



## 2018 recommendations for the management of community acquired pneumonia

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### ABSTRACT

Community-acquired pneumonia (CAP) is the leading cause of death worldwide. Despite the vast diversity of respiratory microbiota, *Streptococcus pneumoniae* remains the most prevalent pathogen among etiologic agents. Despite the significant decrease in the mortality rates for lower respiratory tract infections in recent decades, CAP ranks third as a cause of death in Brazil. Since the latest Guidelines on CAP from the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) were published (2009), there have been major advances in the application of imaging tests, in etiologic investigation, in risk stratification at admission and prognostic score stratification, in the use of biomarkers, and in the recommendations for antibiotic therapy (and its duration) and prevention through vaccination. To review these topics, the SBPT Committee on Respiratory Infections summoned 13 members with recognized experience in CAP in Brazil who identified issues relevant to clinical practice that require updates given the publication of new epidemiological and scientific evidence. Twelve topics concerning diagnostic, prognostic, therapeutic, and preventive issues were developed. The topics were divided among the authors, who conducted a nonsystematic review of the literature, but giving priority to major publications in the specific areas, including original articles, review articles, and systematic reviews. All authors had the opportunity to review and comment on all questions, producing a single final document that was approved by consensus.

**Keywords:** Pneumonia/diagnosis; Pneumonia/prevention & control; Pneumonia/therapy; Pneumonia/drug therapy.

### INTRODUCTION

Community-acquired pneumonia (CAP) is the leading cause of death worldwide, with a significant impact on morbidity rates.<sup>(1)</sup> Despite the vast diversity of respiratory microbiota, the widespread dissemination of potentially pathogenic agents, the phenomenon of globalization, and the occurrence of viral epidemics, *Streptococcus pneumoniae* remains the most prevalent pathogen among the etiologic agents of CAP.<sup>(2)</sup>

In Brazil, as well as in other countries, there has been a significant decrease in the mortality rates for respiratory tract infections, although the magnitude of this decrease has lessened in recent decades. Among pneumonias, CAP remains the one with the greatest impact and is the third leading cause of mortality in Brazil. Although the absolute number of deaths in Brazil has increased because of population growth and aging, when the mortality rate for CAP is standardized by age, a 25.5% decrease is observed between 1990 and 2015.<sup>(3)</sup> An improved socioeconomic situation, greater access to health care, national availability of antibiotics, and vaccination policies partially explain the decrease in mortality rates in Brazil.<sup>(4)</sup>

Since the latest Guidelines on CAP from the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) were published,<sup>(5)</sup> several topics have been reviewed, such as advances in the application of imaging tests; advances in and impact of etiologic investigation, particularly investigation of viral etiology and atypical pathogens in subgroups of patients; risk stratification at admission; prognostic score stratification; the role of biomarkers in therapeutic management;

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recommendations for antibiotic therapy and its duration; and recommendations regarding influenza and pneumococcal vaccination.

## METHODS

The authors consensually determined specific topics to be addressed, on the basis of relevant publications in the literature on CAP with regard to imaging tests, etiologic investigation, risk stratification at admission and prognostic score stratification, use of biomarkers, recommendations for antibiotic therapy and its duration, and prevention through vaccination. To review these topics, the SBPT Committee on Respiratory Infections summoned 13 members with recognized experience in CAP in Brazil who developed 12 questions concerning the previously determined topics. The questions were divided among the authors, who conducted a nonsystematic review of the literature, but giving priority to major publications in the specific areas, including original articles, review articles, and systematic reviews. All participants had the opportunity to review and comment on all questions, producing a document that was approved by consensus at the end of the process.

## RECOMMENDATIONS FOR IMAGING METHODS IN CAP

### *Chest X-ray*

Chest X-ray, in combination with anamnesis and physical examination, is part of the classic diagnostic triad for CAP; it is recommended that, when available, posteroanterior and lateral chest X-rays should be routinely performed. In addition to contributing to diagnosis, chest X-ray allows us to assess the extent of the lesions and detect complications, as well as facilitating differential diagnosis.<sup>(6)</sup>

Despite the existence of numerous guidelines, there is no consensus regarding recommendations for the management of CAP in primary care, especially in terms of ancillary tests, which are often not readily available. At this level of care, when the clinician is sure of the diagnosis, chest X-ray is not required for treatment initiation, and antimicrobials can be prescribed appropriately. However, fewer than 40% of physicians are able to diagnose pneumonias solely on the basis of physical examination. In this context, chest X-ray should be mandatory for patients with suspected CAP.<sup>(7)</sup> Chest X-ray is also recommended if there is doubt about the diagnosis or differential diagnosis from lung cancer is required and if, during treatment follow-up, clinical response is unsatisfactory. Chest X-ray is recommended for all patients admitted to the hospital.<sup>(8,9)</sup>

### *Chest ultrasound*

Chest ultrasound (CUS) has greater sensitivity and accuracy in detecting parenchymal changes than does chest X-ray. Major ultrasound findings in CAP include consolidations, a focal interstitial pattern, subpleural lesions, and pleural line abnormalities. The specificity

of CUS for consolidations is 100%, whereas chest X-ray reaches a sensitivity of only 94% for this type of change.<sup>(10)</sup>

Bedside ultrasound performed by clinicians in the emergency department has a sensitivity of 95% and a negative predictive value of 67% in the diagnosis of CAP, compared with 60% and 25%, respectively, for chest X-ray. Specificity is similar for both diagnostic methods.<sup>(11,12)</sup>

When conducted by ultrasound specialists, ultrasound reaches a sensitivity of 94% and a specificity of 96%. However, the yield of ultrasound conducted by clinicians in the emergency department has yet to be further evaluated, and more robust evidence is needed. It is important to bear in mind the usefulness of U/S in pregnant women and bedridden individuals, in whom X-ray quality is lower than desired. In addition, CUS has a high yield in detecting complications such as pleural effusion, as well as permitting visualization of loculations in the cavity. Referral for aspiration of pleural effusion (whether loculated or not) is one of the indications for CUS.<sup>(13-16)</sup> Therefore, the need for specific training in ultrasound and the unavailability of the method in primary care and in many health care facilities in Brazil currently restrict the use of ultrasound to advanced care centers.

### *Chest CT*

Chest CT is the most sensitive method for identifying infectious involvement of the lung parenchyma, despite its high cost and the high level of radiation exposure.<sup>(17)</sup>

Chest CT is especially useful in cases in which the accuracy of chest X-ray and chest U/S is low, such as in obese patients, immunosuppressed patients, and individuals with previous abnormal radiological findings. In addition, chest CT is indicated in suspected fungal infections and for assisting the exclusion of other diagnoses in selected cases. In one study, the use of chest CT in patients with suspected CAP in the emergency department resulted in 16% of the patients having alternative diagnoses or findings, such as pulmonary thromboembolism and neoplasia, and, of those, 8% were diagnosed with pulmonary tuberculosis.<sup>(18)</sup> More recently, other authors have demonstrated that the use of chest CT increases the rate of diagnosis in patients with CAP and normal chest X-rays, but it may also not confirm the disease in patients with opacities on chest X-rays, which would allow the discontinuation of antibiotics in a significant proportion of cases.<sup>(19,20)</sup>

Because of the high radiation exposure from CT, some authors have suggested the use of chest U/S as an intermediate ancillary test before the use of CT in the diagnosis of difficult-to-diagnose cases.<sup>(21)</sup>

In addition, the importance of chest CT in the assessment of CAP-related complications, such as lung abscess and loculated pleural effusion, and in the investigation of reasons for the lack of clinical response to treatment has been emphasized.<sup>(22,23)</sup>

## ETIOLOGIC INVESTIGATION OF OUTPATIENT AND INPATIENT CAP: WHAT ARE THE RECOMMENDATIONS?

Although there may be inadequate response to empiric treatment, etiologic testing is not necessary in patients with non-severe CAP receiving outpatient treatment. Therefore, the recommendations that etiologic testing be performed only in patients with severe CAP or CAP unresponsive to the initial empiric treatment regimen, as well as in ICU patients, remain valid.

In selecting tests to be performed, one should take into account patient age, presence of comorbidities, disease severity, and prior anti-infective therapy.<sup>(24)</sup>

The development of new methods for microbiological identification in general, and for microbiological identification of CAP in particular, has increased the chances of adequately choosing the spectrum of the antibiotic to be used in the treatment of pneumonia. Of note are radiological methods, such as chest U/S, and microbiological methods, namely Multiplex PCR<sup>(25)</sup> and matrix-assisted laser desorption ionization-time of flight mass spectrometry, a promising method for rapid identification of pathogens.<sup>(26)</sup>

With regard to microbiological studies, direct examination and culture of sputum samples (or of nasotracheal aspirates for patients who cannot expectorate) should meet sample quality criteria, that is, fewer than 10 epithelial cells and more than 25 leukocytes per field examined. In addition, technical norms for collection, transport, and analysis of biological samples should be adhered to.<sup>(27)</sup>

In an observational study of 670 hospitalized patients with CAP, 478 good quality sputum samples were obtained of a total of 591 samples. Specificity was much higher than sensitivity (*S. pneumoniae*: 91.5% vs. 62.5%), very similar to those of other bacterial agents identified. It is of note that the treatment of the cases in which the pathogen was identified was similar to the treatment started empirically.<sup>(28)</sup>

Molecular tests have been shown to be more effective in detecting atypical agents. Film array respiratory panel is a rapid (1 hour), multiplex molecular test that detects 20 respiratory pathogens (17 viruses and three bacteria: *Mycoplasma pneumoniae*, *Chlamydomphila pneumoniae*, and *Bordetella pertussis*). Another test (Nxtag respiratory pathogen panel) can identify 18 viruses, *M. pneumoniae*, and *C. pneumoniae*.<sup>(29)</sup> The current recommendations for the use of molecular tests include: (1) highly accurate rapid testing for influenza; (2) rapid molecular testing for *M. tuberculosis* (feasible in a few hours); (3) rapid testing for respiratory viruses that can cause CAP or lower respiratory tract infection; and (4) rapid testing for detecting atypical pathogens (*M. pneumoniae*, *C. pneumoniae*, *Legionella* sp., and *B. Pertussis*).<sup>(30)</sup>

Patients with severe CAP should be etiologically investigated with the basic tests available: sputum smear microscopy and sputum culture; blood culture; urinary antigen testing for *S. pneumoniae* and *Legionella* sp.;

serological tests; and, eventually, culture for atypical pathogens. In selected cases and in an appropriate clinical context, special cultures and galactomannan and (1-3)- $\beta$ -D-glucan tests for fungi, as well as the latest antigen or molecular biology tests for viruses and atypical pathogens, may be performed, but are not indicated in the routine management of CAP.

In patients on mechanical ventilation, in nonresponders to the initial empiric therapy, and in those in whom less common etiologic agents are suspected, as well as in cases in which differential diagnosis from noninfectious lung diseases, such as tumors, vasculitis, or interstitial lung disease, is required, it may be necessary to collect samples invasively via bronchoscopy, endotracheal aspiration, bronchoalveolar lavage, or thoracentesis, in cases of ipsilateral pleural effusion.<sup>(5)</sup>

## ROLE OF VIRUSES AND RECOMMENDATIONS FOR THEIR INVESTIGATION IN CAP

The advent of the use of molecular tests in clinical practice has signaled that viruses play a more relevant role as possible etiologic agents of CAP. Studies including PCR as a diagnostic tool in their scope have detected viruses in approximately one third of CAP cases in adults,<sup>(20,21)</sup> with influenza being the most commonly isolated virus. In addition of influenza, other viral agents, such as rhinovirus, respiratory syncytial virus, parainfluenza virus, adenovirus, and metapneumovirus, are considered possible etiologic agents of CAP.<sup>(31)</sup> Musher et al. evaluated 259 patients hospitalized for CAP, in order to identify the etiologic agents. Forty-four viruses were identified in 42 patients: rhinovirus, in 26; coronavirus, in 7; parainfluenza, in 4; respiratory syncytial virus, in 3; metapneumovirus, in 1; and influenza, in 1. Viruses were the only pathogens detected in 30 of the patients. The authors found strong evidence of the activity of viruses as causative agents of pneumonia in 28 of the 42 patients.<sup>(32)</sup>

However, uncertainty remains as to the true role of viruses in CAP because of the difficulty in determining whether viruses act as co-pathogens or as colonizers. One example of this is in a study by Jartti et al., which showed the presence of viruses in nasopharyngeal swabs in approximately 30% of healthy adults. However, isolation of influenza, respiratory syncytial virus, and metapneumovirus is rare in asymptomatic adults.<sup>(33)</sup>

Another possible activity of viruses in CAP would be impairment of the defense mechanisms of the upper airways, facilitating the establishment of another microorganism in the lower airways; this seems to be the role of rhinovirus and coronavirus.<sup>(34,35)</sup> Interaction between viruses and bacteria seems to be associated with a more severe clinical profile of CAP. Johansson et al. demonstrated that viral-bacterial coinfection occurred in 20% of the cases, being responsible for more severe pneumonia requiring longer hospitalization than does CAP caused by a bacterial agent alone.<sup>(34)</sup>

The evidence from those studies support that ancillary tests, particularly molecular tests, such as PCR, are indicated for the diagnosis of viruses especially in cases of severe CAP.<sup>(36)</sup>

### CURRENT STATUS OF SCORING SYSTEMS FOR THE ASSESSMENT OF CAP SEVERITY AT ADMISSION AND SCORING SYSTEMS FOR EARLY IDENTIFICATION OF RISK FOR THE NEED VENTILATORY AND/OR VASOPRESSOR SUPPORT TO PREVENT THE DEVELOPMENT OF SEVERE SEPSIS OR TREATMENT FAILURE. WHAT ARE THE RECOMMENDATIONS?

Patients with a diagnosis of CAP should always be assessed for disease severity, a precaution that has a direct positive impact on mortality.<sup>(37-40)</sup> Currently available prognostic scoring systems measure severity and help predict prognosis in CAP, informing the decision regarding site of care (outpatient, inpatient, or ICU), the need for etiologic investigation, and the choice of antibiotics and their route of administration.<sup>(5,37)</sup>

Validated instruments include the Pneumonia Severity Index (PSI); mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age  $\geq 65$  years (CURB-65); CRB-65 (no measurement of urea); the 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines; **S**ystolic blood pressure, **M**ultilobar involvement, **A**lbumin, **R**espiratory rate, **T**achycardia, **C**onfusion, **O**xygenation, and **pH** (SMART-COP); and Severe Community-Acquired Pneumonia (SCAP)—the last three being related to severe pneumonia and ICU admission.<sup>(41-46)</sup>

It is important to stress that disease severity as determined by scoring systems is a major factor in the decision regarding hospital admission; however, other factors, such as the possibility of using oral drugs, comorbidities, psychosocial factors and socioeconomic characteristics that indicate vulnerability of the individual, should be taken into account.<sup>(5,22,44)</sup> Ideally, SpO<sub>2</sub> should always be monitored: SpO<sub>2</sub> values below 92% should be an indication for hospital admission.<sup>(22,47)</sup>

#### PSI

The PSI comprises 20 items including demographic characteristics, comorbidities, abnormal laboratory test results, abnormal radiological findings, and physical examination findings.<sup>(41)</sup> The PSI classifies patients into five categories, estimating 30-day mortality and suggesting the site of care (Charts 1 and 2). However, the PSI may underestimate CAP severity in young patients without concomitant diseases because its scoring system gives too much weight to age and presence of comorbidities.<sup>(22,39)</sup>

Another negative point is the use of many variables, which makes calculation complex; however, this calculation can be facilitated by using calculators available online, such as the PSI/Pneumonia Patient

Outcomes Research Team (PORT) Score: PSI for CAP and PSI Calculator.<sup>1</sup>

#### CURB-65 and CRB-65

CURB-65 is an acronym for the variables it assesses: mental **C**onfusion (an Abbreviated Mental Test score  $\leq 8$ )<sup>(48)</sup>; **U**rea  $> 50$  mg/dL; **R**espiratory rate  $> 30$  breaths/min; **B**lood pressure (systolic  $< 90$  mmHg or diastolic  $< 60$  mmHg; and age  $\geq 65$  years (Figure 1).<sup>(42)</sup> CRB-65 (no measurement of urea), which is a simplified version of CURB-65, is useful in settings in which laboratory tests are not available, such as in primary care (Figure 2).<sup>(43)</sup>

The major limitation of CURB-65 and CRB-65 is the exclusion of comorbidities that may increase the risk of complications in CAP, such as alcoholism, heart or liver failure, and neoplasia, which results in their negative predictive value for mortality being slightly lower than that of the PSI.<sup>(5,40)</sup> However, CURB-65 and CRB-65 are qualified by their simplicity, immediate applicability, and ease of use, whether in the hospital setting or elsewhere.

#### 2007 ATS/IDSA guidelines

The severity criteria proposed in the ATS/IDSA consensus guidelines<sup>(44)</sup> and their simplified version<sup>(49)</sup> are classified as major or minor (Chart 3). The presence of one of the major criteria (septic shock or need for mechanical ventilation) is an indication for ICU admission. The presence of three or more minor criteria is also an indication for intensive care. These criteria, however, do not lend themselves to the assessment of outpatients, which is why the guidelines themselves recommend the use of the PSI or CURB-65 to inform decision-making about outpatients.

#### SCAP and SMART COP

Other tools for predicting the occurrence of severe CAP have been developed to assess outcomes other than the generic risk of death or ICU admission. These outcomes include, in addition to the need for ICU admission, the development of severe sepsis, the need for mechanical ventilation, and the risk of treatment failure, for SCAP, and outcomes more specifically associated with the need for the use of invasive or noninvasive mechanical ventilatory support or the use of vasopressors for circulatory support, for SMART-COP.<sup>(45,46)</sup>

These outcomes have been considered more objective markers of CAP severity, given the heterogeneity of indications and protocols for ICU admission across different institutions and health care systems.

#### SCAP

The major criteria are pH  $< 7.30$  (13 points) and systolic blood pressure  $< 90$  mmHg (11 points). The

1 <https://www.mdcalc.com/psi-port-score-pneumonia-severity-index-cap>

[https://www.thecalculator.co/health/Pneumonia-Severity-Index-\(PSI\)-Calculator-977.html](https://www.thecalculator.co/health/Pneumonia-Severity-Index-(PSI)-Calculator-977.html)

**Chart 1.** Pneumonia Severity Index scoring.

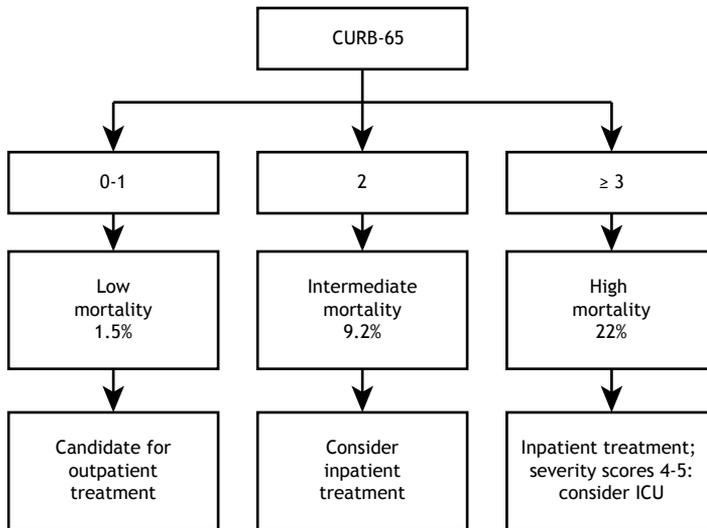
Demographic factors	Score	Laboratory and radiological findings	Score
Age, years		pH < 7.35	+30
Men	n	Urea > 65 mg/L	+20
Women	n - 10	Sodium < 130 mEq/L	+20
Nursing home residents	+10	Glucose > 250 mg/L	+10
		Hematocrit < 30%	+10
		PO <sub>2</sub> < 60 mmHg	+10
		Pleural effusion	+10
Comorbidities		Physical examination	
Neoplasia	+30	Altered mental status	+20
Liver disease	+20	RR > 30 breaths/min	+20
CHF	+10	SBP < 90 mmHg	+20
Cerebrovascular disease	+10	Temperature < 35° or > 40° C	+15
Kidney disease	+10	HR ≥ 125 bpm	+10

Adapted from Corrêa et al.<sup>(5)</sup> CHF: congestive heart failure; and SBP: systolic blood pressure.

**Chart 2.** Risk stratification by the Pneumonia Severity Index.

Class	Points	Mortality, %	Suggested site of care
I	-	0.1	Outpatient
II	≤ 70	0.6	Outpatient
III	71-90	2.8	Outpatient or brief inpatient
IV	91-130	8.2	Inpatient
V	> 130	29.2	Inpatient

Adapted from Corrêa et al.<sup>(5)</sup>



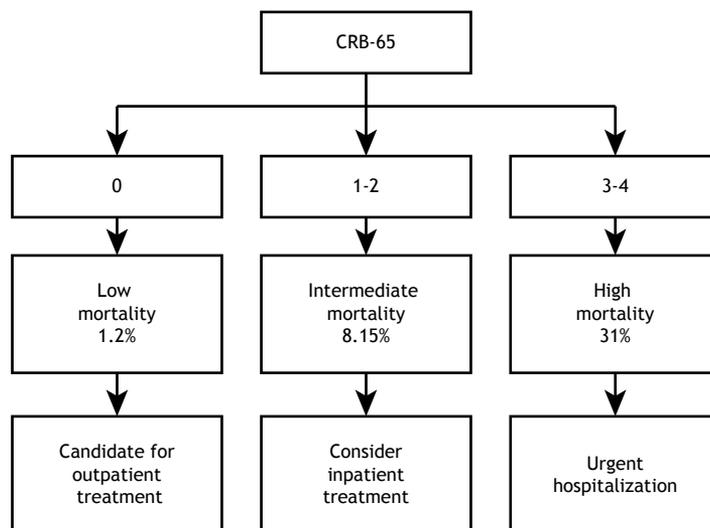
**Figure 1.** CURB-65 score and suggested site of care for patients with community-acquired pneumonia. Adapted from Corrêa et al.<sup>(5)</sup> CURB-65: mental Confusion; Urea > 50 mg/dL; Respiratory rate > 30 breaths/min; Blood pressure (systolic < 90 mmHg or diastolic < 60 mmHg); and age ≥ 65 years; and CAP: community-acquired pneumonia.

minor criteria are RR > 30 breaths/min (9 points); PaO<sub>2</sub>/FiO<sub>2</sub> < 250 (6 points); urea > 30 mg/dL (5 points); altered level of consciousness (5 points); age ≥ 80 years (5 points); and radiological findings of multilobar or bilateral infiltrate (5 points).<sup>(46)</sup>

A score ≥ 10 predicts an increased risk for the use of mechanical ventilation and the need for vasoactive drugs.<sup>(46)</sup>

### SMART-COP

The SMART-COP scoring system is as follows: systolic blood pressure < 90 mmHg (2 points); multilobar involvement (1 point); albumin < 3.5 g/dL (1 point); RR ≥ 25 breaths/min (1 point); HR > 125 bpm (1 point); mental confusion (1 point); SpO<sub>2</sub> < 93% or PaO<sub>2</sub> < 70 mmHg (2 points); and pH < 7.30 (2 points).<sup>(45)</sup> A score greater than 3 identified 92% of the patients



**Figure 2.** CRB-65 score and suggested site of care for patients with community-acquired pneumonia. Adapted from Corrêa et al.<sup>(5)</sup> CRB-65: **C**onfusion; **R**espiratory rate > 30 breaths/min; **B**lood pressure (systolic < 90 mmHg or diastolic < 60 mmHg); and age  $\geq$  65 years.

**Chart 3.** Risk stratification based on a simplified version of the American Thoracic Society/Infectious Diseases Society of America consensus guidelines criteria.

Major criteria	
Septic shock	Need for mechanical ventilation
Minor criteria	
RR > 30 breaths/min	Mental confusion
PaO <sub>2</sub> /FiO <sub>2</sub> < 250	Urea $\geq$ 20 mg/dL
Multilobar infiltrates	SBP < 90 mmHg

SBP: systolic blood pressure.

who required mechanical ventilation or vasoactive drugs during the course of CAP.

Therefore, it is recommended that patients with CAP should be objectively evaluated in the emergency room for initial disease severity and for early identification of risk of developing severe outcomes, such as the need for ICU admission, the development of severe sepsis, the need for invasive or noninvasive ventilatory support, the need for inotropic support, or the risk of treatment failure (SCAP, SMART-COP, or the simplified version of the ATS/ISDA criteria, although further external validation is still required). In the absence of severe CAP, socioeconomic indications for hospital admission, concomitant decompensated diseases, and hypoxemia, and when oral intake of medications is possible and there is a score of 0-1 on CURB-65 (or a score of 0 on CRB-65 or a score of 70 or less on the PSI), the attending physician should consider outpatient treatment for patients with CAP.

### RECOMMENDATIONS FOR THE USE OF BIOMARKERS IN THE MANAGEMENT OF CAP

A biomarker is defined as any measurable molecule that can help diagnose or estimate prognosis of patients

with a clinical condition. Since CAP is a condition with intense inflammatory activity, several studies have evaluated various biomarkers (C-reactive protein, procalcitonin, proadrenomedullin, lactate, natriuretic atrial peptide, D-dimers, cortisol, etc.) in recent years, with C-reactive protein and procalcitonin being the most commonly studied. Procalcitonin is produced in large quantities by parenchymal cells in response to bacterial toxins and proinflammatory cytokines, but its production is minimized in the presence of viral infections. Procalcitonin levels increase within 2 h after bacterial stimulation, more rapidly than do C-reactive protein levels, and are even more specific for bacterial infections, given that C-reactive protein levels increase in any inflammatory process.<sup>(50,51)</sup>

C-reactive protein is secreted by hepatic cells in response to an increase in interleukin-6, interleukin-1 $\beta$ , and TNF- $\alpha$  levels. Other recognized sources of C-reactive protein are lymphocytes, monocytes, neurons, and atherosclerotic plaques. C-reactive protein levels peak approximately 48 h after an injurious stimulus, and the plasma half-life of C-reactive protein is approximately 19 h both in health and in disease. Müller et al.<sup>(52)</sup> demonstrated a significant improvement in diagnostic accuracy when they combined the determination of procalcitonin and C-reactive protein levels with clinical signs and symptoms in patients with suspected CAP who were treated in primary care and emergency settings. These biomarkers outperformed increased leukocyte counts and body temperature, and helped differentiate between patients with bacteria and those without. The area under the curve for clinical signs and symptoms alone was 0.79 (95% CI: 0.75-0.83), whereas, for clinical signs and symptoms combined with procalcitonin and ultra-sensitive C-reactive protein levels, it was 0.92 (95% CI: 0.89-0.94;  $p < 0.001$ ). A recent study investigated the value of four biomarkers

and three severity scales in predicting 28-day mortality in patients with CAP who were treated in emergency settings.<sup>(53)</sup> The results showed that procalcitonin was the best single biomarker for predicting mortality. The models combining procalcitonin and/or C-reactive protein with the PSI showed better results than did the PSI alone.<sup>(53)</sup> A recent study demonstrated that, if C-reactive protein levels do not decrease by 50% within 3 days of treatment and remains above 75 mg/L, the risk of 30-day mortality is increased.<sup>(54)</sup> A study of 191 patients with CAP admitted to the ICU showed that mortality was 4.8% among those in whom C-reactive protein levels decreased rapidly (n = 66), 17.3% among those in whom C-reactive protein levels decreased slowly (n = 81), and 36.4% among those in whom C-reactive protein levels did not decrease (n = 44).<sup>(55)</sup> Therefore, on the basis of the findings of those studies, procalcitonin can be used as an aid in the diagnosis of CAP, and procalcitonin and/or C-reactive protein can be used in the assessment of treatment response. It is important to emphasize that biomarkers should be used in complement to clinical evaluation rather than as a single criterion to determine or change the therapeutic approach (Chart 4 and Figure 3).

A recently updated meta-analysis of 50 clinical trials, including data from 12 countries, demonstrated that the use of procalcitonin as a guide for initiation and duration of antibiotic therapy resulted in a reduced risk of mortality, reduced antibiotic use, and a reduced risk of antibiotic-related side effects.<sup>(56)</sup> The results were similar for any type of lower respiratory tract infection. It is important to emphasize that treatment failure was similar between cases in which antibiotic discontinuation was guided by a decrease in procalcitonin levels and those cases in which procalcitonin was not used to guide antibiotic discontinuation.<sup>(56,57)</sup>

## ANTIBIOTIC THERAPY IN CAP: RECOMMENDATIONS FOR THE USE OF MONOTHERAPY AND COMBINATION THERAPY

### Treatment of outpatients

The initial antibiotic regimen is determined empirically because it is impossible to obtain microbiological results, which would enable the choice of antibiotics directed at specific agents, immediately after the diagnosis of CAP. The choice of an antibiotic should take the following into account: 1) the most likely pathogen in the site of disease acquisition; 2) individual risk factors; 3) presence of concomitant diseases; and 4) epidemiologic factors, such as recent trips, allergies, and cost-effectiveness ratio.

Antibiotic coverage for atypical pathogens in cases of less severe CAP remains controversial, and several studies have shown no advantages with the use of this approach. A crossover study comparing  $\beta$ -lactams vs.  $\beta$ -lactams plus macrolides vs. new fluoroquinolones against respiratory pathogens (levofloxacin, moxifloxacin, or gemifloxacin) demonstrated that  $\beta$ -lactams alone were not inferior to the other antibiotic regimens in non-severe CAP in terms of 90-day mortality.<sup>(58)</sup>

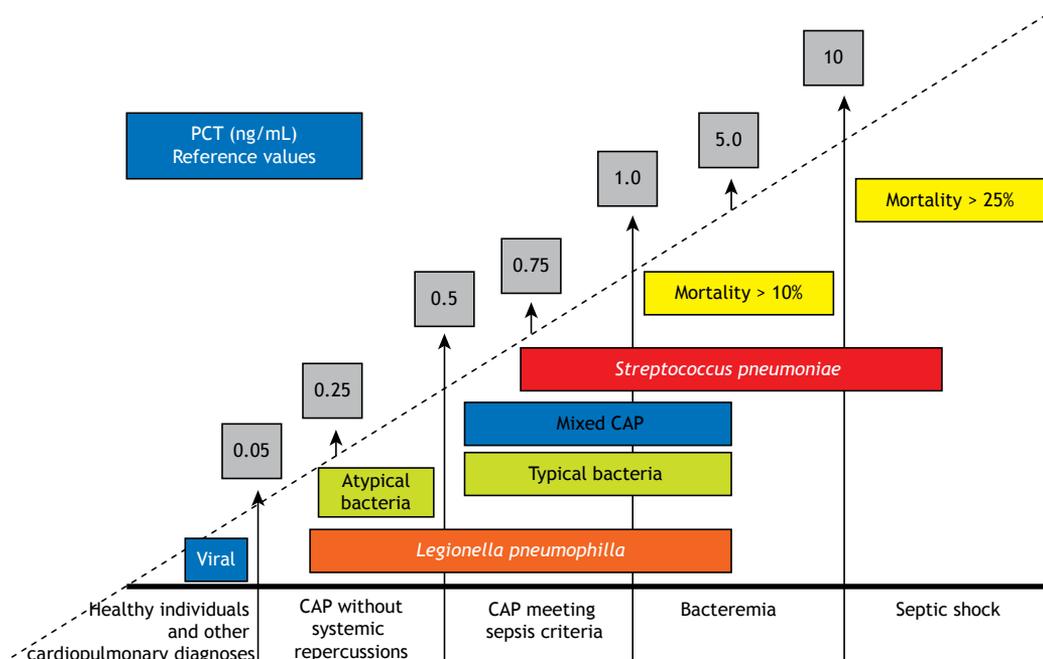
American, European, British, and Latin-American guidelines differ with regard to the treatment of outpatients. British and European guidelines, as well guidelines by the *Asociación Latinoamericana del Tórax*, place less importance on atypical pathogens for less severe cases and do not recommend initial coverage for these pathogens. British and European guidelines recommend amoxicillin as the treatment of choice, reserving macrolides as alternatives.<sup>(59-62)</sup>

The 2007 ATS/IDSA guidelines advocate treatment of atypical pathogens and pneumococci and suggest macrolides or doxycycline if no antibiotic resistance

**Chart 4.** Advantages and disadvantages of using biomarkers in infectious diseases.

Advantages
Provide information that is specific to infections requiring antibiotics
High levels in bacterial infections and low levels in viral infections
Levels increase rapidly in bacterial infections
Response does not depend on the organism
Levels may be altered at disease onset, before clinical and radiological abnormalities
May help define prognosis
Improve the yield of severity scores
Help monitor therapeutic response
May be more specific than clinical manifestations
May help reduce antibiotic use without adverse consequences
Disadvantages
Results may conflict with careful clinical assessment
Previous use of antibiotics may rapidly reduce levels and lead to false-negative findings
May not differentiate between pneumonia caused by atypical pathogens and viral pneumonia
Do not always recognize influenza complicated by bacterial infection
Do not distinguish between chemical aspiration pneumonia and secondary bacterial aspiration pneumonia

Adapted from Müller et al.<sup>(52)</sup>



**Figure 3.** Serum procalcitonin (PCT) levels in community-acquired pneumonia (CAP). Adapted from Julián-Jiménez et al.<sup>(57)</sup>

is suspected.<sup>(44)</sup> A retrospective cohort study of outpatients with CAP who received monotherapy, conducted between 2011 and 2015, showed that 22.1% of the patients required additional treatment.<sup>(63)</sup> This occurred in older patients, women, and patients with comorbidities. The drugs most associated with treatment failure were  $\beta$ -lactams (in 25.7%), followed by macrolides (in 22.9%), tetracyclines (in 22.5%), and new fluoroquinolones (in 20.8%).<sup>(63)</sup> In Brazil, the most recent data indicate that pneumococcal resistance to penicillin should not be a concern for less severe cases of CAP.<sup>(64)</sup>

The proposal by the executive group responsible for the present recommendations is the use of monotherapy with a  $\beta$ -lactam or macrolides for outpatients with no comorbidities, no recent use of antibiotics, no risk factors for resistance, and no contraindication or history of allergy to these drugs (Chart 5).

For such cases, it is suggested that fluoroquinolone use be avoided because of the recent warning from the U.S. Food and Drug Administration regarding the potential risk of severe side effects.<sup>(65)</sup> Fluoroquinolones should be reserved for patients with risk factors and more severe disease or if there is no other treatment option, situations in which the benefits would outweigh the potential risks. Regarding macrolides, azithromycin is more effective *in vitro* against most strains of *Haemophilus influenzae* than is clarithromycin and should therefore be preferred in patients with COPD.<sup>(44,66)</sup>

The risk of infection with resistant pathogens and the risk of treatment failure are higher when patients have used an antibiotic within the previous three months, when patients come from regions where the

local rate of resistance to macrolides is greater than 25%—which occurs, for instance, in the United States and some other countries—and when patients have concomitant diseases (COPD, liver or kidney disease, cancer, diabetes, congestive heart failure, alcoholism, or immunosuppression). For these specific cases, combination therapy with a macrolide and a  $\beta$ -lactam or monotherapy with a respiratory fluoroquinolone for at least 5 days is recommended for the outpatient treatment of CAP.

### Treatment of ward patients

Monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxacin) or combination therapy with a  $\beta$ -lactam and a macrolide has been guideline recommended for the treatment of ward patients with CAP because these regimens provide good coverage and produce good results in infections caused by *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, *H. influenzae*, or *Legionella* sp.<sup>(29,51,54)</sup> Respiratory fluoroquinolones provide wide microbiological coverage, have a convenient dosing schedule, and have the ability to switch from parenteral to oral therapy. However, excessive use of respiratory fluoroquinolones can induce subsequent emergence of multidrug-resistant organisms among treated patients, as has also been observed with  $\beta$ -lactams.<sup>(67)</sup> It is of note that ciprofloxacin, despite being a second-generation fluoroquinolone, is not recommended for the treatment of CAP caused by community pathogens because it lacks activity against the pneumococcus and other gram-positive organisms. Monotherapy with a macrolide is not indicated in Brazil for use in such cases because of the high prevalence of *S. pneumoniae* resistance to this class of antibiotics. According to data from a 2014 survey, in the 5–49-year

**Chart 5.** Empiric antibiotic therapy for community-acquired pneumonia.

Treatment of outpatients	
With no comorbidities, no recent use of antibiotics, no risk factors for resistance, no contraindications or history of allergy to these drugs	
Amoxicillin or amoxicillin + clavulanic acid or macrolides: azithromycin or clarithromycin	7 3-5 7
With risk factors, more severe disease, recent use of antibiotics	
β-lactam + macrolide	5-7
If allergic to β-lactams/macrolides	
Moxifloxacin or levofloxacin or gemifloxacin	5-7
Treatment of ward patients	
Third-generation cephalosporins (ceftriaxone or cefotaxime) or amoxicillin + clavulanic acid + a macrolide (azithromycin or clarithromycin) or	7-10
Third-generation cephalosporins (ceftriaxone or cefotaxime) or amoxicillin + clavulanic acid or macrolides: azithromycin or	7-10
Levofloxacin or moxifloxacin or gemifloxacin as monotherapy	5-7
Treatment of ICU patients	
Third-generation cephalosporins (ceftriaxone or cefotaxime) or ampicillin/sulbactam + a macrolide (azithromycin or clarithromycin) or	7-14
Third-generation cephalosporins (ceftriaxone or cefotaxime) + respiratory quinolone	
Target-specific therapy	
Penicillin-resistant pneumococcus	
Not severe: high-dose β-lactam (amoxicillin 3 g/day or amoxicillin + clavulanic acid 4 g/day; alternatives: ceftriaxone, cefotaxime, cefepime, or ceftaroline) + macrolide or respiratory fluoroquinolone	5-7
Severe: ceftriaxone, cefotaxime, cefepime, or ceftaroline	7-10
Methicillin-resistant <i>Staphylococcus aureus</i> : community-acquired	
Clindamycin or linezolid or vancomycin	7-21
Methicillin-resistant <i>S. aureus</i>	
Linezolid or vancomycin	7-21
Extended-spectrum β-lactamase-producing enterobacteriaceae	
Ertapenem	7-14
<i>Pseudomonas</i> spp.	
Antipseudomonal fluoroquinolones, piperacillin/tazobactam, meropenem, polymyxin B (monotherapy or combined therapy)	10-14
Patients with suspected aspiration pneumonia	
Aspiration pneumonia: quinolones or third-generation cephalosporins Aspiration of gastric contents, and necrotizing pneumonia, lung abscess, or severe periodontal disease: β-lactam + β-lactamase inhibitor, piperacillin/tazobactam, clindamycin, or moxifloxacin	7-10 7-21

age group, pneumococcal resistance to erythromycin was found in 16.9% of a total of 425 samples and sensitive strains were found in 83.1%. Among patients over 50 years of age, resistance was found in 13.6% of a total of 418 samples. For the total of 986 samples, including all age groups (from under 12 months to over 60 years of age), the rate of *S. pneumoniae* resistance to erythromycin was 17.2%.<sup>(64)</sup>

The actual need for specific coverage for atypical pathogens has been debated in the current literature. Studies investigating this issue have demonstrated that, because the incidence of *Legionella* sp. was low in non-severe CAP, monotherapy with a β-lactam was not inferior to combination therapy with a β-lactam and a macrolide or monotherapy with a fluoroquinolone.<sup>(68,69)</sup> The result of the investigation was that dose adjustment occurred only if *Legionella* sp. was found.<sup>(68,69)</sup> Studies comparing combination therapy with a β-lactam and

a macrolide with monotherapy with a fluoroquinolone have shown no differences in 90-day mortality, length of hospital stay, or prescription of an oral antibiotic.<sup>(67,69,70)</sup>

The current recommendation is to use a β-lactam plus a macrolide or a respiratory fluoroquinolone alone. A β-lactam alone can be used if *Legionella* sp. is positively excluded (Chart 5).

#### Treatment of ICU patients

In severe CAP, studies evaluating combination therapy have shown favorable results regarding various clinical outcomes. A large observational study of patients with severe CAP (N = 956) compared monotherapy with combination therapy (two antibiotics) in terms of early mortality (60 days). In multivariate analysis, 60-day mortality was not significantly different between dual therapy and monotherapy (hazard ratio [HR]: 1.14; 95% CI: 0.86-1.50; p = 0.37).<sup>(71)</sup> In contrast, combination

therapy increased the likelihood of adequate initial therapy, defined as one or more antibiotics with in vitro activity against the microorganisms identified or, in the absence of such identification, treatment started at ICU admission and requiring no adjustment 48 h later. Adequate initial therapy was independently associated with better survival in the general cohort (HR: 0.63; 95% CI: 0.42-0.94;  $p = 0.02$ ).<sup>(71)</sup> An observational study<sup>(72)</sup> compared the impact on mortality of combination therapy with at least two antimicrobials with different mechanisms of action with that of monotherapy and other antimicrobial combinations in ICU patients with severe sepsis or septic shock. Among 1,022 patients with community-acquired infection, 362 had CAP. The mortality rate was significantly lower in patients receiving combination therapy with different classes of antibiotics than in those receiving monotherapy or other antimicrobial combinations (34% vs. 40%;  $p = 0.042$ ).<sup>(72)</sup> In a case-control study, a change in antibiotic therapy prescription and administration practices in favor of combination therapy (a macrolide plus a  $\beta$ -lactam) and, at the same time, early administration, was associated with a 15% reduction in mortality from pneumococcal pneumonia in ICU patients.<sup>(73)</sup> A similar result was observed in a study using a similar methodology and involving ICU patients with CAP caused by various etiologic agents, excluding pneumococci.<sup>(74)</sup>

A prospective observational study<sup>(75)</sup> including 218 intubated patients with CAP (75.7% of whom were in septic shock or had severe sepsis) found, after a severity-adjusted statistical analysis, that macrolide use was associated with lower ICU mortality (HR: 0.48; 95% CI: 0.23-0.97;  $p = 0.04$ ) when compared with fluoroquinolone use. A separate analysis of patients with severe sepsis and septic shock ( $n = 92$ ) revealed similar results (HR: 0.44; 95% CI: 0.20-0.95;  $p = 0.03$ ).<sup>(75)</sup> In a systematic review with meta-analysis involving almost 10,000 patients with severe CAP, macrolide use was associated with an 18% relative reduction and a 3% absolute reduction in mortality compared with nonmacrolide therapies.<sup>(76)</sup> Dual antibiotic therapy with a  $\beta$ -lactam and a macrolide was superior to combination therapy with a  $\beta$ -lactam and a quinolone in a systematic review with meta-analysis, but randomized studies are needed to confirm these results because of the high risk of methodological bias across the studies analyzed.<sup>(77)</sup>

Therefore, combination therapy should be recommended for patients with severe CAP and an indication for ICU admission, because it reduces mortality. Antibiotics should be administered as early as possible, and antibiotic regimens should preferably include a macrolide and a  $\beta$ -lactam, both administered intravenously.

Except for clinical settings in which there is a great likelihood that specific pathogens are the causal agents (see Antibiotic therapy in CAP: recommendations for the use of monotherapy and combination therapy), the suggestions for initial antibiotic therapy in severe CAP are described in Charts 5 and 6.

## RECOMMENDATIONS FOR PATHOGEN-SPECIFIC, TARGETED THERAPY IN PATIENTS AT RISK FOR INFECTION WITH GRAM-NEGATIVE ROD BACTERIA, STAPHYLOCOCCUS AUREUS, AND OTHER POTENTIALLY DRUG-RESISTANT PATHOGENS IN THE COMMUNITY

The recognition of risk factors for the leading etiologic agents of CAP helps determine optimal therapy, especially in an age of dissemination of drug-resistant bacteria in the community. Currently, we can classify bacterial etiologic agents into standard pathogens—*S. pneumoniae*, *H. influenzae*, *S. aureus*, *M. pneumoniae*, group A *Streptococcus* sp., *Legionella* sp., *Chlamydomphila* sp., and *Moraxella catarrhalis*<sup>(78,79)</sup>—and multidrug-resistant pathogens—community-acquired methicillin-resistant *S. aureus* (CA-MRSA) and penicillin-resistant pneumococcus.<sup>(80,81)</sup>

Pneumonias caused by standard pathogens have age, occupational exposure, and presence of comorbidities as risk factors, as occurs in invasive pneumococcal disease of the lung, common in patients with chronic respiratory disease, diabetes, heart disease, or immunosuppression.<sup>(82)</sup> Pneumonias caused by multidrug-resistant pathogens are mainly dependent on local epidemiology. In addition, rapidly progressive necrotizing pneumonia is a typical presentation of CA-MRSA, which can be associated with skin lesions or with group sports participation in healthy individuals.<sup>(81)</sup>

Recently, a new group of multidrug-resistant bacteria has been associated with CAP in patients with previous contact with a health care service, such as home care services, dialysis services, outpatient services for chronic wound care, and nursing homes. In these patients, MRSA, extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae, and multidrug-resistant *Pseudomonas* sp. have been common agents of pneumonia, even without recent hospitalization, simply because patients remain colonized.<sup>(83)</sup> The following are risk factors for infection with these bacteria: hospitalization within 90 days before the episode of pneumonia; antibiotic use within the previous 90 days; immunosuppression; use of gastric acid-suppressive agents; enteral feeding; hemodialysis; and previous intestinal colonization by multidrug-resistant bacteria or nasal MRSA.<sup>(84)</sup>

Unlike in first-line therapy for CAP, which is based on regional factors, such as the local incidence of standard pathogens and a patient's severity factors,<sup>(69,85)</sup> in specific targeted therapy, the risk factors for and the local prevalence of drug-resistant microorganisms are assessed with a view to guiding therapy. In Brazil, there have been few publications on the epidemiology of multidrug-resistant bacteria in the respiratory tract. Data from a regional report revealed a mean penicillin sensitivity of 93% for respiratory isolates, with an observed increase in the circulation of serotype 19A in adults, which had a penicillin sensitivity of only 50%.<sup>(64)</sup> The same report described a mean ceftriaxone sensitivity of 95%, a mean erythromycin sensitivity

of 83%, a mean trimethoprim/sulfamethoxazole sensitivity of 66%, and a mean chloramphenicol sensitivity of 99%.<sup>(64)</sup>

For CA-MRSA, national data are scarce, and risk factors should be taken into account, as occurs for multidrug-resistant pathogens associated with health care services. The drugs of choice for the treatment of CA-MRSA infection are those that inhibit toxin production: clindamycin, linezolid, or vancomycin, which can be used as monotherapy, as combination therapy with each other (linezolid plus clindamycin or vancomycin plus clindamycin), or as combination therapy with rifampin in cases of drug-resistant strains or difficulty in penetrating necrotic tissue.<sup>(86,87)</sup>

Penicillin-resistant pneumococcal infection is treated with cephalosporins, including ceftriaxone, cefotaxime, and cefepime.<sup>(63)</sup> Recently, a study of a new cephalosporin, ceftaroline, demonstrated the superiority of ceftriaxone over ceftriaxone for the treatment of pneumococcal pneumonia.<sup>(88)</sup> In cases of non-severe infection, in which oral monotherapy is a choice, cefuroxime and ampicillin-sulbactam have been safe options in regions with low resistance to  $\beta$ -lactams, as have fluoroquinolones, since pneumococci are rarely resistant.<sup>(89)</sup> In cases of CA-MRSA infection, the objective is to suppress toxin production, and the treatment of choice is clindamycin, trimethoprim/sulfamethoxazole, or linezolid. The potential for inducible clindamycin resistance in high-inoculum infections via efflux or ribosomal alterations should be taken into account.<sup>(90)</sup> An antibiotic disc diffusion assay (D-test) identified inducible clindamycin resistance in erythromycin-resistant, clindamycin-susceptible *S. aureus* isolates.<sup>(91)</sup> Linezolid has been shown to be superior to vancomycin in the treatment of severe MRSA infections, especially in ICU patients. Infection with extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae can be treated on an outpatient basis with ertapenem, because of its dosing schedule of a single intramuscular or intravenous daily dose, which allows it to be administered on a day-hospital basis. Infections with drug-resistant strains of *Pseudomonas* sp. have been treated with fluoroquinolones, piperacillin/tazobactam, meropenem, or polymyxin B, as monotherapy or combination therapy (Chart 6).<sup>(92,93)</sup>

## DURATION OF ANTIBIOTIC THERAPY FOR OUTPATIENTS AND INPATIENTS WITH CAP

The optimal duration of antibiotic therapy for the treatment of CAP has yet to be definitively established. Short-term antibiotic therapy seems to be the most appropriate, given that it provides less patient exposure to the effects of antibiotics, reduces the occurrence of adverse effects, reduces the development of drug resistance by microorganisms, improves patient adherence, and can minimize length of hospital stay and financial costs.<sup>(94)</sup> In addition, very long-term treatments favor the development of bacterial resistance and the occurrence of potentially severe

adverse effects, such as infections with *Clostridium difficile*.<sup>(95)</sup> However, short-term treatment should be as effective as longer-term treatments in terms of rates of mortality, complications, and disease recurrence.

Recommendations regarding the optimal duration of antibiotic therapy have changed over time, and there are discrepancies on this issue across guidelines (Table 1).

Treatment duration sufficient to ensure CAP treatment success (considering mortality as the primary outcome, but also considering adverse effects and treatment failure) may vary based on CAP severity as defined by currently available severity scores. Treatments lasting 5 to 7 days seem to be sufficient in most cases, especially in non-severe infections.

According to a meta-analysis evaluating the efficacy of short-term (less than 7 days) regimens in adult patients with mild to moderate CAP and involving 2,796 patients in 15 selected studies, shorter-term treatments did not underperform relative to traditional regimens.<sup>(95)</sup> Another meta-analysis investigated the efficacy and safety of short-term (equal to or less than 7 days) treatments vs. long-term (greater than or equal to 2 days' difference) treatments for CAP with the same antibiotics and the same dosing schedules.<sup>(94)</sup> Five randomized controlled trials involving adult patients of mild to moderate severity were included. No differences were found between short-term (3 to 7 days) treatments and long-term (7 to 10 days) treatments regarding clinical success (N = 1,095 patients; OR = 0.89; 95% CI: 0.74-1.07), microbiological improvement, recurrence and mortality rates, or adverse effects.<sup>(94)</sup>

A document by the U.K. National Institute for Health and Care Excellence, published in 2014, recommends that the duration of treatment should be determined by the severity of pneumonia rather than by the etiologic agents or the antibiotic chosen.<sup>(60)</sup> Therefore, for mild CAP, monotherapy for 5 days seems to be sufficient; extending treatment should be considered if symptoms do not improve after 3 days. For moderate to severe CAP, the document recommends that treatment for 7 to 10 days should be sufficient, according to the working group's consensus opinion, given that the available evidence comes from the analysis of a subgroup of patients from only one study.<sup>(96)</sup>

Strategies and procedures aimed at shortening the duration of antibiotic therapy have been tested by comparing short- and long-term treatments in terms of efficacy. Murray et al.<sup>(97)</sup> evaluated the impact of a multidisciplinary intervention intended to reduce the duration of antibiotic therapy: stop dates of antibiotic therapy were determined on the basis of severity of disease as assessed by the CURB-65 score. On those dates, clinicians received a reminder from the clinical pharmacy department, after which the attending physicians decided, on the basis of data regarding the patient's clinical course, whether or not to continue treatment. The intervention resulted in an 18% reduction in the duration of antibiotic therapy and a 39% reduction in the rate of antibiotic-related adverse

**Chart 6.** Dosing, dosing schedule, and routes of administration of antibiotics that can be used in the treatment of community-acquired pneumonia.

Drug	Route	Dose	Interval, h
Amoxicillin/clavulanic acid	Oral	875/125 mg	8
Amoxicillin/clavulanic acid	Oral	2,000/135 mg	12
Amoxicillin/clavulanic acid	Intravenous	1,000-2,000/200 mg	8-12
Ampicillin/sulbactam	Intravenous	1.5/3.0 g	6-8
Azithromycin	Oral-Intravenous	500 mg	24
Cefepime	Intravenous	2 g	12
Cefotaxime	Intravenous	1-2 g	8
Ceftaroline	Intravenous	600 mg	12
Ceftriaxone	Intravenous	1 g	12
Ciprofloxacin	Oral	500-750 mg	12
Ciprofloxacin	Intravenous	400 mg	8-12
Clarithromycin	Oral	500 mg	12
Extended-release clarithromycin	Oral	1,000 mg	24
Clarithromycin	Intravenous	500 mg	12
Clindamycin	Oral	600 mg	12
Clindamycin	Intravenous	600 mg	8
Ertapenem	Intravenous	1 g	24
Imipenem	Intravenous	1 g	8
Levofloxacin	Oral	500-750 mg	24
Levofloxacin	Intravenous	750 mg	24
Linezolid	Oral-Intravenous	600 mg	12
Meropenem	Intravenous	1 g	8
Moxifloxacin	Oral	400 mg	24
Piperacillin/tazobactam	Intravenous	4 g/0.5 g	6-8
Vancomycin	Intravenous	500 mg/1,000 mg	6/12

Note: If the infection is caused by a microorganism requiring a minimal inhibitory concentration > 0.5 mg/L, the antimicrobial should be administered every 8 h to prevent the selection of resistant strains.

effects. There was no reduction in mortality or length of hospital stay.<sup>(97)</sup> Other authors evaluated the use of a three-step systematized pathway to transition from intravenous to oral antibiotic therapy and thereby reduce length of hospital stay. Those authors demonstrated that using objective criteria for switching to oral antibiotic therapy and deciding on hospital discharge results in a reduction in length of hospital stay and duration of intravenous antibiotic therapy, without any adverse consequences.<sup>(98)</sup> In addition, biomarkers (especially C-reactive protein and procalcitonin) have been widely studied to help in the clinical monitoring of patients with CAP, as a method to help decide whether to change or discontinue treatment.

It is recommended that, for mild CAP treated on an outpatient basis, treatment should be 5-day monotherapy. Moderate to severe CAP should be treated with the antibiotic regimens discussed above, for periods of 7 to 10 days. Treatment can be extended up to 14 days at the discretion of the attending physicians.

#### RECOMMENDATIONS FOR CORTICOSTEROID USE AS ADJUVANT TREATMENT IN CAP

During an infectious course, an adequate balance between activation of the immune response and control

of inflammation is key to fighting the infection without adjacent tissue injury. Activation of the hypothalamic-pituitary-adrenal axis is responsible for the production of cortisol, an endogenous corticosteroid, which, during an pneumonic course, induces the expression of anti-inflammatory proteins and the inhibition of pro-inflammatory molecules.<sup>(101)</sup>

In recent years, randomized clinical trials and meta-analyses evaluating the role of corticosteroids in CAP have been published, but some gaps still have to be filled. Moderate- to high-quality evidence suggests that, when combined with antibiotics and usual therapy, corticosteroids improve the course of treated patients with CAP. The benefits include a reduction in length of hospital stay and time to clinical stability, as well as a reduction in the rate of mechanical ventilation and progression to acute ARDS.<sup>(102-106)</sup>

Most of those studies evaluated the role of corticosteroids in severe CAP requiring hospitalization. With regard to mortality, the role of corticosteroids in preventing CAP-related deaths has yet to be well defined,<sup>(103)</sup> although data regarding individuals with a severe presentation suggest benefits of this therapy in this subgroup.<sup>(102,104,107)</sup> Another important aspect to take into account is the fact that the treatment regimens used in clinical trials are not standardized.

**Table 1.** Guideline recommendations on duration of antibiotic therapy for community-acquired pneumonia.<sup>a</sup>

Authors (reference)	Recommended duration	Level of evidence
Mandel et al. <sup>(99)</sup>	- At least 5 days (level 1), no fever for 48-72 h and no signs of clinical instability before discharge (level 2) - Longer duration: if the initial therapy is inactive against a previously identified pathogen or if there are extrapulmonary complications, such as meningitis or endocarditis (level 3)	Level 1: high (RCT) Level 2: moderate (nonrandomized controlled studies, cohort studies, series of patients, case-control studies) Level 3: low (case studies and expert opinion)
Lim et al. <sup>(59)</sup>	- Outpatient and non-severe inpatient CAP and uncomplicated CAP: 7 days of antibiotic therapy - Severe CAP caused by an unidentified agent: 7-10 days - 14-21 days if there is suspicion or confirmation of <i>Staphylococcus aureus</i> or gram-negative enteric bacilli (C)	C: formal combination of expert opinions
Corrêa et al. <sup>(5)</sup>	- Mild to moderate CAP: up to 7 days - Recommendation valid for the classes of antibiotics then recommended	A: randomized controlled trials and/or rich database
Torres et al. <sup>(100)</sup>	- Duration should not exceed 8 days in patients responsive to treatment (C2)	C2: insufficient evidence, from one or more randomized controlled trials, but without systematic review or meta-analysis
Eccles et al. <sup>(60)</sup>	- Mild CAP: 5 days of antibiotic therapy - Consider extending if there is no clinical improvement within 3 days - Patients and caregivers: if there is no improvement of symptoms (or there is worsening) within 3 days, seek medical attention again - Moderate to extremely severe CAP: 7-10 days of treatment	- Low and moderate quality evidence; heterogeneous studies, but with consistency in demonstrating equivalence in efficacy between short- and long-term treatments - Low quality evidence; recommendation based on the consensus of the members of the working group

RCT: randomized clinical trials; and CAP: community-acquired pneumonia.

Table 2 shows the main corticosteroid treatment regimens used for the treatment of CAP.<sup>(107-113)</sup>

In 2015, two important randomized clinical trials were published. Blum et al.<sup>(108)</sup> evaluated the use of prednisone (50 mg/day for 7 days) in 785 patients. Patients in the corticosteroid-treated group had shorter time to clinical stability than did those in the control group (3.0 days vs. 4.4 days;  $p < 0.0001$ ). Clinical stability was defined as a return to normal levels of temperature, HR, RR, SpO<sub>2</sub>, mental status, systolic blood pressure, and ability to tolerate oral food intake.<sup>(108)</sup> Torres et al.<sup>(109)</sup> tested the effects of the use of methylprednisolone (0.5 mg/kg every 12 h for 5 days) in individuals with severe CAP, as defined by ATS criteria or high PSI risk class, and with high inflammatory response, characterized as a serum C-reactive protein level  $> 150$  mg/L. Patients who received methylprednisolone had a lower risk of treatment failure compared with those in the control group (OR = 0.34; 95% CI: 0.14-0.87;  $p = 0.02$ ). In addition, the study showed that the radiological course was better in the group of patients who received methylprednisolone. A distinguishing positive aspect of the study, compared with previous research, is that the sample was more homogeneous, including a phenotype of individuals with increased inflammatory expression (high C-reactive protein levels).<sup>(109)</sup>

With regard to safety outcomes, corticosteroid use resulted in good tolerance without increasing the incidence of adverse effects, except for hyperglycemia, which was more commonly reported in the group receiving corticosteroid therapy. However, the rates of other complications usually attributed to corticosteroid use, such as gastrointestinal bleeding, neuropsychiatric complications, and hospital readmission, were similar in the corticosteroid and control groups.<sup>(102-104)</sup>

In conclusion, corticosteroid use in severe CAP has proved to be both safe and beneficial in several important clinical outcomes. However, further studies are needed to confirm the impact of corticosteroid therapy on CAP-related mortality, although meta-analyses have suggested a reduction in this rate, especially in the subgroup of patients with a more severe presentation.

On the other hand, it should be emphasized how important it is to avoid the indiscriminate use of corticosteroid therapy, prioritizing its use in individuals who are most likely to benefit clinically from it, such as those with a higher level of systemic inflammation. In this context, C-reactive protein can be considered a useful biomarker, identifying patients who are at higher risk of CAP-related complications and who, consequently, may benefit from adjuvant corticosteroid therapy.

These recommendations should not be extrapolated to patients with less severe CAP who are treated on an outpatient basis.

## CURRENT RECOMMENDATIONS FOR VACCINATION IN ADULTS: INFLUENZA AND PNEUMOCOCCAL VACCINES

### *Influenza vaccine*

Influenza is a viral infection with systemic manifestations, caused by viruses of the family *Orthomyxoviridae*, which are classified as antigenic types A, B, or C. Influenza type A infection is associated with pandemics and with disease of greater severity; influenza type B infection is associated with regional epidemics; and influenza type C infection is associated with small isolated outbreaks, which have little clinical relevance in humans.

The flu, caused by influenza types A and B viruses, is associated with increased morbidity and mortality in patients with chronic diseases.<sup>(114,115)</sup> There is a strong relationship between influenza infections and secondary bacterial pneumonias following viral infections.<sup>(116)</sup> Vaccination reduces the intensity of symptoms, the need for hospitalization, and mortality.<sup>(117,118)</sup>

The influenza virus has high mutation rates, and annual (seasonal) epidemics are due to new subtypes arising from small antigenic drifts that occur during viral replication. The occurrence of these mutations in the viral structure contributes to an increase in the seasonal incidence of the disease and justifies the need for annual influenza vaccination, given that the vaccine's protection is temporary.<sup>(115)</sup> The composition of the influenza vaccine is determined by the World Health Organization on the basis of information from referral laboratories regarding the prevalence of circulating strains. The World Health Organization usually makes annual recommendations on the composition of the vaccine in the second semester so that the next year's vaccine can be developed to cover the influenza strains most likely to be circulating that subsequent year.<sup>(119)</sup>

In Brazil, the available influenza vaccines are made up of inactivated fragmented viruses (therefore, carrying no risk of infecting patients), which are obtained from cultures derived from embryonated chicken eggs. Inactivated vaccines reduce the magnitude of the respiratory symptoms when the circulating virus strain is similar to the vaccine strains, leading to a greater than 60% decrease in the incidence of the disease.<sup>(120)</sup> There are two types of influenza vaccine that are approved by the Brazilian National Health Oversight Agency for use in the country:

- Trivalent influenza vaccine (influenza A/H1N1, influenza A/H3N2, and influenza B): available for specific indications, through the Brazilian Unified Health Care System, in primary health care clinics during vaccination campaigns (and subsequently until there are no more doses available)
- Tetravalent—or quadrivalent—influenza vaccine (influenza A/H1N1, influenza A/H3N2, and two

strains of influenza B): available in private clinics and administered for the same indications

Although the influenza vaccine can be used from the age of 6 months onward, the vaccine has been prioritized for high-risk groups by the vaccination schedule of the Brazilian National Ministry of Health.<sup>(5,121-123)</sup>

### *Priority (non-exclusive) indications*

- Adults aged 60 years or older
- Patients with chronic pulmonary, cardiovascular (except systemic arterial hypertension), renal, hepatic, hematologic, or metabolic disorders
- Adults who are immunosuppressed
- Individuals with neuromuscular disorders, pulmonary function impairment, and difficulty in clearing secretions
- Women who are, or are planning to become, pregnant and women who are breastfeeding
- Residents of nursing homes
- Potential transmitters of the virus to individuals at higher risk
- Health professionals
- Home caregivers of children (under 5 years of age) and of adults (over 50 years of age)
- Indigenous people and people deprived of their liberty

### *Individuals who should not be vaccinated*

- People with severe allergy (anaphylaxis) to chicken eggs, to any component of the vaccine, or to a previous dose of the vaccine
- Children under 6 months of age
- People with a history of Guillain-Barré syndrome, especially if the syndrome developed after influenza vaccination

### *Notes*

- People with a history of severe allergy to chicken eggs, with signs of anaphylaxis, should receive the vaccine in a setting in which anaphylactic reactions can be treated and should remain under observation for at least 30 minutes
- In cases of fever, vaccination should be postponed until remission occurs
- In cases of a history of Guillain-Barré syndrome occurring within 6 weeks after a previous dose of the vaccine, careful medical evaluation of the risk-benefit ratio is recommended before administration of another dose
- Except for the aforementioned cases, no precautions are needed before vaccination
- Cold compresses can relieve reactions at the vaccine injection site, and, for more severe cases, medically prescribed pain medication can be used
- Any severe and/or unexpected symptom after vaccination should be reported to the facility where vaccination was performed
- Persistent symptoms or adverse events lasting more than 72 h (depending on the symptom) should be investigated for other causes

### *Pneumococcal vaccine*

Two types of pneumococcal vaccine are currently available: a 23-valent pneumococcal polysaccharide

**Table 2.** Main corticosteroid treatment regimens used for the treatment of community-acquired pneumonia.

Study (reference)	Country	Treatment regimen
Torres et al. <sup>(109)</sup>	Spain	Methylprednisolone 0.5 mg/kg every 12 h for 5 days
Fernandez-Serrano et al. <sup>(107)</sup>	Spain	Methylprednisolone 20 mg every 6 h for 3 days, 20 mg every 12 h for 3 days, 20 mg/day for 3 days
Blum et al. <sup>(108)</sup>	Switzerland	Prednisone 50 mg/day for 7 days
Snijders et al. <sup>(110)</sup>	The Netherlands	Prednisolone 40 mg/day for 7 days
Confalonieri et al. <sup>(111)</sup>	Italy	Hydrocortisone 200 mg/day for 7 days
Sabry et al. <sup>(112)</sup>	Egypt	Hydrocortisone 300 mg/day for 7 days
Li et al. <sup>(113)</sup>	China	Methylprednisolone 80 mg/day for 7 days

vaccine (PPSV23), not conjugated to a carrier protein, containing the capsular polysaccharide antigens of 23 pneumococcal serotypes; and a pneumococcal conjugate vaccine (PCV) composed of capsular polysaccharide antigens conjugated to a carrier protein. This latter formulation increases immunogenicity and, because it stimulates immune memory by T cells, provides longer-lasting protection. Two new conjugated vaccine formulations containing the capsular polysaccharide antigens of 10 (PCV10) and 13 (PCV13) pneumococcal serotypes are available in Brazil. PCV10 is approved for preventing invasive pneumococcal disease in children aged 2 years or younger, whereas PCV13 is approved for children aged 6 weeks or older and for adults. Pneumococcal serotypes are associated with disease severity, and, therefore, the clinical impact of vaccination is dependent on serotype coverage.<sup>(124)</sup>

PCV13 should be administered as a single dose to adults aged 50 years or older, including those previously vaccinated with the pneumococcal polysaccharide vaccine. The need for revaccination with a subsequent dose of PCV13 has not been established.

Routine sequential administration of PCV13 and PPSV23 is recommended by the Brazilian Immunization Society for individuals aged 60 years or older.<sup>(125)</sup> For individuals with comorbidities, sequential administration of PCV13 and PPSV23 is recommended. A dose of PCV13 should be given first, followed by a dose of PPSV23 6-12 months later and a second dose of PPSV23 5 years after the first one. For people who have received a dose of PPSV23, a 1-year interval is recommended, that is, PCV13 should be given 1 year after PPSV23. The second dose of PPSV23 should be given 5 years after the first one and 6-12 months after PCV13. For those who have received two doses of PPSV23, it is recommended that a dose of PCV13 be given at

least 1 year after the most recent dose of PPSV23. If the second dose of PPSV23 was given before age 65 years, it is recommended that a third dose be given after this age, at least 5 years after the most recent dose. According to this vaccination schedule, PCV13 can be administered to adults aged 50-59 years, at the discretion of the attending physician. Pneumococcal polysaccharide vaccines result in a reduction in the occurrence of invasive pneumococcal disease in the adult population and are less effective in preventing CAP in patients with reduced immunity. The pneumococcal conjugate vaccine results in a 45.6% reduction in cases of vaccine-serotype CAP, a 45% reduction in cases of bacterial pneumonia, and a 75% reduction in cases of invasive pneumococcal disease.<sup>(126)</sup> The vaccine is indicated for individuals at increased risk of CAP.<sup>(82,115,126-129)</sup>

#### Indications for the vaccine

- Adults aged 60 years or older
- Individuals between 2 and 59 years of age with chronic heart disease, chronic lung disease, sickle cell disease, diabetes, alcoholism, liver cirrhosis, cerebrospinal fluid fistulas, or cochlear implants
- Individuals between 2 and 59 years of age with an immunosuppressive disease or condition, such as Hodgkin disease, lymphoma, or leukemia; kidney failure; multiple myeloma; nephrotic syndrome; HIV infection or AIDS; damaged spleen or no spleen, or organ transplant
- Individuals between 2 and 59 years of age who are receiving immunosuppressive drugs, such as long-term corticosteroids or drugs used to treat cancer, or who have undergone radiotherapy
- Adults between 19 and 59 years of age who smoke or have asthma
- Residents of nursing homes or long-term care facilities

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**ERRATUM****Manuscript:** 2018 recommendations for the management of community acquired pneumonia**Publication:** J Bras Pneumol. 45(5):405-423.**DOI:** 10.1590/S1806-37562018000000130

On page 411, where is written:

"A recent study demonstrated that, if **procalcitonin** levels do not decrease by 50% within 3 days of treatment and remains above 75 mg/L, the risk of 30-day mortality is increased.<sup>(54)</sup> A study of 191 patients with CAP admitted to the ICU showed that mortality was 4.8% among those in whom **procalcitonin** levels decreased rapidly (n = 66), 17.3% among those in whom **procalcitonin** levels decreased slowly (n = 81), and 36.4% among those in whom **procalcitonin** levels did not decrease (n = 44).<sup>(55)</sup>"

It should be read:

"A recent study demonstrated that, if **C-reactive protein** levels do not decrease by 50% within 3 days of treatment and remains above 75 mg/L, the risk of 30-day mortality is increased.<sup>(54)</sup> A study of 191 patients with CAP admitted to the ICU showed that mortality was 4.8% among those in whom **C-reactive protein** levels decreased rapidly (n = 66), 17.3% among those in whom **C-reactive protein** levels decreased slowly (n = 81), and 36.4% among those in whom **C-reactive protein** levels did not decrease (n = 44).<sup>(55)</sup>"