# Factors associated with complications of community-acquired pneumonia in preschool children*

## Fatores associados às complicações em crianças pré-escolares com pneumonia adquirida na comunidade

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## Abstract

**Objective:** To identify socioeconomic factors and clinical factors associated with the development of complications in preschool children hospitalized with community-acquired pneumonia (CAP). **Methods:** This was a prospective longitudinal study involving children (12-59 months of age) diagnosed with CAP and admitted to the pediatric wards of two hospitals in the metropolitan area of Campinas, Brazil. Children with cystic fibrosis, heart disease, pulmonary malformations, neurological disorders, or genetic diseases were excluded. The diagnosis of CAP was based on clinical and radiological findings. Data were collected from the medical records and with a semi-structured questionnaire. The subjects were divided into two groups (complicated and uncomplicated CAP). Socioeconomic and clinical variables were compared, and multivariate logistic regression analysis was performed. **Results:** Of the 63 children included, 29 and 34, respectively, presented with uncomplicated and complicated CAP. No statistically significant differences were found between the groups regarding age at admission, gestational age, birth weight, gender, or socioeconomic variables. Significant differences were found between the groups regarding history of pneumonia ($p = 0.03$), previous antibiotic therapy ($p = 0.004$), time elapsed since the onset of CAP ($p = 0.01$), duration of fever prior to admission ($p < 0.001$), duration of antibiotic therapy ($p < 0.001$), and length of hospital stay ($p < 0.001$). In the multivariate analysis, only duration of fever prior to admission remained in the model (OR = 1.97; 95% CI: 1.36-2.84; $p < 0.001$). **Conclusions:** Biological variables, especially duration of fever prior to admission, appear to be associated with the development of complications in children with CAP.

**Keywords:** Community-acquired infections; Pneumonia; Pleural Effusion.

## Resumo

**Objetivo:** Identificar os fatores socioeconômicos e clínicos associados à evolução para complicações em crianças internadas com pneumonia adquirida na comunidade (PAC). **Métodos:** Estudo longitudinal prospectivo em crianças diagnosticadas com PAC (12-59 meses de idade) internadas em enfermarias gerais de pediatria de dois hospitais na região de Campinas (SP). Os critérios de exclusão foram ter fibrose cística, cardiopatia, malformação pulmonar, neuropatias e doenças genéticas. PAC foi diagnosticada por características clínicas e radiológicas. Os dados foram coletados dos prontuários médicos e por um questionário semiestruturado. Os sujeitos foram divididos em dois grupos (PAC complicada e não complicada). Foram comparadas variáveis socioeconômicas e clínicas, e foi realizada análise de regressão logística multivariada. **Resultados:** Das 63 crianças incluídas, 29 e 34, respectivamente, apresentaram PAC não complicada e PAC complicada. Não houve diferenças estatisticamente significantes entre os grupos quanto a idade na admissão, idade gestacional, peso ao nascer, gênero ou variáveis socioeconômicas. Houve diferenças significantes entre os grupos em relação a pneumonia anterior ($p = 0,03$), antibioticoterapia prévia ($p = 0,004$), tempo de início da doença ($p = 0,01$), duração da febre antes da internação ($p < 0,001$), duração da antibioticoterapia ($p < 0,001$) e tempo de internação ($p < 0,001$). Na análise multivariada, somente permaneceu no modelo a duração da febre antes da internação (OR = 1,97; IC95%: 1,36-2,84; $p < 0,001$). **Conclusões:** Variáveis biológicas, com destaque para o tempo de febre anterior à internação, parecem estar associadas com a evolução para complicação em crianças com PAC.

**Descritores:** Infecções comunitárias adquiridas; Pneumonia; Derrame pleural.

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## Introduction

Acute respiratory infection is one of the five leading causes of death among children under 5 years of age in developing countries, accounting for approximately three million deaths/year.[1-4] Community-acquired pneumonia (CAP) is the most severe form of acute respiratory infection, accounting for 80% of all deaths from acute respiratory infection.[1] The impact of CAP on childhood mortality is a cause for concern, especially in developing countries.[1,2,5-7] Factors associated with CAP-related mortality include clinical signs of cyanosis, sensory abnormalities, wheezing, intercostal retractions, inability to drink fluids at hospital admission, and comorbidities, including heart disease, anemia, and rickets.[6,8]

It is estimated that the worldwide incidence of CAP among children under 5 years of age is 0.29 cases/year, the annual incidence of CAP being therefore 150.7 million cases, over 11 million of which require hospitalization.[9] Factors such as day care center attendance, a high number of individuals residing in the same location, and passive smoke exposure, as well as a history of wheezing and pneumonia, are associated with an increased risk of CAP.[6,10,11]

In Brazil, 373,622 children ≤ 14 years of age were hospitalized for pneumonia in 2004; of those children, 48% were in the 1-4 year age bracket.[12] In this year age bracket, bacterial pneumonia gains importance, being associated with an increased risk of complications, such as pleural effusion and pulmonary parenchymal injury.[13,14] These complications are the main determinants of clinical worsening and risk of death in children under 5 years of age.[2,15]

Factors associated with CAP-related complications have been studied, maternal age, level of maternal education, acute malnutrition, lack of breastfeeding, and age of the child being of note.[10,16]

In recent years, there has been an epidemiological transition from acute infectious diseases (including CAP) to chronic diseases. This raises the question of whether the abovementioned factors still have an impact on the incidence of complications, morbidity, and mortality due to acute bacterial pneumonia in children living in developed regions of Brazil. Therefore, it is relevant to determine the clinical and epidemiological profile of children with CAP requiring hospitalization in those regions and the factors associated with CAP-related complications. The objective of the present study was to identify the socioeconomic, environmental, and clinical factors that were associated with complicated and uncomplicated CAP in preschool children hospitalized with CAP.

## Methods

This was a prospective longitudinal study of a cohort of children (12-59 months of age) diagnosed with CAP and admitted to the pediatric wards of two university hospitals in the metropolitan area of Campinas, Brazil, namely the São Paulo State Hospital at Sumaré and the State University at Campinas *Hospital de Clínicas*. The study was conducted between June of 2010 and November of 2011.

In 2007, the mortality rates for children under 1 year of age in the state of São Paulo, Brazil, and in the metropolitan area of Campinas were, respectively, 13.4 and 11.55 deaths/1,000 live births. In Campinas, the gross domestic product per capita was 21,549.20 Brazilian reals in that year.

Children with cystic fibrosis, heart disease with hemodynamic repercussions, pulmonary malformations, neurological disorders, or genetic diseases were excluded from the study. Data were collected from the medical records and with a semi-structured questionnaire comprising closed questions. The questionnaire was administered to the parents/legal guardians of the CAP patients at the time of admission to the pediatric ward. The main variables studied were gestational age at birth, breastfeeding, chronological age at admission, gender, level of maternal education, maternal employment status, family income, day care center attendance, smoking, housing conditions, comorbidities (a history of pneumonia and recurrent wheezing), previous use of antibiotics, complications, clinical variables, and variables related to disease progression. The children were divided into two groups (complicated and uncomplicated CAP).

The diagnosis of pneumonia was based on clinical findings (fever, cough, and difficulty breathing), physical examination findings (chest retraction and decreased breath sounds or rales), and radiological findings (unilateral or bilateral homogeneous consolidation on chest X-ray).[8]

Pleural effusion, pneumothorax, pneumatocele, and lung abscess were considered complications of CAP. The patients who were included in the

complicated CAP group presented with such complications at admission.

The sample size was calculated on the basis of the two main epidemiological variables, i.e., family income and level of maternal education, at least 12 and 14 children being required for each group.

The data were processed by the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA) and presented in tables showing the absolute frequency (n) and relative frequency (%) of qualitative variables, as well as showing the means, standard deviations, minimum values, medians, and maximum values of quantitative variables. In order to evaluate the association between the dependent variable and qualitative independent variables, we used the chi-square test or Fisher's exact test, as appropriate. In addition, we determined the crude OR and its 95% CI using the program Epi Info, version 6.04d. We performed a multivariate unconditional logistic regression analysis using the Wald method (forward stepwise technique), the probability of inclusion in the model being 0.05 and the probability of exclusion from the model being 0.10. All of the variables with a value of $p < 0.200$ in the bivariate analysis were preselected for inclusion in the model. In all cases, the level of significance was set at $\alpha = 5\%$.

The present study was approved by the Research Ethics Committee of the State University at Campinas School of Medical Sciences and the Education and Research Committee of the São Paulo State Hospital at Sumaré (CEP-FCM Ruling no. 616/2010).

## Results

A total of 63 children were included in the present study. Of those, 29 were included in the uncomplicated CAP group and 34 were included in the complicated CAP group. Of the 34 children with complicated CAP, 33 presented with pleural effusion (associated with pneumothorax in 3 and with pneumatoceles in 2) and 1 presented with pneumothorax alone. The procedures performed in order to treat the complications included pleural drainage (in 13 patients) and pleural puncture (in 4). Of the 34 patients, 10 were submitted to mechanical ventilation.

There were no statistically significant differences between the complicated CAP group and the uncomplicated CAP group regarding age ($p = 0.36$), gestational age ($p = 0.60$), birth weight ($p = 0.32$), or gender ($p = 0.99$; Table 1). In addition, there were no statistically significant differences between the groups regarding the epidemiological variables (Table 1). Regarding housing conditions, most of the patients in both groups lived in homes in areas where there was garbage collection, a sewage system, and running water.

As can be seen in Table 2, there were statistically significant differences between the groups regarding history of pneumonia ($p = 0.03$) and previous antibiotic therapy ($p = 0.004$). As can be seen in Table 3, there were statistically significant differences between the groups regarding time elapsed since the onset of CAP ($p = 0.01$), duration of fever prior to admission ($p < 0.001$), duration of antibiotic therapy ($p < 0.001$), and length of hospital stay ($p < 0.001$).

Variables with a value of $p < 0.200$ were used as predictor variables in the multivariate analysis, including history of pneumonia, wheezing, previous antibiotic therapy, onset of CAP, number of individuals sharing the bedroom with the child, number of children under 5 years of age living in the household, time elapsed since the onset of CAP, and duration of fever prior to admission. After adjustment, duration of fever prior to admission was the only variable that remained in the model (adjusted OR = 1.97; 95% CI: 1.36-2.84; $p < 0.001$).

Of the total of children included in the present study, 1 died (on postadmission day 3). The child was 27 months of age and had a history of wheezing. She developed extensive pleural effusion (which was drained) and required ventilatory support.

## Discussion

The present study described the characteristics of patients who were diagnosed with complicated or uncomplicated CAP and who were admitted to the pediatric wards of two university hospitals in the metropolitan area of Campinas. We sought to identify variables associated with the development of complications and to determine whether epidemiological or clinical conditions played a role in this unfavorable outcome. The most common complication was pleural effusion, a finding that is consistent with those of other authors.[12,14,17,18]

**Table 1 -** Distribution of epidemiological variables and gender according to the groups of children hospitalized with complicated or uncomplicated community-acquired pneumonia (CAP).

| Variables | Groups | | | | Total | | p* | Crude OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| | Complicated CAP | | Uncomplicated CAP | | | | | | |
| | n | % | n | % | n | % | | | |
| Gender | | | | | | | | | |
| Male | 21 | 55.3 | 17 | 44.7 | 38 | 100.0 | 0.996 | 1.14 | 0.37-3.55 |
| Female | 13 | 52.0 | 12 | 48.0 | 25 | 100.0 | | | |
| Level of maternal education, years | | | | | | | | | |
| < 5 | 3 | 60.0 | 2 | 40.0 | 5 | 100.0 | 1.000** | 1.33 | 0.15-13.38 |
| 5-8 | 12 | 52.2 | 11 | 47.8 | 23 | 100.0 | 0.830 | 0.97 | 0.29-3.20 |
| ≥ 9 | 18 | 52.9 | 16 | 47.1 | 34 | 100.0 | | 1.00 | |
| Work | | | | | | | | | |
| Formal | 10 | 47.6 | 11 | 52.4 | 21 | 100.0 | 0.647 | 0.66 | 0.19-2.31 |
| Informal | 6 | 54.5 | 5 | 45.5 | 11 | 100.0 | 1.000** | 0.87 | 0.18-4.26 |
| No work | 18 | 58.1 | 13 | 41.9 | 31 | 100.0 | | 1.00 | |
| Per capita income, number of times the national minimum wage | | | | | | | | | |
| < 0.5 | 24 | 68.6 | 11 | 31.4 | 35 | 100.0 | 1.000** | 1.45 | 0.14-13.32 |
| 0.5-1.0 | 7 | 30.4 | 16 | 69.6 | 23 | 100.0 | 0.315** | 0.29 | 0.03-2.93 |
| ≥ 1.0 | 3 | 60.0 | 2 | 40.0 | 5 | 100.0 | | 1.00 | |
| Breastfeeding | | | | | | | | | |
| No | 3 | 50.0 | 3 | 50.0 | 6 | 100.0 | 1.000** | 0.84 | 0.12-5.83 |
| Yes | 31 | 54.4 | 26 | 45.6 | 57 | 100.0 | | | |
| Day care center attendance | | | | | | | | | |
| Full time | 17 | 54.8 | 14 | 45.2 | 31 | 100.0 | 0.819 | 1.34 | 0.38-4.71 |
| Part time | 7 | 63.6 | 4 | 36.4 | 11 | 100.0 | 0.624 | 1.92 | 0.34-11.25 |
| No time | 10 | 47.6 | 11 | 52.4 | 21 | 100.0 | | 1.00 | |
| Smokers in the household | | | | | | | | | |
| Yes | 16 | 61.5 | 10 | 38.5 | 26 | 100.0 | 0.451 | 1.69 | 0.54-5.33 |
| No | 18 | 48.6 | 19 | 51.4 | 37 | 100.0 | | | |
| Individuals living in the household, n | | | | | | | | | |
| > 4 | 13 | 68.4 | 6 | 31.6 | 19 | 100.0 | 0.594 | 1.77 | 0.40-8.08 |
| 4 | 10 | 41.7 | 14 | 58.3 | 24 | 100.0 | 0.562 | 0.58 | 0.15-2.28 |
| < 4 | 11 | 55.0 | 9 | 45.0 | 20 | 100.0 | | 1.00 | |
| Rooms in the household, n | | | | | | | | | |
| > 4 | 10 | 45.5 | 12 | 54.5 | 22 | 100.0 | 0.974 | 0.83 | 0.20-3.48 |
| 4 | 15 | 65.2 | 8 | 34.8 | 23 | 100.0 | 0.507 | 1.88 | 0.45-8.06 |
| < 4 | 9 | 50.0 | 9 | 50.0 | 18 | 100.0 | | 1.00 | |
| Individuals sharing the bedroom with the child, n | | | | | | | | | |
| ≥ 3 | 13 | 68.4 | 6 | 31.6 | 19 | 100.0 | 1.000** | 0.54 | 0.02-7.78 |
| 2 | 9 | 33.3 | 18 | 66.7 | 27 | 100.0 | 0.131** | 0.13 | 0.00-1.54 |
| 1 | 8 | 66.7 | 4 | 33.3 | 12 | 100.0 | 1.000** | 0.50 | 0.02-8.82 |
| 0 | 4 | 80.0 | 1 | 20.0 | 5 | 100.0 | | 1.00 | |
| Children under 5 years of age living in the household, n | | | | | | | | | |
| 2 | 5 | 100.0 | 0 | 0 | 5 | 100.0 | 0.067** | No data | No data |
| 1 | 2 | 25.0 | 6 | 75.0 | 8 | 100.0 | 0.252** | 0.28 | 0.04-1.81 |
| 0 | 27 | 54.0 | 23 | 46.0 | 50 | 100.0 | | 1.00 | |

*Chi-square test, except where otherwise indicated. **Fisher's exact test.

**Table 2 -** Previous findings in the groups of children hospitalized with complicated or uncomplicated community-acquired pneumonia (CAP).

| Previous findings | Groups | | | | Total | | p* | Crude OR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| | Complicated CAP | | Uncomplicated CAP | | | | | | |
| | n | % | n | % | n | % | | | |
| Pneumonia | | | | | | | | | |
| Yes | 4 | 26.7 | 11 | 73.3 | 15 | 100.0 | 0.033 | 0.22 | 0.05-0.90 |
| No | 30 | 62.5 | 18 | 37.5 | 48 | 100.0 | | | |
| Wheezing | | | | | | | | | |
| Yes | 4 | 30.8 | 9 | 69.2 | 13 | 100.0 | 0.116 | 0.30 | 0.07-1.26 |
| No | 30 | 60.0 | 20 | 40.0 | 50 | 100.0 | | | |
| Antibiotic therapy | | | | | | | | | |
| Yes | 23 | 74.2 | 8 | 25.8 | 31 | 100.0 | 0.004 | 5.49 | 1.64-19.06 |
| No | 11 | 34.4 | 21 | 65.6 | 32 | 100.0 | | | |

*Chi-square test.

**Table 3 -** Clinical/disease progression variables in the groups of children hospitalized with complicated or uncomplicated community-acquired pneumonia (CAP).

| Variables | Groups | n | Mean | SD | Min | Md | Max | p* |
|---|---|---|---|---|---|---|---|---|
| Onset of CAP | Complicated CAP | 34 | 8.15 | 6.81 | 1 | 7 | 30 | 0.017 |
| | Uncomplicated CAP | 29 | 4.86 | 2.67 | 2 | 4 | 13 | |
| Duration of fever prior to admission | Complicated CAP | 34 | 6.35 | 3.23 | 1 | 6 | 15 | < 0.001 |
| | Uncomplicated CAP | 29 | 3.21 | 1.40 | 1 | 3 | 7 | |
| Duration of antibiotic therapy during hospitalization | Complicated CAP | 34 | 10.21 | 6.66 | 3 | 9 | 33 | < 0.001 |
| | Uncomplicated CAP | 29 | 5.24 | 2.17 | 2 | 5 | 11 | |
| Length of hospital stay | Complicated CAP | 34 | 12.18 | 9.34 | 3 | 9 | 44 | < 0.001 |
| | Uncomplicated CAP | 29 | 5.52 | 1.90 | 3 | 5 | 11 | |

Min: minimum; Md: median; and Max: maximum. *Mann-Whitney test.

In the present study, age was not associated with the development of complications. Some studies support this finding,[15,18,19] whereas others have found a direct relationship between low age and the development of complications in children with CAP, the relationship being due to the fact that these patients have narrower airways and limited defense mechanisms of the airways, which are still immature.[10,13,16,20] Our finding might be due to the fact that patients under 12 months of age were excluded from the present study. We had to exclude patients in that age bracket because of the higher prevalence of viral pneumonia among such patients and because of the inclusion of children in the 1-4 year age bracket in most CAP studies defined by the World Health Organization.[21]

We found no association between gender and complications of CAP in our sample. There is no consensus in the literature. Some studies have reported that complications of CAP are more common in males,[6,16,22] whereas others have reported that such complications are more common in females[18] or that there is no association between gender and complications of CAP.[14,23]

Most of the patients investigated in the present study were children with no history of prematurity or low birth weight. This reflects the ease of access to health care in the study area, where health care facilities offer good coverage for prenatal care and delivery. Therefore, we were unable to determine whether the risk of complications was higher in such patients. In children with CAP and a history of prematurity and low birth weight, studies have shown an increased risk of death[6,10,16,24] rather than an increased risk of complications.[18]

Breast milk seems to play a protective role against infectious diseases.[6,10] Early weaning and lack of breastfeeding have been associated with an increase in the number of cases of severe pneumonia.[16,23] Most of the patients in our sample were breastfed, a finding that supports

the hypothesis that the study population had good nutritional status and easy access to health care, including clinical follow-up and nutritional guidance in the first year of life.

We found that epidemiological variables such as age, level of maternal education, mothers working outside the home, and day care center attendance had no impact on the development of CAP-related complications, a finding that is consistent with those reported by other authors.[15,18] One group of authors[25] found higher mortality in children with CAP attending a day care center; however, the authors reported no association between day care center attendance and an increased risk of complications. Although children attending a day care center are more exposed to bacterial agents and show a high rate of colonization by *Streptococcus pneumoniae* (the major etiologic agent of CAP), day care center attendance appears to influence the acquisition of CAP rather than the complications thereof. The same seems to be true for the variables associated with close living quarters, including family size and number of rooms in the household, which were also found to have no association with complications of CAP. We also found that income had no influence on the development of CAP-related complications. Although the study population had a low income, the impact of having a low income appears to have been minimized by the good health care coverage provided by the facilities in the study area.

Passive smokers are at a higher risk of respiratory morbidity and mortality because cigarette pollutants act on the defense mechanisms of the respiratory mucosa, affecting mucociliary transport and alveolar macrophage activity; this induces pulmonary infections, as well as leading to an increase in the allergic response to inhaled antigens.[10] Studies have shown that children whose parents smoke have a higher risk of having pneumonia and being hospitalized for it.[16,26] However, no studies have established a direct relationship between smoking and a higher occurrence of CAP-related complications.[6,15]

Although epidemiological variables were not associated with the development of CAP-related complications in the present study, biological variables such as history of pneumonia and wheezing and previous use of antibiotics were found to be associated with such complications. The association of biological variables (particularly a history of pneumonia and wheezing) with complications of CAP has been reported by other authors. In one study,[16] children with a history of recurrent respiratory infections and wheezing were found to be up to five times more likely to be hospitalized for pneumonia. Other authors[14] found that children who had used aminopenicillins before hospitalization had more complications than did those who used other types of antibiotics. This finding might be due to the fact that amoxicillin is widely used in patients with acute respiratory infections at doses that are insufficient to have an effect on *S. pneumoniae*, particularly on bacterial serotypes showing intermediate resistance to penicillin. The question is whether the use of higher doses of amoxicillin in patients with CAP whose etiology is probably bacterial can prevent this unfavorable outcome.

The longer hospital stays in the patients with complicated CAP in the present study were due to the need for maintaining intravenous antibiotic therapy until patients had been afebrile for 48 h, as well as being due to the need for additional care in cases in which pleural drainage was performed. It is of note that most of the patients included in the present study received beta-lactam antibiotics at admission and responded well to the treatment.

Our multivariate analysis revealed that duration of fever prior to admission was the only variable that was more closely related to the development of complications, with an OR of nearly 2. Other authors have reported the risk of complications in such cases, given that a timely diagnosis can prevent progression to pleural effusion in patients with CAP.[14,17,19,27-29] A delay in the initiation of antibiotic therapy, an inappropriate choice of antibiotics, and the use of lower than recommended doses of antibiotics can have a negative impact on the clinical course of bacterial pneumonia. However, there is a concern about the incorrect indication of penicillins in viral processes; this is a commonplace practice in emergency rooms and can lead to increased bacterial resistance to the antibiotics that are widely used in pediatric patients.[30]

In summary, the present study showed that the development of complications in children with CAP is directly associated with biological variables such as patient history, previous use

of antibiotics, and, first and foremost, duration of fever prior to admission.

The limitations of the present study include the difficulty in determining the etiology of localized CAP (even in patients with pleural effusion) and the number of patients included in the study. However, empirical antibiotic therapy remains the most common approach to CAP, being based on age and on clinical and radiological data. In the present study, this was the therapeutic approach to CAP. Failure to determine the etiology of CAP should not be an obstacle to the decision-making process regarding antibiotic therapy. Clinical follow-up studies involving a higher number of patients and the use of various methods for bacterial identification can confirm or refute our findings.

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