. The impact of C-reactive protein levels on the diagnosis requires further investigation and definition of cut-off values before it can be used routinely in clinical practice. There is a lack of consistent data as to whether or not C-reactive protein can aid in the decision of using antibiotics.<sup>(32-35)</sup>

#### Procalcitonin

Procalcitonin is a marker of inflammatory activity that can be determined in various manners: using a commercially available mono-

**Chart 2** - Most common pathogens in community-acquired pneumonia, in decreasing order.

| Outpatients with CAP (mild)  | Inpatients with CAP (not in ICU)  | ICU patients with CAP (severe)   |
|--|---|--|
| <ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i></li> <li>• <i>M. pneumoniae</i></li> <li>• <i>C. pneumoniae</i></li> <li>• Respiratory viruses</li> <li>• <i>Haemophilus influenzae</i></li> </ul> | <ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i></li> <li>• <i>M. pneumoniae</i></li> <li>• <i>C. pneumoniae</i></li> <li>• Respiratory viruses</li> <li>• <i>Haemophilus influenzae</i></li> <li>• <i>Legionella</i> sp.</li> </ul> | <ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i></li> <li>• Gram-negative bacilli</li> <li>• <i>H. influenzae</i></li> <li>• <i>Legionella</i> sp.</li> <li>• <i>S. aureus</i></li> </ul> |

CAP: community-acquired pneumonia; and ICU: intensive care unit.



clonal immunoluminometric assay, considered a less sensitive method; using a polyclonal immunoassay system (Kryptor; B•R•A•H•M•S Aktiengesellschaft, Hennigsdorf, Germany), considered a more sensitive method but not widely available in practice; and more recently, using the VIDAS system of ELISA (bioMérieux, Marcy l'Étoile, France), which is almost as sensitive as the Kryptor system and more readily available, although the assay kit is expensive. Studies involving patients at different levels of risk of death have demonstrated that procalcitonin levels tend to be higher in bacterial pneumonia patients with pneumonia severity index (PSI) scores of I or II than in nonbacterial pneumonia patients with the same PSI scores.<sup>(36-38)</sup> No etiology-related differences were found among patients with pneumonia that was more severe; however, higher procalcitonin levels correlated with complications and death.<sup>(37)</sup> Procalcitonin is a better marker of severity than are C-reactive protein, IL-6 and lactate. Elevated serum procalcitonin levels are also found in other lung diseases such as chemical pneumonitis and smoke inhalation injury in burn patients.<sup>(34,36,39,40)</sup>

**Etiologic investigation**

The methods used for determining the etiology of CAP have low immediate yield and are unnecessary in outpatients, which is due

to the high efficacy of empirical treatment and the low mortality among such patients (< 1%). The elucidation of the etiology of CAP does not result in lower mortality when compared with early, appropriate empirical antibiotic therapy.<sup>(41)</sup> When empirical treatment fails in severe CAP patients, etiologic diagnosis and specific treatment correlate with lower mortality. Treatment initiation should not be delayed in order to perform tests to determine the etiology of CAP.<sup>(41,42)</sup> The most common etiologic agents according to CAP severity and treatment locale are shown in Chart 2.

**Sputum examination**

Although sputum examination is commonly used for establishing the etiologic diagnosis of CAP, the beneficial role of this examination in the initial management of CAP is still controversial.<sup>(43,44)</sup> Some of the obstacles to the performance of sputum examination include the need for collecting the samples in an appropriate manner, the lack of standardization of the techniques used for sample preparation, the variable examiner ability to interpret the results and the lack of a gold standard for the microbiological diagnosis of CAP.<sup>(45)</sup> Valid sputum samples are defined as those that contain < 10 epithelial cells and > 25 polymorphonuclear cells per low-power microscopic field.

**Chart 3 - Complementary tests indicated for etiologic investigation of community-acquired pneumonia.**

| Evidence                    | Blood culture | Sputum smear microscopy and sputum culture | Urinary antigen test for pneumococcus and <i>Legionella</i> sp. | Bronchoalveolar lavage or transtracheal aspiration | Other  |
|-----------------------------|---------------|--|---|--|--|
| ICU admission<br>Severe CAP | Yes           | Yes  | Yes   | Yes  | Aspirate if tracheal intubation is performed |
| Alcohol abuse               | Yes           | Yes  |   |  |  |
| Clinical treatment failure  | Yes           | Yes  | Yes   | Yes*   |  |
| Structural disease          | No            | Yes  | No  | No   |  |
| Cavitation                  | Yes           | Yes  | No  | No   | AFB  |
| Pleural effusion            | Yes           | Yes  | Yes   | No   | Thoracentesis                                |

ICU: intensive care unit; CAP: community-acquired pneumonia; and AFB: acid-fast bacilli.

\*Not to be performed in cases of outpatient treatment failure.

Due to the high prevalence of pulmonary TB and mycoses in Brazil, screening for acid-fast bacilli in the sputum using the Ziehl-Neelsen technique, as well as screening for fungi, should be performed in suspected cases of CAP, according to the Tuberculosis Control Guidelines.<sup>(46)</sup>

### **Blood culture**

Because blood culture commonly shows a low yield, it should be reserved for severe CAP patients and for inpatients who do not respond to the therapeutic approach used. False-positive results are common, especially if antibiotics have previously been used, and rarely result in a change of approach. Sputum samples should be collected before initiation or change of treatment and should not delay the administration of the first dose of antibiotics.<sup>(28,29,47,48)</sup>

### **Other techniques for the collection of samples for microbiological examination**

Other available techniques for obtaining samples from the lower airways include tracheal aspirate, mini-bronchoalveolar lavage and bronchoscopic protected specimen brush or bronchoalveolar lavage, as well as transthoracic needle aspiration biopsy.

These procedures should not be routinely recommended for most CAP patients. However, such procedures are useful in patients admitted to the intensive care unit (ICU) and in those

who do not respond to empirical treatment. Percutaneous puncture lung biopsy is contraindicated in patients on invasive mechanical ventilation.<sup>(49-51)</sup>

When tracheal intubation and initiation of mechanical ventilation are indicated, material should be collected from the lower airways using tracheal aspirate or bronchoscopic techniques, in order to perform quantitative culture.

Secretion collection through bronchoscopy poses lower risks to patients than does transtacheal aspiration and lung puncture.<sup>(52-57)</sup>

### **Serologic tests**

Serologic tests should not be routinely requested. Serologic tests allow the establishment of retrospective diagnosis of infection caused by certain microorganisms that are difficult to culture (*Mycoplasma*, *Coxiella*, *Chlamydomphila* and *Legionella*, as well as viruses). Serologic tests are considered positive when the titer obtained in the convalescent phase, i.e., four to six weeks after defervescence, is four times greater than that obtained in the acute phase. Because of this technical characteristic, serologic tests are not useful in treating patients individually; they are, however, useful in establishing the epidemiological profile of a given region or an epidemic outbreak.<sup>(1,58)</sup>

### **Urinary antigen tests**

Urinary antigen tests are simple, rapid and not influenced by the use of antibiotics. The

**Chart 4** – Scores according to demographic, clinical and laboratory factors, as proposed by Fine et al.<sup>a</sup>

| Demographic factors     |                     | Radiological and laboratory findings |     |
|-------------------------|---------------------|--------------------------------------|-----|
| Age                     |                     | pH < 7.35                            | +30 |
| Men                     | 1 point/year of age | Urea > 65 mg/dL                      | +20 |
| Women                   | age -10             | Sodium < 130 mEq/L                   | +20 |
| Nursing home residents  | age +10             | Glucose > 250 mg/dL                  | +10 |
|                         |                     | Hematocrit < 30%                     | +10 |
|                         |                     | PaO <sub>2</sub> < 60 mmHg           | +10 |
|                         |                     | Pleural Effusion                     | +10 |
| Comorbidities           |                     | Physical examination                 |     |
| Neoplasia               | +30                 | Altered mental status                | +20 |
| Liver disease           | +10                 | Respiratory rate > 30 breaths/min    | +20 |
| CHF                     | +10                 | Systolic BP < 90 mmHg                | +20 |
| Cerebrovascular disease | +10                 | Temperature < 35°C or > 40°C         | +15 |
| Kidney disease          | +10                 | Heart rate ≥ 125 bpm                 | +10 |

CHF: congestive heart failure; PaO<sub>2</sub>: arterial oxygen tension; and BP: blood pressure. <sup>a</sup>Adapted from reference 73.

test for *Legionella pneumophila* becomes positive from day 1 of disease and remains so for weeks. Its sensitivity ranges from 70 to 90%, and its specificity is approximately 100%. Since the test detects the *L. pneumophila* serogroup 1 antigen (the most prevalent serogroup), infections caused by other serogroups, although less common, might not be identified.<sup>(59-62)</sup>

The test for pneumococci has a sensitivity ranging from 50% to 80% (greater than that of sputum examination and blood culture) and a specificity of 90%.<sup>(63,64)</sup> Previous use of antibiotics does not affect the results. False-positive results can occur in cases of colonization of the oropharynx, especially among children with chronic lung diseases. The test is rapid and effective, with good sensitivity and specificity.<sup>(65-68)</sup>

### PCR

The greatest potential of PCR lies in the identification of *L. pneumophila*, *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae*, as well as of other habitually noncolonizing pathogens.

The use of PCR, for the detection of one causative agent, or multiplex PCR, for the detection of *M. pneumoniae*, *C. pneumoniae* and *Legionella* spp., shows good sensitivity and specificity; however, these tests are not available in most clinical laboratories.<sup>(68-71)</sup>

The etiologic tests recommended for use in specific situations are shown in Chart 3.

### Recommendations

- Although glycemia, electrolyte and transaminase levels have no diagnostic value, they can influence the decision to hospitalize a patient by allowing the identification of concomitant diseases (level II evidence).
- Because blood culture commonly has a low yield, it should be reserved for use in severe CAP patients and for inpatients who do not respond to the therapeutic approach used (level III evidence).
- Serologic tests are not useful in treating patients individually; they are, however, useful in establishing the epidemiological profile of a given region or epidemic outbreak (level III evidence).
- Screening for the etiologic agent should be performed in severe CAP patients and

inpatients who do not respond to the initial treatment (level III evidence).

- In cases of severe CAP, microbiological investigation should be performed through blood culture, sputum culture, culture of tracheal aspirate or culture of samples obtained by bronchoscopy in patients on mechanical ventilation (level II evidence).
- Screening for the *S. pneumoniae* urinary antigen should be performed in severe CAP patients, and screening for the *L. pneumophila* urinary antigen should be performed specifically in all patients who do not respond to the initial treatment (level II evidence).

### Classification of severity and choice of treatment locale

Patients diagnosed with CAP should be evaluated for disease severity. This evaluation will aid in the choice of treatment locale, in the extent of etiologic investigation and in the choice of antibiotic therapy. Socioeconomic factors should also be taken into consideration when making this decision.

Disease severity scores<sup>(72)</sup> or prognostic models<sup>(73)</sup> evaluate the 30-day mortality risk and are used to identify low-risk patients, who are therefore candidates for outpatient treatment.

#### *Pneumonia severity index*

The PSI score comprises 20 variables that include demographic characteristics, concomitant diseases, abnormal laboratory test results, radiological alterations and physical examination findings. The points attributed to each variable allow the severity to be stratified into five

**Chart 5** - Classification of patients with community-acquired pneumonia based on risk, according to the Pneumonia Severity Index score.<sup>(73)</sup>

| Score | Points | Mortality, % | Recommended treatment locale      |
|-------|--------|--------------|-----------------------------------|
| I     |        | 0.1          | Outpatient clinic                 |
| II    | ≤ 70   | 0.6          | Outpatient clinic                 |
| III   | 71-90  | 2.8          | Outpatient clinic or day hospital |
| IV    | 91-130 | 8.2          | Hospitalization                   |
| V     | > 130  | 29.2         | Hospitalization                   |



classes, based on the risk of death (Charts 4 and 5). However, the primary objective of the original study was to identify low-risk patients.<sup>(30,73,74)</sup> The PSI score might underestimate CAP severity among young patients without concomitant diseases. In addition, because the PSI is complex and requires extensive laboratory evaluation, it is not considered ideal for routine use in clinical practice.

**The British Thoracic Society disease severity score**

The disease severity score proposed by the British Thoracic Society is based on variables indicative of severe CAP, as follows: mental confusion (defined as an abbreviated mental test score ≤ 8); urea > 50 mg/dL; respiratory rate ≥ 30 breaths/min; systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg; and age ≥ 65 years. The name of this score (CURB-65) is an acronym based on the key term of each risk factor assessed (confusion, urea, respiratory and blood) and can be presented in its simplified form, CRB-65 (without urea levels). In this score, each variable represents 1 point, and the total possible score comprises 4 points (CRB-65) or 5 points (CURB-65), as shown in Figures 2 and 3.<sup>(25,72,75-77)</sup>

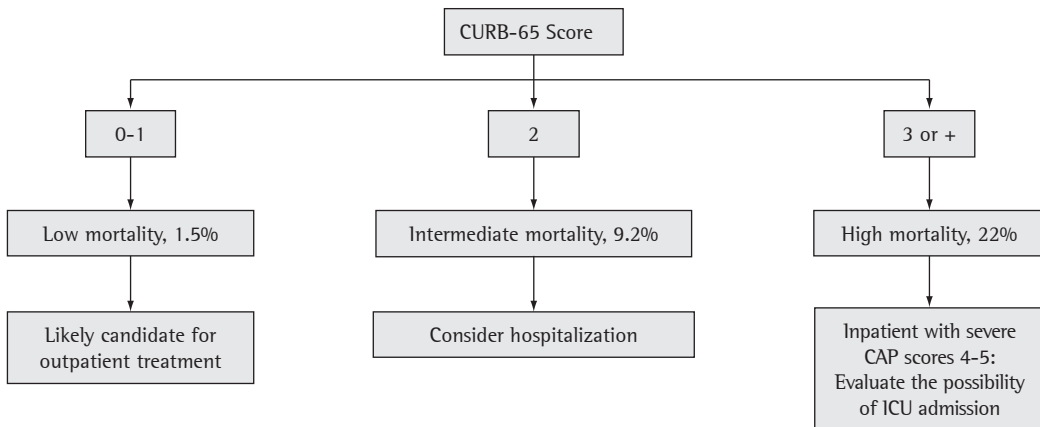
The greatest limitation of the CURB-65 and CRB-65 is the fact that they do not include concomitant diseases that can increase the risk of CAP, e.g., alcoholism, heart failure, liver failure and neoplasia.

The present guidelines reiterate the recommendation of the previous guidelines regarding the need to evaluate concomitant diseases, the extent of radiological involvement, the degree of oxygenation, psychosocial factors, socioeconomic factors and the viability of oral medication use in terms of their influence on the choice of treatment locale. Due to the simplicity of the CURB-65 and CRB-65 scores, as well as the fact that they are immediately applicable and easy to use, we recommend their use as appropriate criteria for the stratification of CAP severity at the primary and emergency care levels (Chart 6).

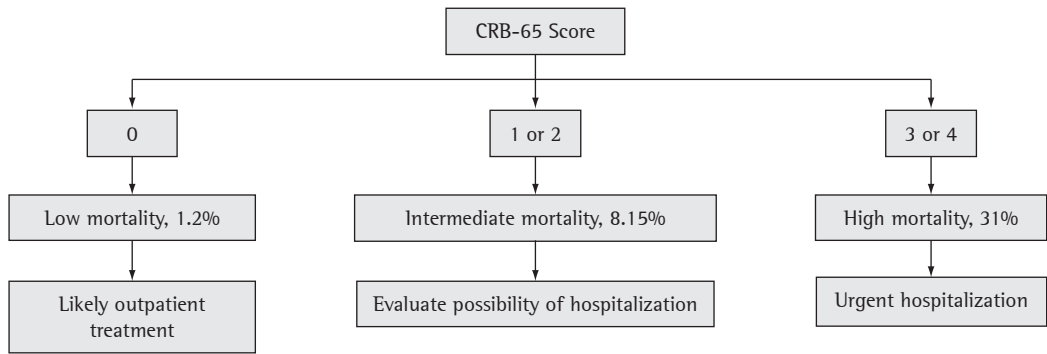
If not contraindicated by socioeconomic complications, decompensated concomitant diseases, hypoxemia or inability to take oral medication, hospital admission is indicated for patients with a score of at least two points on the CURB-65 or at least one point on the CRB-65. When such contraindications exist, the attending physician should prescribe outpatient treatment.

**Severe community-acquired pneumonia**

From a practical standpoint, severe CAP is defined as CAP in which the clinical profile is more likely to worsen or the risk of death is higher. Admission to the ICU is mandatory for the appropriate management of severe CAP patients. Septic shock and the need for mechanical ventilation are absolute criteria for ICU admission.<sup>(78)</sup>



**Figure 2** – CURB-65 score. CAP: community-acquired pneumonia; ICU: intensive care unit; CURB-65: C: mental confusion; U: urea > 50 mg/dL; R: respiratory rate ≥ 30 breaths/min; B: blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg); and 65: age ≥ 65 years.



**Figure 3** – CRB-65 score. CRB-65: C: mental confusion; R: respiratory rate  $\geq 30$  breaths/min; B: blood pressure (systolic  $< 90$  mmHg or diastolic  $\leq 60$  mmHg); and 65: age  $\geq 65$  years.

The currently used criteria were defined by Ewig et al. and have a sensitivity of 78%, a specificity of 94%, a negative predictive value of 95% and a positive predictive value of 75% in selecting patients who require ICU admission.<sup>(78-80)</sup>

The present guidelines corroborate the adoption of such criteria in order to define severe CAP and to recommend ICU admission (Chart 7). If a patient meets two of the minor criteria or one of the major criteria for CAP severity, ICU admission is indicated.<sup>(81,82)</sup>

### Recommendations

- The decision of whether to hospitalize a CAP patient is the prerogative of the attending physician, and the currently available evaluation scores are tools that inform that decision (level III evidence).
- The use of the CURB-65 or CRB-65 scores is recommended to aid in the choice of treatment locale (level III evidence).
- Psychosocial and socioeconomic factors should be taken into consideration when selecting the treatment locale (level III evidence).
- CAP patients presenting with septic shock, requiring vasopressors or with acute respiratory failure (requiring mechanical ventilation) should be admitted to the ICU, as should patients who meet at least two of the minor criteria for CAP severity (level III evidence).

- The possibility of treatment reevaluation should be guaranteed for CAP patients receiving home treatment (level III evidence).
- CAP patients who meet major or minor criteria for severe CAP should receive ICU treatment (level I evidence).

### Treatment

#### *Empirical treatment vs. specific treatment*

In the vast majority of CAP cases, it is not possible to determine the etiologic agent prior to the therapeutic moment of decision. Empirical antibiotic therapy is habitually targeted at the most prevalent microorganisms. More often than not, more than one pathogen is present and atypical pathogens are included. This requires wider empirical coverage, particularly in cases that are more severe. Specific therapy has the potential to minimize adverse effects, decrease the induction of resistance to antimicrobial agents and reduce costs.<sup>(42,81,83,84)</sup> Specific therapy can replace empirical treatment of hospitalized patients when the specific pathogen is identified within the first 48-72 h after treatment initiation. In this context, the identification of the agent can narrow the empirical regimen or influence the choice of antimicrobial agent to be administered orally in the subsequent therapeutic approach.<sup>(81)</sup>

#### *Recommendations*

- The selection of the initial therapeutic regimen for CAP patients takes into

**Chart 6** – Steps for evaluating treatment locale of patients with community-acquired pneumonia.

- 1 - Evaluate the presence of concomitant diseases
- 2 - Evaluate CRB-65
- 3 - Evaluate the degree of oxygenation and radiological involvement
  - SpO<sub>2</sub> < 90% - indication for hospitalization
  - Chest X-ray
    - Radiological extent
    - Pleural effusion suspected of empyema
- 4 - Evaluate social and cognitive factors
  - Absence of a family member or caregiver in the residence
    - need for observing treatment response
  - Capacity of understanding the treatment prescribed
- 5 - Evaluate economic factors
  - Access to medication
  - Return for evaluation
- 6 - Evaluate acceptability of oral medication
- 7 - Clinical judgment

CRB-65: mental confusion (defined as an abbreviated mental test score  $\leq 8$ ); respiratory rate  $\geq 30$  breaths/min; systolic blood pressure  $< 90$  mmHg or diastolic blood pressure  $\leq 60$  mmHg; and age  $\geq 65$  years.

consideration the most prevalent microorganisms (level III evidence).

- Specific treatment targeted at a previously identified pathogen or pathogens is to be preferred over empirical treatment. However, specific treatment is typically unfeasible at the therapeutic moment of decision (level III evidence).
- The identification of the agent(s) allows the selection of specific therapy targeted at the pathogen(s) and the selection of antimicrobial agent to be used in the subsequent therapeutic approach, potentially reducing treatment cost, adverse effects and resistance induction (level II evidence).

### ***Empirical antibiotic coverage of atypical pathogens***

When CAP patients are submitted to specific diagnostic tests, atypical pathogens are frequently identified. Depending on the methodology employed, these agents can appear in isolation or as an integral part of a polymicrobial etiology.<sup>(85)</sup> In a large study based on the secondary analysis of international registries of hospitalized patients, the incidence of CAP

caused by atypical pathogens showed that values were similar in North America, Europe, Latin America and Asia (22%, 28%, 21% and 20%, respectively).<sup>(86)</sup> However, in that study, the proportion of patients who received empirical antibiotic therapy with coverage of atypical pathogens was 91%, 74%, 53% and 10%, respectively. Comparing those patients with those not receiving such therapy, the authors observed the following: less time to achieve clinical stability (3.2 vs. 3.7 days;  $p < 0.001$ ); shorter hospital stay (6.1 vs. 7.1 days;  $p < 0.01$ ); lower overall mortality rate (7.0% vs. 11.1%;  $p < 0.01$ ); and lower CAP-related mortality (3.8% vs. 6.4%;  $p < 0.05$ ).

In general, the empirical antibiotic therapy for CAP covers atypical pathogens.<sup>(87)</sup> Although most guidelines recommend empirical antibiotic coverage of atypical pathogens, there is controversy regarding the level of scientific evidence on which this practice is based. A recently published observational study involving hospitalized patients ( $n = 201$ ) revealed that previous outpatient treatment with a beta-lactam antibiotic correlated with an increased possibility (approximately three times greater) of an atypical pathogen being present, whereas the possibility of pneumococci being present was reduced to one third.<sup>(88)</sup> The need for and effectiveness of empirical antibiotic coverage of atypical pathogens in hospitalized patients with mild CAP have been recently reevaluated in three studies (systematic review or meta-analysis), the outcome measures of which were the efficacy of the practice and on the related mortality rates.<sup>(83,89,90)</sup> These reviews principally compared quinolone monotherapy with beta-lactam monotherapy. In the most recent of the three, which included 5,244 patients from 25 randomized studies, no significant difference in mortality was observed between patients treated with antibiotics that cover atypical pathogens (quinolones) and those treated with a beta-lactam (relative risk = 1.15; 95% CI: 0.85-1.56). No significant difference was observed regarding adverse effects or the need to discontinue treatment. In these reviews, the overall frequency of adverse effects was similar; however, patients treated with beta-lactam antibiotics presented more adverse effects in the gastrointestinal tract than did those treated with quinolones.<sup>(90)</sup> The two systematic reviews presented similar results.<sup>(83,89)</sup> In the three reviews previously cited, the use of empir-

**Chart 7** – Criteria for defining severe community-acquired pneumonia.

- Major criteria: the presence of one criterion is an indication for ICU treatment
  - Septic shock requiring vasopressors
  - Acute respiratory failure requiring mechanical ventilation
- Minor criteria: the presence of two criteria is an indication for ICU treatment
  - Arterial hypotension
  - PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 250
  - Presence of multilobar infiltrate

ICU: intensive care unit.

ical antibiotic coverage of atypical pathogens showed better results only in the subgroup of patients in which *Legionella* sp. was subsequently detected. Quinolone coverage did not result in worse disease progression in patients with CAP caused by pneumococci.<sup>(83,90)</sup> However, the validity of such observational studies is questionable.<sup>(87)</sup> Further prospective studies of such patients, comparing beta-lactam monotherapy with beta-lactam-macrolide combination therapy and electing the mortality rate as the primary outcome measure, are needed.

### **Recommendation**

- Although there is no conclusive evidence that empirical antibiotic coverage of atypical pathogens is superior, this therapeutic approach to hospitalized patients might result in lower mortality rates among patients with pneumonia caused by *Legionella* sp. It might also result in reduced hospital stay, overall mortality and mortality from pneumonia caused by atypical pathogens (level II evidence).

### **Combination therapy vs. monotherapy**

Combination antibiotic therapy for CAP patients aims to broaden the coverage of atypical pathogens and of potentially resistant bacteria, as well as to reduce mortality in cases of bacteremia caused by *Streptococcus pneumoniae*. Few studies have compared the two most widely recommended antimicrobial regimens for CAP patients requiring hospitalization: combination therapy (a beta-lactam associated with a macrolide or quinolone); and monotherapy

with coverage of atypical pathogens (quinolone or macrolide). In a retrospective study involving 515 patients (of which 261 received combined therapy) with severe CAP (cases of severe CAP were defined as those with a PSI score of V), lower 14-day and 30-day mortality rates were found among the patients who received combination antibiotic therapy, a result that was not observed among patients with CAP that was less severe.<sup>(91)</sup> In another observational study, survival rates were higher among patients with severe CAP and septic shock who received combination therapy than they were among patients who received monotherapy, even when the latter was considered appropriate for the etiologic agent. Combination therapy showed no advantage over monotherapy in patients without septic shock.<sup>(92)</sup> Combination therapy also seems to be more beneficial than monotherapy in cases of pneumococcal CAP with bacteremia.<sup>(93)</sup> Possible explanations include a possibly unapparent coinfection caused by atypical pathogens (found in 18-38% of the cases in some studies) or the immunomodulatory effects of macrolides, or a combination of the two.<sup>(94)</sup>

### **Recommendations**

- Combination therapy is not superior to monotherapy among low-risk patients (level II evidence).
- Combination therapy should be recommended for patients with severe CAP, particularly for those with accompanying bacteremia, respiratory failure or septic shock (level II evidence).
- In comparison with monotherapy, combination therapy with two effective antibiotics reduces mortality among bacteremic pneumococcal pneumonia (level II evidence).

### **Predictors of specific pathogens**

The principal predictive factors of CAP caused by penicillin-resistant pneumococci are age ≤ 4 years (OR = 5.3; 95% CI: 2.2-12.6), immunosuppression (OR = 3.0; 95% CI: 1.5-6.0) and recent use of a beta-lactam (OR = 2.1; 95% CI: 1.0-4.5).<sup>(95)</sup> The principal independent predictors of CAP caused by gram-negative bacilli include likely aspiration (OR = 2.3; 95% CI: 1.02-5.20; p = 0.04), hospitalization within the past 30 days

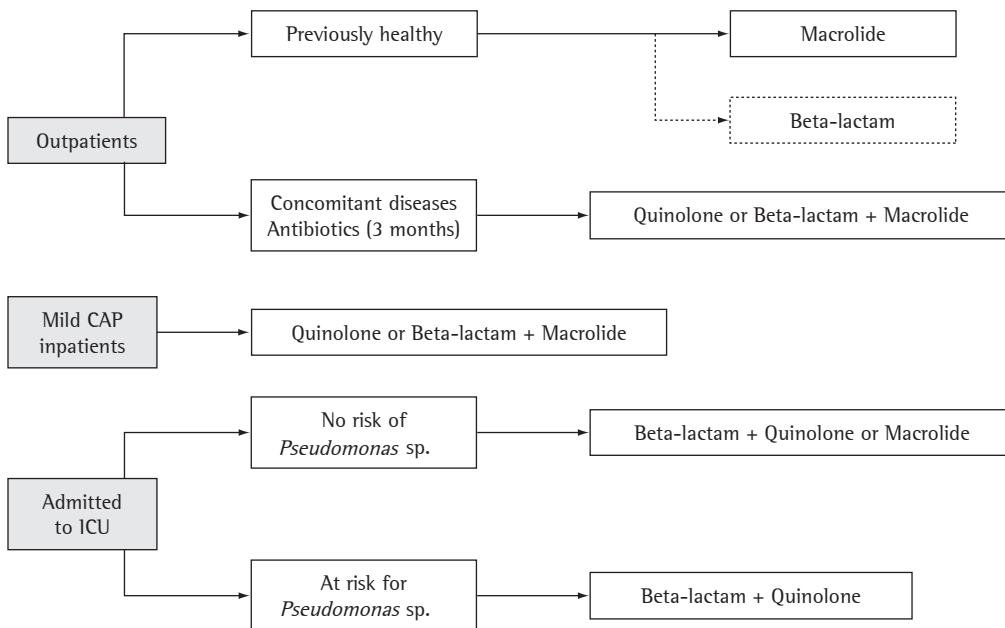
(OR = 3.5; 95% CI: 1.7-7.1; p < 0.001), antibiotic use for more than 48 h within the past 30 days (OR = 1.9; 95 CI%: 1.01-3.70; p = 0.049) and parenchymal lung diseases (OR = 2.8; 95% CI: 1.5-5.5; p = 0.02).<sup>(96)</sup> A specific analysis of a subgroup of patients with CAP caused by *Pseudomonas aeruginosa* showed that a history of lung disease (OR = 5.8; 95% CI: 2.2-15.3; p < 0.001) and recent hospitalization (OR = 3.8; 95% CI: 1.8-8.3; p = 0.02) were independent predictors of CAP caused by *P. aeruginosa*. In that study, infection caused by gram-negative bacilli was an independent variable for risk of death (OR = 3.4; 95% CI: 1.6-7.4; p = 0.002).<sup>(96)</sup>

**Recommendation**

- The predictors of risk for specific pathogens should be taken into consideration when selecting the empirical antibiotic therapy for CAP patients (level II evidence).

**Potential benefits of early initiation of antibiotic therapy**

At least two retrospective studies involving CAP patients aged ≥ 65 years who were hospitalized in the USA demonstrated lower mortality among patients who received earlier antibiotic therapy.<sup>(97,98)</sup> One of the studies<sup>(98)</sup> proposed an interval of 8 h between patient admission and the administration of the first dose, whereas the other<sup>(97)</sup> established a 4-h limit for the administration of the first dose. Another group of authors reported that early antibiotic therapy can reduce the length of hospital stays.<sup>(99)</sup> Among patients with bacteremic pneumococcal pneumonia, initiation of antibiotic therapy within the first 4 h after hospital admission reduces mortality and length of hospital stay.<sup>(100)</sup> However, in a prospective observational study involving 409 patients with moderate to severe CAP, no direct correlation was found between early antibiotic therapy and the time required



**Figure 4** - Initial empirical antibiotic therapy according to degree of severity.

†In cases of beta-lactam use in isolation, consider the possibility of treatment failure in 1 of every 14 treated patients. Amoxicillin: 500 mg, 1 tablet to be taken orally every 8 h for 7 days; azithromycin: single daily dose of 500 mg to be taken orally for 3 days or 500 mg on the first day, followed by 250 mg/day for 4 days; rapid-release clarithromycin: 500 mg orally every 12 h for up to 7 days; slow-release clarithromycin: single daily dose of 500 mg to be taken orally for up to 7 days. ‡Quinolones: levofloxacin 500 mg/day; moxifloxacin: 400 mg/day. \*Antipneumococcal/antipseudomonal antibiotics: piperacillin/tazobactam, cefepime, imipenem or meropenem. \*\*levofloxacin (750 mg) or ciprofloxacin.



to achieve clinical stability, considering periods of less than 4 h, of 4-6 h and of more than 6 h.<sup>(101)</sup> In a recent review of the topic, it was suggested that early antibiotic therapy is potentially more beneficial for elderly patients who are antimicrobial treatment-naïve.<sup>(102)</sup> However, the pressure to administer the first dose in less than 4 h rather than in 8 h might lead to errors in the diagnosis of CAP.<sup>(103)</sup> Therefore, the ideal time frame between admission and the first dose of antibiotics remains controversial. It is recommended, however, that the first dose be administered to hospitalized patients “as early as possible”, preferably at admission, particularly in the emergency room.<sup>(81)</sup>

### Recommendation

- Antibiotic therapy for CAP patients should be initiated as early as possible, since it can reduce mortality rates, shorten hospital stays and control costs (level III evidence).

### Antibiotic resistance in *S. pneumoniae*: major changes in the Clinical Laboratory Standards Institute criteria

The selection of an antimicrobial agent to treat infections caused by *S. pneumoniae* is based on various factors, such as the site of infection, resistance to penicillin (and other agents), degree of severity, pharmacokinetics/pharmacodynamics of the drug and patient age. In community-acquired infections, empirical treatment can be guided by local epidemiological surveillance studies. In severe infections, it is important that culture and antibiogram be performed when treatment adjustment is needed. The interpretation of the minimum inhibitory concentration (MIC) of penicillin for *S. pneumoniae* should always consider the clinical sample in which the agent was isolated, as well as clinical suspicion of the type of infection. The disk method routinely used in laboratories is not definitive in detecting penicillin resistance, and the results obtained should always be confirmed by determining the MIC (mg/L).

The definition of penicillin resistance based on the MIC for *S. pneumoniae* strains was changed in 2008 by the Clinical Laboratory Standards Institute (CLSI) as a result of evidence of the pharmacokinetics and pharmacodynamics

of penicillin and its derivatives (amoxicillin and ampicillin) in respiratory tract infections.<sup>(104)</sup> The original definition of penicillin resistance (MIC  $\geq$  2 mg/L) was based on populations of patients with meningitis. This criterion was—and is—indistinctly applied to pneumonia isolates. In various regions, this has given rise to policies regarding the use of non-beta-lactam antibiotics that are based on questionable resistance rate data. These resistance rates need to be definitively reevaluated. For pneumonia-related *S. pneumoniae* strains (i.e., those unrelated to meningitis) isolated from the respiratory tract, the blood, or both, separate categories of i.v.

**Chart 8** - Principal causes and patterns of treatment failure.

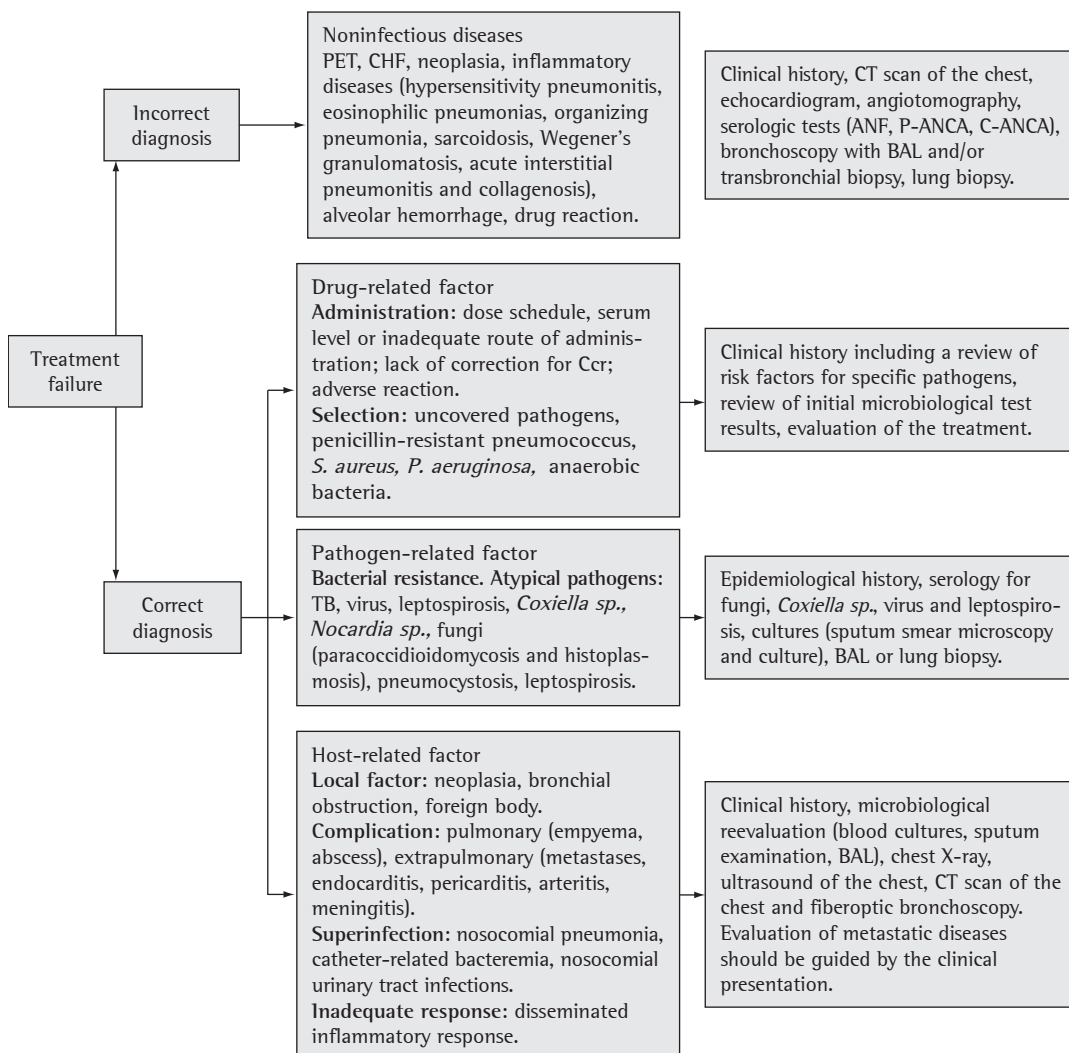
|  |
|--|
| Progressive (respiratory failure, shock)                               |
| < 72 h   |
| Severity of disease presentation                                       |
| Microorganismo não tratado   |
| Atypical pathogens (mycobacteria, viruses, <i>Nocardia</i> sp., fungi) |
| Antimicrobial resistance   |
| Infectious complication  |
| Pulmonary (empyema, parapneumonic effusion)                            |
| Metastatic (endocarditis, meningitis, arteritis)                       |
| Noninfectious cause  |
| Incorrect diagnosis (PET, ARDS, vasculitis)                            |
| > 72 h   |
| Infectious complication  |
| Nosocomial superinfection  |
| Exacerbation of underlying disease                                     |
| Noninfectious cause (PET, AMI)   |
| Nonresponsive (persistent symptoms)                                    |
| > 72 h   |
| Nonresponsive microorganism  |
| Not covered  |
| Resistant  |
| Local complication (empyema, parapneumonic effusion)                   |
| Nosocomial superinfection  |
| Noninfectious causes   |
| Pneumonia-related complication (COP)                                   |
| Incorrect diagnosis (PET, CHF, vasculitis, II, neoplasia)              |
| Antibiotic-related fever   |

PTE: pulmonary thromboembolism; ARDS: acute respiratory distress syndrome; AMI: acute myocardial infarction; COP: cryptogenic organizing pneumonia; CHF: congestive heart failure; II: interstitial inflammation.

penicillin sensitivity, based on the MIC, have been established: sensitive,  $\leq 2$  mg/L; intermediate,  $\geq 4$  mg/L  $< 8$  mg/L; and resistant,  $\geq 8$  mg/L. It should be borne in mind that these criteria do not apply to penicillin V (oral). According to the new CLSI guidelines, meningitis-related *S. pneumoniae* strains (isolated from the cerebrospinal fluid, blood, or both) are classified (based on the MIC) as penicillin-sensitive ( $< 0.06$  mg/L) or penicillin-resistant ( $\geq 0.12$  mg/L).

Local rules for the use of antibiotic therapy in CAP patients need to be revised, since they were based on earlier studies. Although routine labo-

ratory tests can screen for penicillin resistance using an oxacillin disk, which indicates decreased sensitivity when it reveals halos  $< 20$  mm, this interpretation should be confirmed by a quantitative method for the determination of penicillin (MIC), because sensitive strains might be present even if halos of 20 mm are shown. Only the MIC value can definitively classify a *S. pneumoniae* strain as being resistant.<sup>(105)</sup> Knowledge of the distinct local mechanisms of resistance and their clinical and laboratory interpretation are of utmost importance in order to select the appropriate treatment and contribute to the



**Figure 5** - Principal causes of treatment failure and specific diagnostic approach. PTE: pulmonary thromboembolism; CHF: congestive heart failure; BAL: bronchoalveolar lavage; Ccr: creatinine clearance; ANF: antinuclear factor; and ANCA: antineutrophil cytoplasmic antibody.

development of strategies for the use of the different classes of antimicrobial agents. The Brazilian Epidemiological Surveillance Program evaluated 6,470 invasive *S. pneumoniae* strains (isolated from respiratory samples, cerebrospinal fluid samples and blood samples) between 1993 and 2004.<sup>(106)</sup> The proportion of penicillin-resistant strains was found to range from 10.2% to 27.9%. In 1993 and 2004, respectively, 9.1% and 22.0% of the strains were classified as intermediate, compared with 1.1% and 5.9% that were classified as resistant, the rates for both categories presenting a temporal increase. These rates were cross-referenced with the CLSI criteria of the year of publication and will need to be recalculated according to the 2008 classification of resistance. It is of note, however, that none of the strains showed a MIC > 4 mg/L. Therefore, according to the new CLSI criteria, none of the invasive pneumonia-related strains evaluated in that study were resistant to penicillin (MIC ≥ 8 mg/L). Most of those isolates were from patients less than 5 years of age and belonged to serotype 14, which is part of the heptavalent pneumococcal conjugate vaccine. Other resistance rates shown in that study were as follows: trimethoprim-sulfamethoxazole (65%), tetracycline (14.6%), erythromycin (6.2%), chloramphenicol (1.3%) and rifampicin (0.7%). None of the strains showed resistance to levofloxacin. Based on the new CLSI criteria, pneumonia-related strains isolated in Brazil show higher rates of resistance to macrolides than they do to penicillin.

### **Recommendations**

- Surveillance studies show that, according to the 2008 CLSI criteria, invasive strains of *S. pneumoniae* isolated in Brazil are uniformly sensitive to penicillin (level III evidence).
- Penicillin resistance can only be characterized by determination of the MIC, interpreted in view of the new cut-off values established in the 2008 CLSI criteria.

### **Monotherapy with intravenous azithromycin for hospitalized patients**

The recommendation of empirical treatment with intravenous azithromycin as monotherapy for low-risk hospitalized patients is based on

two studies.<sup>(107,108)</sup> One of the studies, an open randomized study, compared azithromycin with cefuroxime and erythromycin, as well as with the cefuroxime-erythromycin combination, in terms of efficacy and safety. In that study, 80% of the patients were low-risk patients (Fine score I-III). In the other study, which involved two groups of patients, azithromycin and the cefuroxime-erythromycin combination were both effective in 91% of the patients (61/67 and 71/78, respectively). Despite the similar effectiveness of the two treatments ( $p = 0.95$ ), the incidence of adverse effects was higher in the latter group ( $p < 0.001$ ). The degree of CAP severity was not reported in that study.

### **Recommendation**

- In hospitalized patients, empirical treatment with azithromycin as monotherapy should be limited to patients with mild CAP (level II evidence).

### **Ertapenem for hospitalized patients**

Ertapenem is a beta-lactam that is structurally similar to meropenem (possessing a 1-beta-methyl group) and is indicated for patients with moderate to severe infection caused by gram-positive pathogens, as well as infection caused by aerobic or anaerobic gram-negative bacteria. It is administered i.m. or i.v. in a single daily dose of 1 g. It can be used to treat infections (soft tissue infections, abdominal infections, acute pelvic infections and complicated urinary tract infections), CAP and sepsis. It is particularly useful in cases of infection caused by bacteria producing extended spectrum beta-lactamases. It is not indicated in cases of infection caused by penicillin-resistant *S. pneumoniae*, methicillin-resistant *S. aureus*, *Pseudomonas* spp. and *Acinetobacter* spp.<sup>(109)</sup>

Two studies compared ertapenem with ceftriaxone in terms of their efficacy and safety when used in the treatment of CAP patients. One of the studies ( $n = 658$ ), a double-blind, randomized, prospective multicenter study, showed no significant difference between the two regimens regarding their efficacy (91.9% vs. 92.0%, respectively; 95% CI: 4.5-4.4). The incidence of adverse effects was similar for the two treatments.<sup>(110)</sup>

The overall analysis of two studies involving a total of 857 severe CAP patients (defined as those with PSI scores of IV or V), 31% of whom had accompanying COPD and were treated with ertapenem or ceftriaxone, revealed that clinical responses were similar between patients with COPD and those without (90% vs. 93%; OR = 0.7; 95% CI: 0.4-1.2).<sup>(111)</sup>

The initial antibiotic therapy for CAP outpatients recommended in the present guidelines takes into consideration three important aspects: the high proportion of CAP agents that are sensitive to beta-lactams in Brazil; the lack of definitive data with regard to empirical antibiotic coverage of atypical pathogens in cases of mild CAP; and the predominance of studies involving inpatients, rather than outpatients. However, it is of note that the coverage of macrolides has been broader than has that of amoxicillin (Figure 4). In all situations, patients undergoing treatment should be reevaluated at 48-72 h after treatment initiation. This reevaluation should be based almost exclusively on clinical data, and the repetition, in this period, of radiological examinations is not justified in stable patients showing satisfactory clinical evolution.

### Recommendations

- Ertapenem constitutes an acceptable alternative for CAP patients presenting risk factors for gram-negative pathogens, except *Pseudomonas* spp. and *Acinetobacter* spp. (level III evidence).
- Ertapenem might be useful in CAP patients who have recently used antibiotics and in those with polymicrobial infection (level III evidence).
- The initial antibiotic therapy for CAP outpatients recommended in the present guidelines takes into consideration the high proportion of CAP agents that are sensitive to beta-lactams in Brazil and the lack of definitive data with regard to empirical antibiotic coverage of atypical pathogens in cases of mild CAP; in addition, the coverage of macrolides is broader than is that of amoxicillin (level II evidence).

### Treatment duration

Reduced treatment duration reduces CAP patient exposure to antibiotics, limits the risk

of induction of resistance and reduces costs, as well as improving treatment adherence and tolerability. The bactericidal activity of fluoroquinolones is concentration-dependent. The pharmacodynamic properties of fluoroquinolones (the ratio between the area under the curve and the MIC required to inhibit 90% of the colonies [ $MIC_{90}$ ] and the ratio between maximum concentration [ $C_{max}$ ] and  $MIC_{90}$ ) allow a reduction in treatment duration without jeopardizing treatment efficacy. A double-blind, randomized, multicenter, phase III study demonstrated that gemifloxacin mesylate, when used at a dose of 320 mg/day for 7 days, shows the same clinical, bacteriological and radiological efficacy as the amoxicillin-clavulanate combination (1 g/125 mg three times a day for 10 days).<sup>(112)</sup> Another study compared the efficacy of gemifloxacin (320 mg/day) for 5 days is not inferior to 7 days with respect to clinical, bacteriological and radiological efficacy in the CAP population studied.<sup>(113)</sup> Yet another study demonstrated that the use of moxifloxacin (400 mg/day) and levofloxacin (500 mg/day), for 7-14 days, produced comparable results in a population of elderly CAP inpatients, except for the fact that treatment duration was shorter when moxifloxacin was used.<sup>(114)</sup> Because the  $C_{max}/MIC_{90}$  of levofloxacin is inferior to that of moxifloxacin, the use of higher doses (750 mg/day) makes it possible to reduce treatment duration without jeopardizing treatment efficacy. A double-blind, randomized, multicenter study compared the efficacy of levofloxacin at 750 mg/day for 5 days with that of levofloxacin at 500 mg/day for 10 days in patients with moderate to severe CAP and obtained similar results (92.4% vs. 91.1%, respectively).<sup>(115)</sup> A meta-analysis performed to evaluate the efficacy of regimens of short duration (< 7 days) in adult patients with mild to moderate CAP, totaling 2,796 patients in 15 selected studies, showed that the efficacy of such regimens is similar to that of traditional regimens.<sup>(116)</sup>

Two recent randomized comparative studies demonstrated the efficacy and safety of a new microsphere formulation of azithromycin (not available in Brazil), used orally in a single dose, in patients with low-risk CAP.<sup>(117,118)</sup> A double-blind, randomized, multicenter, phase III study (n = 499) compared the efficacy (bacteriological and clinical cure) of the treatment of patients

with low-risk CAP (Fine score I or II) using 2 g of azithromycin microspheres taken orally in a single dose (efficacy of 92.6%) with the efficacy of slow-release clarithromycin at 1 g/day for 7 days (efficacy of 94.7%). No significant difference was found between the treatments regarding the incidence of adverse effects.<sup>(117)</sup> Another study, which involved 427 CAP patients (Fine scores I-III), compared the efficacy of azithromycin microspheres taken orally in a single dose (n = 213, azithromycin group) with that of levofloxacin at 500 mg/day for 7 days (n = 214, levofloxacin group). The rate of clinical cure was similar in the two groups (89.7% and 93.7%, respectively). The two groups behaved similarly with regard to bacterial eradication (90.7% vs. 92.3%; 95% CI: 5.5-8.8). No significant difference was observed between the two groups regarding the incidence of adverse effects (19.9% vs. 12.3%).<sup>(118)</sup>

The C<sub>max</sub> and the area under the curve 24 h after a 2-g dose of azithromycin microspheres have been found to be twice and three times greater, respectively, than those observed when the traditional regimens of 1.5 g of azithromycin (500 mg/day for 3 days or 500 mg on day 1 and 250 mg/day for 4 more days) are used.<sup>(117)</sup> Therefore, higher serum and tissue concentration, reduced treatment duration and greater treatment adherence can be achieved, maintaining efficacy without jeopardizing tolerability.

### **Recommendations**

- Adult patients with mild to moderate CAP can be effectively treated with antibiotics administered for a period ≤ 7 days (level I evidence).
- This recommendation is consistent with the classes of antibiotics habitually recommended (level I evidence).
- Although the results have been promising, there is still no solid clinical evidence for the empirical use of azithromycin microspheres, taken in a single dose, in the treatment of patients with low-to-moderate-risk CAP (level II evidence).

### **Treatment failure: definition, predictors of risk, markers and practice**

Most patients diagnosed with CAP respond adequately to treatment; however, it has been

shown that 10-24% of inpatients<sup>(119-122)</sup> and 7% of outpatients<sup>(123,124)</sup> do not present an adequate clinical response. Treatment failure is an important prognostic factor for mortality among CAP patients, CAP-related mortality rates being approximately 40%.<sup>(119)</sup> The relevance of treatment failure can also be measured by the morbidity associated with it, which translates to longer hospital stays, need for ICU admission, complications and, indirectly, increased treatment costs.<sup>(121)</sup> There is no consensus regarding the definition of treatment failure. Among outpatients, treatment failure is defined as the need for hospitalization or for a change in the antibiotic therapy.<sup>(123,124)</sup> Among inpatients, treatment failure is classified as early or late.<sup>(120-122)</sup> Early treatment failure is characterized by respiratory failure (requiring mechanical ventilation) or septic shock, or both, within the first 72 h after admission. Late treatment failure occurs after 72 h of treatment and is characterized by persistent or recurrent fever associated with respiratory symptoms, by respiratory failure (requiring mechanical ventilation), by septic shock or by a combination of respiratory failure and septic shock. The principal causes of early and late treatment failure are summarized in Chart 8.

Few prospective studies have been conducted with the specific objective of evaluating the risk factors related to treatment failure by means of multivariate analysis.<sup>(120-122)</sup> The independent risk factors for early treatment failure include age > 65, PSI score > 90, inappropriate treatment, infection caused by *Legionella* sp. or by gram-negative bacteria, presence of multilobar infiltrate, pleural effusion and cavitation.<sup>(121,122)</sup> Late treatment failure has been linked to neoplasm, high PSI score, neurological disease, aspiration, liver cirrhosis, multilobar infiltrate and pleural effusion.<sup>(120,122)</sup> Influenza vaccination, initial treatment with fluoroquinolones and the presence of COPD have been considered protective factors against treatment failure.<sup>(120)</sup>

Biological markers have been shown to be useful in identifying patients at increased risk of treatment failure. In a recent study, C-reactive protein levels higher than 21.9 mg/dL on the first day of treatment were an independent predictor of treatment failure (OR = 2.6).<sup>(125)</sup> In the same study, C-reactive protein levels higher than 21.9 mg/dL and procalcitonin levels higher



than 2.2 ng/mL on the first day of treatment showed high positive predictive value in diagnosing early treatment failure.

Treatment failure should be approached in an early, practical and systematized manner; potential causes and patterns of treatment failure should be investigated before changes in the therapeutic regimen are made. The principal causes of treatment failure and its diagnostic approach are summarized in Figure 5. A reevaluation of the therapeutic regimen and of the diagnosis before 72 h of treatment should only be considered in cases of progressive clinical deterioration, conflicting culture results or alternative microbiological diagnosis.

### **Recommendations**

- After the initiation of treatment for CAP, all patients (including outpatients) should be systematically evaluated for clinical evolution (level III evidence).
- In suspected cases of treatment failure, clinical history of patients and initial results of microbiological tests should be initially reviewed.
- Microbiological reevaluation can be performed using noninvasive or invasive techniques or a combination of the two (level III evidence).
- Procalcitonin and C-reactive protein can be used as biological and inflammatory markers for the identification, since the initial evaluation, of patients at risk for treatment failure (level II evidence).

## **Prevention through vaccination**

### **Influenza vaccine**

The influenza vaccine can be administered to all those who wish to reduce the risk of becoming infected with the flu or of transmitting the virus to others. However, systematic annual vaccination should be aimed at groups of individuals at higher risk of becoming infected with influenza and of experiencing the complications thereof.<sup>(126)</sup>

The following are considered adult individuals at high risk of flu-related complications<sup>(126)</sup>:

- Adults aged  $\geq 50$  years

- Patients with chronic lung diseases (including asthma), cardiovascular diseases (except systemic arterial hypertension), kidney diseases, liver diseases, hematologic diseases and metabolic diseases (including diabetes mellitus)
  - Immunosuppressed adults, including those immunosuppressed by medication use and by HIV
  - Patients with neuromuscular disorders, because lung function is affected and because it is difficult to clear secretions from the respiratory tract
  - Pregnant (or breastfeeding) women and women who plan to become pregnant during the influenza season
  - Nursing home residents and individuals receiving home care
  - Potential transmitters of the virus to individuals at higher risk
  - Health professionals
  - Home caregivers of children ( $< 5$  years of age) and of adults ( $> 50$  years of age), particularly in the presence of other diseases with risk of complications
  - Professionals that provide health care services to patients receiving home care
- The following individuals should not be vaccinated:
- Individuals with known hypersensitivity to egg protein or to certain components of the vaccine
  - Individuals with acute febrile illness

### **Recommendations**

- All individuals aged  $\geq 50$  years, individuals at increased risk of flu-related complications, people in household contact with others at high risk and health professionals should be given inactivated influenza vaccine (level I evidence).
- The following individuals are particularly susceptible to flu-related complications: patients with chronic lung diseases (including asthma); patients with chronic cardiovascular diseases; patients with metabolic diseases (including diabetes mellitus); patients with renal dysfunction; patients with hemoglobinopathies; immunosuppressed patients (including patients with treatment-induced or HIV-related immu-

nosuppression); pregnant women; and nursing home residents (level I evidence).

- Individuals with hypersensitivity to egg protein should not be given influenza vaccine (level III evidence).
- Patients with acute febrile illness should only be given influenza vaccine after the resolution of the symptoms (level III evidence).

### ***Pneumococcal vaccine***

Pneumonia, bacteremia and meningitis are the principal clinical syndromes associated with invasive pneumococcal disease. In approximately 50% of all adult cases of CAP, *S. pneumonia* is the causative agent. Together with influenza, pneumococcal disease constitutes one of the leading causes of death among elderly individuals. Bacteremia occurs in up to one third of the cases. Approximately 20% of individuals aged 80 years or older die from pneumococcal bacteremia.<sup>(127)</sup> The bacterial capsule, composed of polysaccharides, is the principal element responsible for the virulence of the pneumococcus. Vaccines composed of polysaccharides have been used to prevent invasive pneumococcal infections. The current pneumococcal polysaccharide vaccine provides protection against 23 of the 90 known pneumococcal serotypes (23-valent pneumococcal polysaccharide vaccine).

According to the current recommendation of the Advisory Committee of Immunization Practices of the Centers for Disease Control, target populations include the following<sup>(127)</sup>:

- Individuals aged  $\geq 65$  years
- Individuals with chronic disease, ranging in age from 2 to 64 years, particularly vulnerable to invasive infections, e.g., chronic cardiovascular diseases and chronic lung diseases (except asthma), and the complications thereof, as well as those with diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid fistula, cochlear implants or asplenia (anatomic or functional)
- Immunocompromised individuals: patients with HIV/AIDS; patients with malignant disease or hematologic malignancies; patients with chronic renal failure or nephrotic syndrome; patients using corti-

costeroids or immunosuppressants; and transplant recipients

- Nursing home residents

Most individuals require only one application of the vaccine. Revaccination is recommended after a minimum of 5 years for immunocompromised individuals and for those who received the first dose before 65 years of age. The vaccine is well-tolerated. Local reactions might occur (edema, pain and hyperemia); systemic manifestations (fever, myalgia and arthralgia) are rare and self-limited.

### ***Recommendations***

- The pneumococcal vaccine is recommended for all individuals aged  $\geq 65$  years (level II evidence).
- The vaccine should also be given to individuals (aged 2-64 years) with high-risk comorbidities that make such individuals vulnerable to invasive pneumococcal infections and the complications thereof (level II evidence).
- The pneumococcal vaccine should be given to immunocompromised patients and nursing home residents (level II evidence).

### **Severe community-acquired pneumonia: adjuvant treatment**

#### ***Fluid resuscitation in severe pneumonia***

Within the first hours after the onset of sepsis, venodilation, the transudation of fluid from the vascular space to the tissues and the reduction in oral ingestion, together with the increase in insensible water loss, lead to hypovolemia. Tissue perfusion is further compromised by arteriolar dilation, ventricular dysfunction and vascular obstruction.<sup>(128,129)</sup>

Fluid resuscitation in cases of severe sepsis or septic shock should be initiated as early as possible, preferably in the emergency room, before ICU admission. Hypoperfusion in patients without hypotension, as evidenced by serum lactate levels  $\geq 4$  mmol/dL, indicates higher-risk patients. These patients should be submitted, as soon as possible, to arterial and central venous catheterization, aiming to achieve the following hemodynamic objectives: central venous pressure  $\geq 8$  cmH<sub>2</sub>O; mean arterial pressure

(MAP)  $\geq 65$  mmHg; urinary output  $\geq 0.5$  mL/kg/h and central venous saturation (ScvO<sub>2</sub>)  $\geq 70\%$ . Such objectives should be achieved within the first 6 h after the diagnosis (in many cases, even before ICU admission). If an ScvO<sub>2</sub>  $\geq 70\%$  is not achieved with aggressive fluid resuscitation within the first 6 h after the diagnosis, a packed red blood cell transfusion should be given until hematocrit is  $\geq 30\%$ , and dobutamine should be administered if necessary (maximum dose of 20 mg/kg per min).

There is no definitive evidence that aggressive fluid resuscitation is effective in individuals with severe sepsis showing MAP  $\geq 65$  mmHg or lactate  $< 4$  mmol/L, or a combination of the two. However, ScvO<sub>2</sub> and low urinary output might be early and independent markers of the low flow that precedes hypotension and the significant increase in serum lactate. Therefore, each variable and its respective target should be evaluated in conjunction, respecting the clinical context.<sup>(128-131)</sup>

Fluid resuscitation can be performed by i.v. injection of crystalloids or colloids, which should be administered early.<sup>(131)</sup>

Crystalloids are isotonic or hypertonic ionic solutions. The most commonly used are 0.9% saline solution and lactated Ringer's solution (both isotonic). Crystalloids are inexpensive and nontoxic; however, they produce less volume expansion than do colloids, which are more expensive and pose a higher risk of side effects.<sup>(132)</sup>

Colloids are solutions of high molecular weight that can exert oncotic pressure. The most commonly used are albumin, dextran, gelatins and hydroxyethyl starch. In addition to replacing blood volume, the ideal colloid should have a favorable impact on the modulation of the inflammatory process of sepsis, e.g., increased capillary permeability, tissue edema formation and impaired vasomotor control, as well as rheological alterations caused by abnormalities in the activation and adhesion of neutrophils. The physiological characteristics and clinical effects of colloids and crystalloids are well known. However, a detailed description of crystalloid solutions would be outside the scope of the present guidelines. It should be borne in mind that the effect of colloids, their expansion and their duration depend on molecular weight, molecule size, electric charge and metaboliza-

tion. Some points should be highlighted: all colloids have anti-oncotic properties, not yet fully understood, which can influence vascular integrity and inflammation; all colloids affect the coagulation system, dextran and starch having a greater antithrombotic effect; colloids replace intravascular volume more rapidly than do crystalloids in all shock states, regardless of vascular permeability.

Initial fluid resuscitation in patients with sepsis can be performed with both types of volume expanders, i.e., crystalloids and colloids, since there is no definitive evidence in the literature that one is superior to the other regarding the outcomes of different types and etiologies of shock.

### **Recommendation**

- Volume replacement should be promptly initiated in patients with severe sepsis and hypotension (MAP  $\leq 65$  mmHg), and perfusion parameters should be monitored in order to achieve stable levels within the first 6 h (level III evidence).

### **Activated protein C**

The use of drotrecogin alfa (activated), or activated protein C, albeit still controversial, has been recommended for patients in whom initial therapeutic measures do not result in sepsis control.<sup>(131,133)</sup> In such cases, the use of activated protein C correlates with reduced mortality and improved organ function.<sup>(133)</sup> In one study, patients with severe sepsis and at high risk of death, as indicated by an Acute Physiology and Chronic Health Evaluation score  $\geq 25$ , as well as patients presenting dysfunction of two or more organs, benefitted from activated protein C treatment. Apparently, the best results were observed in a subpopulation composed of patients with pneumonias. The activated protein C dose used was 24  $\mu$ g/kg per min for 96 h. However, because it was an analysis of subgroups of patients, such results need to be confirmed by prospective randomized studies focusing specifically on pneumonia patients.<sup>(131)</sup>

### **Recommendations**

- The current controversy regarding the benefits of activated protein C reported in early studies weighs against its use, which

is not recommended until further data regarding the cost-benefit ratio of the treatment is obtained (level II evidence).

- Activated protein C is not recommended for patients with sepsis and at low risk of death (level II evidence).

### ***Systemic corticosteroid in community-acquired pneumonia***

A large multicenter clinical trial demonstrated that hydrocortisone at doses of 200-300 mg/day had a beneficial effect on vasopressor-dependent patients with septic shock who did not adequately respond to the cortisol test.<sup>(134)</sup> However, in a recent randomized controlled clinical trial, this therapeutic approach was found to offer no advantages, because although septic shock was more easily reversed in the group that received hydrocortisone than it was in the placebo group, episodes of superinfection (including sepsis and septic shock) were more common in the former.<sup>(135)</sup> Four clinical trials evaluated the use of systemic corticosteroids for the treatment of CAP patients. Two of those studies showed a significant improvement of markers of systemic inflammation<sup>(136,137)</sup>; however, due to the small size of the sample, the findings were insufficient to demonstrate improvements in clinical outcomes. One clinical study demonstrated that a 7-day course of treatment with low-dose hydrocortisone injection correlated with significantly reduced duration of mechanical ventilation and of ICU stay, as well as with reduced in-hospital mortality.<sup>(138)</sup> Another study demonstrated that the use of systemic corticosteroids was independently associated with reduced mortality, and severe pneumonia was the only independent factor associated with increased mortality.<sup>(139)</sup> The limiting factors of that study included the retrospective design, the absence of determination of cortisol levels and the administration of corticosteroids at different time points throughout the treatment.

To date, there have been no studies employing adequate methodologies and samples that can warrant the recommendation of systematic use of systemic corticosteroid in all CAP patients. However, in patients with severe pneumonia and septic shock who have previously received adequate fluid replacement and vasopressors and

have not responded satisfactorily, the possibility of suprarenal failure should be considered.

### ***Recommendation***

- Despite having undergone adequate volume replacement and being dependent on vasoactive drugs, patients with severe CAP and arterial hypotension can receive i.v. injection of hydrocortisone (level II evidence).

### ***Noninvasive ventilation***

Patients with severe CAP are known to be at greater risk of early death due to circulatory collapse and of late death due to hypoxemic respiratory failure type.<sup>(140)</sup>

Therefore, noninvasive ventilation might be useful for severe CAP patients with hypoxemia or respiratory failure, unless immediate intubation is needed ( $PaO_2/FiO_2 < 150$  and bilateral alveolar infiltrate).<sup>(81,141)</sup> Patients should be closely monitored in the first 2 h. If respiratory rate, oxygenation or hypercarbia do not improve, invasive ventilation is clearly indicated.

It has also been shown that the use of tidal volume at low levels ( $6 \text{ cm}^3/\text{kg}$  of ideal weight) can have beneficial effects on the survival of severe CAP patients requiring invasive ventilation.<sup>(81,141)</sup>

### ***Recommendations***

- Noninvasive ventilation can be beneficial to severe CAP patients with hypoxemia or hypoxemic respiratory failure (level I evidence).
- The use of low tidal volumes can be beneficial to severe CAP patients requiring invasive ventilation (level I evidence).

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