Clinica Chimica Acta 489 (2019) 212–218

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Recovery from childhood community-acquired pneumonia in a developing country: Prognostic value of serum procalcitonin

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ARTICLE INFO

Keywords:
Procalcitonin
Biomarker
Child
Lower respiratory tract infection
Pneumonia

ABSTRACT

Background: Childhood community-acquired pneumonia is a common and potentially life-threatening illness in developing countries. We assessed the prognostic value of serum procalcitonin level upon admission on clinical response to antibiotic treatment.

Methods: Out of 89 patients, the median (IQR) age was 19(12–29) months and 60% were boys. Viral (49.5%), typical bacterial (38%) and atypical bacterial (12.5%) infections as well as probable pneumococcal infections (26%) were diagnosed.

Results: Seventy-five (84%) children became afebrile ≤ 48 h after treatment. In 14 children who remained febrile after 48 h of treatment, median[*IQR*] serum procalcitonin (ng/ml) level on admission was higher than in those with rapid recovery (2.1[0.8–3.7] vs 0.6[0.1–2.2]; P = 0.025). In the slow-responding children, pneumococcal infections were more common (71% vs 17%; P < 0.001). Procalcitonin concentrations on admission were higher in children with pneumococcal pneumonia compared to children with non-pneumococcal pneumonia (2[0.7–4.2] vs 0.5[0.08–2.1]; P = 0.002). The ROC curve found that < 0.25 ng/ml of serum procalcitonin had a high negative predictive value (93%[95%CI:80%–99%]) for pneumococcal infection. All children that remained febrile after 48 h of treatment had procalcitonin > 0.25 ng/ml on admission. The majority of children with pneumonia in a developing country become afebrile within 48 h after onset of antibiotic treatment.

Conclusions: Serum procalcitonin < 0.25 ng/ml predicted rapid clinical response and non-pneumococcal etiology.

1. Introduction

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in children under-5 years in developing countries [1]. According to distinct guidelines, the chest radiograph (CXR) is useful in confirming the clinical diagnosis of CAP [2]. Etiologic diagnosis is rarely established in routine practice because lower respiratory tract specimens are difficult to obtain [3]. Currently, two diagnostic tools available to investigate bacterial infection are blood culture and blood polymerase chain reaction (PCR), both of which show low rate of positive results [3]. The etiologic agent frequency varies according to the age of the patients. Viral infection, however, is the most common one in all ages between the first month and the 5th year of life [4]. Russkanen et al. [5] showed that up to 85% of CAP episodes are caused by virus. The American and British guidelines have already recognized that not all children will benefit from antibiotic use [6,7]. None of the clinical features, laboratory or radiologic findings, such as reactive-C protein or white blood cell count, though, could be associated to etiologic diagnosis on CAP [3]. Thus, antibiotic therapy is empirically used [2] and is probably over used as defining the causative agent remains a challenge in clinical practice. In this context, Penicillins are the first-line option because *Streptococcus pneumoniae* is the most frequent bacterial causative pathogen [2,6,7]. In a developed country, among children with pneumococcal bacteremic CAP, 94% became

*Abbreviations:*IQR, interval interquartile

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https://doi.org/10.1016/j.cca.2017.12.021
Received 10 November 2017; Received in revised form 11 December 2017; Accepted 15 December 2017
Available online 16 December 2017
0009-8981/

afebrile within 48 h of antibiotic treatment [8]. As such, resolution of fever has been considered a proxy of clinical response to antibiotic therapy [8,9].

Procalcitonin (PCT) is a biomarker that has been studied in children with CAP as a predictor of bacterial infection and to guide antibiotic use [9–11]. In this context, we studied the prognostic value of serum PCT concentration on admission in regard to therapeutic response to aqueous penicillin G, stratified by etiology, among children hospitalized with CAP.

2. Material and methods

2.1. Study design

This was a prospective cohort conducted at the Emergency Room of the Federal University of Bahia hospital, in Salvador, Northeast Brazil, from September 2003 to May 2005. Community-dwelling children under-5 years diagnosed with CAP were enrolled. The diagnosis was made by the pediatrician on duty. Diagnosis was based upon fulfillment of the following criteria: 1) respiratory complaints plus 2) fever or difficulty breathing plus 3) pulmonary infiltrates on the CXR taken at admission. Exclusion criteria included refusal to give informed consent, children born to an HIV-infected woman, chronic lung disease except asthma, other concomitant infectious disease or immunodeficiency. Additional exclusion occurred when: 1) serum PCT was not measured on the serum sample collected upon admission due to lack of serum because it was measured retrospectively on stored samples after data collection was finished; 2) treatment with other antibiotics besides aqueous penicillin G in order to include children receiving homogeneous antimicrobial treatment, or 3) pleural effusion present on admission - as we have previously demonstrated that serum PCT values are higher in children with CAP and pleural effusion than in children with CAP without pleural effusion [12]. Initial antibiotic treatment was chosen at the discretion of the pediatrician on duty, who was blinded to the results of the etiology investigation and of serum PCT levels.

On recruitment, clinical data were collected as well as nasopharyngeal aspirates (NPA) and blood, before antibiotic therapy was initiated, to investigate etiologic pathogens and PCT serum levels. All CXR were subsequently read by a pediatric radiologist blinded to patients' clinical data. Radiographic findings were registered, taking into account the standardized interpretation previously published [13]. Every recruited child was re-evaluated 2–4 weeks after admission when the second blood sample was collected to investigate etiology. Daily evolution data were collected from medical charts by a researcher blinded (TSF) to the etiologic diagnosis, serum PCT levels or final outcome. All collected data were registered in pre-defined forms.

2.2. Clinical definitions

Fever was defined as axillary temperature ≥ 37.5 °C [14] and tachypnea as respiratory rate (RR) ≥ 50 breaths/min in children aged 2–11 months and RR ≥ 40 breaths/min in children from 12 months upwards [15].

2.3. Laboratory procedures

Respiratory virus investigation consisted of searching for viral antigens (influenza A and B viruses, respiratory syncytial virus, parainfluenza virus type 1, 2, and 3, and adenovirus) using a time-resolved fluoroimmunoassay with monoclonal antibodies in NPA [16]. Virus-specific serum antibody titers for these viruses in paired samples were determined using an enzyme-immunoassay (ELISA) with an antigen-coated solid phase and horseradish peroxidase conjugated rabbit anti-human IgG [16]. When a ≥ 3-fold increase was found in virus-specific serum IgG titers on paired samples, the respective virus was considered a potential causative agent. Two previously described different reverse transcription (RT)-PCR assays were used to detect rhinovirus and enterovirus in NPA [17]. The final result was based on the detection of any of these viruses by any of the assays. Human metapneumovirus RNA was detected by monoplex RT-PCR in NPA [18]. Human bocavirus (HBoV) infection was searched for by measuring HBoV IgG in paired serum samples, specific IgM, IgG avidity, by ELISA, as well as quantitative monoplex PCR (qPCR) in serum [19]. The diagnostic criteria for an acute primary HBoV infection were the presence of 2 or more of the following markers: presence of IgM, a 4-fold or greater increase or conversion of IgG in paired sera, low avidity of IgG, or positive qPCR in serum.

Blood culture was performed according to routine procedures (automated BACTEC/Organon) at the same hospital where patients were enrolled. Additionally, bacterial infection caused by *S. pneumoniae*, nontypeable *H. influenzae* and *M. catarrhalis* were investigated by antibody assays in paired serum samples by ELISA. For pneumococcal infections, IgG antibodies to pneumococcal pneumolysin and pneumococcal C-polysaccharide were used; $\geq$ 2-fold or $\geq$ 3-fold increases, respectively, in antibody titers were considered diagnostic [20]. For *H. influenzae* and *M. catarrhalis* infections, Ig (polyvalent) antibodies against whole bacterial cell antigens were measured and a $\geq$ 3-fold antibody increase was considered diagnostic. Real-time quantitative PCR was used for the detection of *S. pneumoniae* DNA in blood buffy-coat, after extraction of DNA using QIAamp DNA Blood Mini Kit (Qiagen) [21]. An in-house microimmunofluorescence test was used to measure IgG, IgA, and IgM antibodies to *Chlamydia pneumoniae* and *Simkania negevensis*, using purified, formalized elementary bodies of strains Kajaani 6 in *C. pneumoniae* [22] and ATCC strain Z (ATCC, Catalog no. VR-1471) in *S. negevensis* tests [23]. Diagnosis was based on a $\geq$ 4-fold increase in IgG or IgA antibodies between paired sera or on the presence of IgM antibodies (a titer of ≥ 10). *Chlamydia trachomatis* IgG antibodies were measured using a commercial, solid-phase ELISA (AniLabsystems Ltd.) [24]. IgM antibodies to *Mycoplasma pneumoniae* were searched for using a commercial ELISA kit (Platelia, Bio-Rad).

PCT concentration was measured by an immunoluminometric assay (LUMItest PCT, Brahms Diagnostica) in blood samples collected upon admission. Serum samples were kept frozen at -80 °C in the Federal University of Bahia hospital laboratory until they were shipped to Université Paris-Descartes, where PCT was measured. The serum samples were transported by airplane in dry ice at -80 °C. The lower and upper detection limits were 0.02 and 5000 ng/ml, respectively.

2.4. Statistical analyses

The cases were classified into three groups: 1) viral infection when only viral infection was detected; 2) atypical bacterial infection when infection by *M. pneumoniae*, *C. trachomatis*, *C. pneumoniae* or *S. negevensis* was detected irrespective of viral infection having also been detected; and 3) typical bacterial infection when infection by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* or *S. aureus* was found irrespective of other agents. To address generalizability, a further analysis was performed with the inclusion of cases with undetected etiology.

Continuous variables were presented as median (interquartile range [IQR]). Clinical characteristics and the detected etiologies are presented as absolute and relative frequencies. Bivariate analysis was performed with Chi-Square test or Fisher's exact test to compare proportions as appropriate, and Mann-Whitney *U* test to compare medians.

Sample size was estimated considering a smaller frequency of serum PCT ≥ 0.25 ng/ml in patients with non-pneumococcal infection of 55% and an expected frequency of serum PCT ≥ 0.25 ng/ml in patients with pneumococcal infection of 85%. Thus, the sample size was estimated as 70 cases, considering $\alpha = 0.05$ and $\beta = 0.20$. All tests were 2-tailed with a significance level of 0.05. Sensitivity, specificity, positive and negative predictive values along with the respective 95% confidence interval (CI) were calculated. The receiver operating characteristic (ROC) curve was used to evaluate the ability of serum PCT

concentrations to distinguish pneumococcal infection from non-pneumococcal infection. To define the predictive value of serum PCT level ≥ 0.25 ng/ml (predictor variable) for pneumococcal pneumonia (outcome variable), a multivariable logistic regression by enter method was constructed in a model adjusted for both age and duration of illness as continuous variables, and the 95%CI of the odds ratio (OR) was calculated. SPSS ver 9.0 was used for analysis. Exclusion criteria were chosen to address potential confounders. Blinding at etiologic diagnosis and serum PCT levels was performed to address potential bias.

2.5. Ethical aspects

The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. It was approved by the Ethics Committee of the Federal University of Bahia. Every patient was enrolled following written informed consent signed by parents/legal guardians.

3. Results

Overall, 277 children were recruited: 209 (75%) had etiology determined and 159 (57%) had PCT measured; 113 had both, out of which 100 received aqueous penicillin G for treatment and 11 had pleural effusion detected at admission. Therefore, the study group comprised 89 children (Fig. 1). The clinical characteristics and duration of symptoms on admission of children hospitalized with CAP and probable etiology found, with or without serum PCT measurement were compared and there was no difference between these groups (Table 1).

The median (IQR) age of the patients was 19 (12–29) months and 53 (60%) were boys. Table 2 shows the clinical characteristics of the study group on admission. The median (IQR) duration of illness before admission was 7 (5–10) days. Table 2 also shows the clinical characteristics on admission of children with pneumococcal pneumonia, among whom the median (IQR) duration of disease was 8 (5–14) days. Overall, CXR findings were alveolar infiltrate (93%), alveolar-interstitial infiltrate (6%) and interstitial infiltrate (1%).

Viral (49.5%), atypical bacterial (12.5%), and typical bacterial (38%) infections were detected. Mixed viral-bacterial infection was

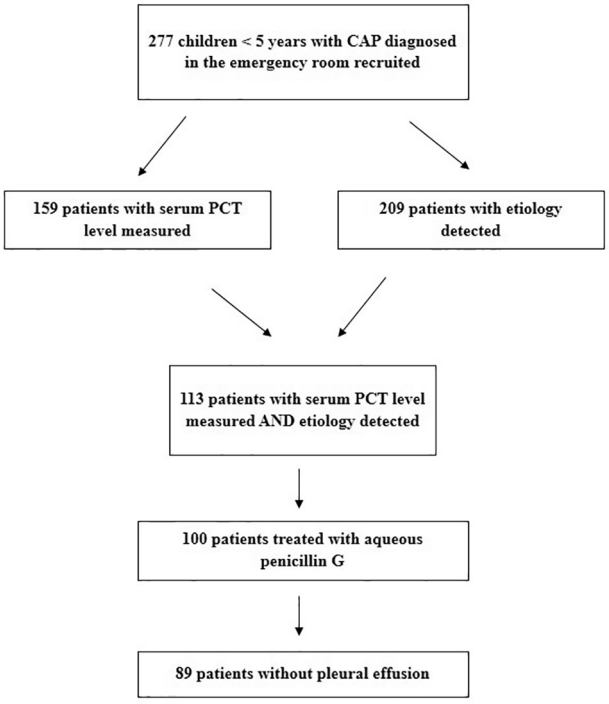

Fig. 1. Flow-chart to compose the study group.

Table 1
Comparison of clinical characteristics and duration of symptoms on admission of children hospitalized with community-acquired pneumonia and probable etiology found with or without procalcitonin (PCT) measured.

Characteristics	PCT measured		P value
	Yes (n = 113)	No (n = 96)	
Male gender[a]	68 (60.2)	49 (51.0)	NS
Symptoms			
Duration of illness[b]	7 (5–10.5)	7 (4–13.5)	NS
Fever[a]	106 (93.8)	90 (93.8)	NS
Duration of fever[b]	5 (4–8)	4.5 (3–7)	NS
Cough[a]	109 (96.5)	91 (94.8)	NS
Duration of cough[b]	7 (4–12)	7 (4–15)	NS
Difficulty breathing[a]	98 (86.7)	79 (82.3)	NS
Duration of difficulty breathing[b]	5 (3–7)	4 (3–7)	NS
Vomiting[a]	62 (54.9)	57 (59.4)	NS
Duration of vomiting[b]	3 (1–5)	3 (2–4)	NS
Wheezing[a]	47 (41.6)	44/95 (46.3)	NS
Duration of wheezing[b]	4 (2–7)	4 (3–6.75)	NS
Convulsion[a]	5 (4.4)	2 (2.1)	NS
For how long has the child had convulsion[b]	7 (4–7.5)	15.5 (1 − 30)	NS
Signs on physical examination	n (%)	n (%)	
Tachypnea	93/112 (83.0)	77/95 (81.1)	NS
Crackles	34 (30.1)	29/95 (30.5)	NS
Thoracic recession	60/112 (53.6)	56/94 (59.6)	NS
Chest indrawing	68/112 (60.7)	59/94 (62.8)	NS
Rhonchi	37 (32.7)	34/91 (37.4)	NS
Bronchial breath sound	11/111 (9.9)	8/95 (8.4)	NS
Supraclavicular recession	3/112 (2.7)	1/94 (1.1)	NS
Etiology	n (%)	n (%)	
Viral infection	54 (47.8)	55 (57.3)	NS
Bacterial infection	59 (52.2)	41 (42.7)	NS

[a] Data is shown as n (%).
[b] Data is shown as median (IQR) in days.

Table 2
Clinical characteristics and duration of symptoms on admission of children hospitalized with community-acquired pneumonia and of the subgroup with pneumococcal infection.

	Children with CAP (n = 89)	Children with pneumococcal infection (n = 23)
Symptoms		
Fever[a]	86 (96.6)	23 (100)
Duration of fever[b]	5 (3–8)	5 (5–8)
Cough[a]	85 (95.9)	22 (95.7)
Duration of cough[b]	6 (4–13)	12 (5–15)
Difficulty breathing[a]	75 (84.3)	21 (91.3)
Duration of difficulty breathing[b]	5 (2–7)	4 (3–5)
Vomiting[a]	49 (55.1)	14 (60.9)
Duration of vomiting[b]	1 (1–2)	1 (1–2)
Wheezing[a]	37 (41.6)	8 (34.8)
Duration of wheezing[b]	4 (2–6)	4 (1–5)
Convulsion[a]	4 (4.5)	2 (8.7)
Duration of convulsion[b]	7 (3–8)	4 (1–7)
Signs on physical examination	n (%)	n (%)
Tachypnea	72 (80.9)	19 (82.6)
Crackles	64 (71.9)	14 (60.9)
Fever (≥ 37.5 °C)	56 (62.9)	15 (65.2)
Chest indrawing	54 (60.7)	16 (69.6)
Thoracic recession	48 (53.9)	14 (60.9)
Rhonchi	28 (31.5)	8 (34.8)
Tubal murmur	5 (5.6)	4 (17.4)
Supraclavicular recession	2 (2.2)	1 (4.3)

[a] Data is shown as n (%).
[b] Data is shown as median (IQR) in days.

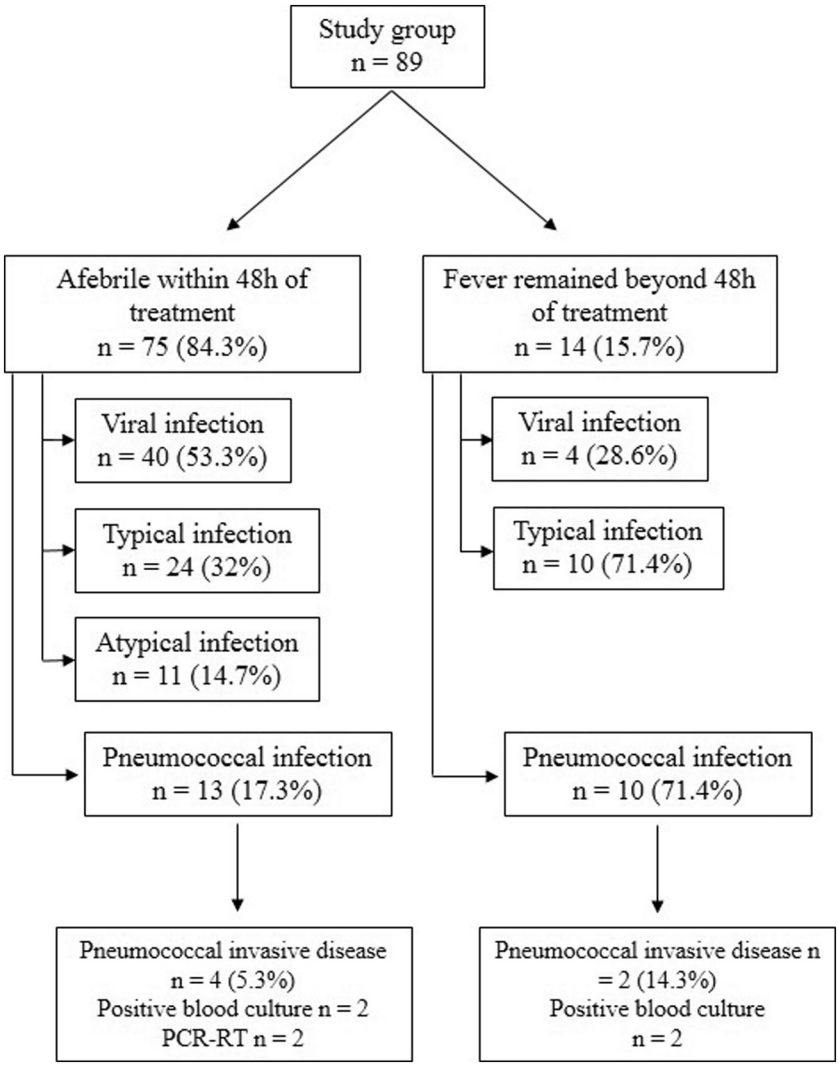

Fig. 2. Distribution of etiologies between patients who did or did not become febrile within 48 h of treatment.

Table 3
Absolute frequency of the etiological agents found among hospitalized children with community-acquired pneumonia with or without fever at 48 h of treatment.

	Fever at 48 h of treatment	
	Yes (n = 14)[a]	No (n = 75)[b]
Viral infection	Parainfluenza (6) Rhinovirus (4) Human bocavirus (4) Respiratory syncytial virus (2) Influenza (1) Adenovirus (1) Human metapneumovirus (1) Enterovirus (1)	Parainfluenza (12) Rhinovirus (19) Human bocavirus (8) Respiratory syncytial virus (17) Influenza (14) Adenovirus (5) Human metapneumovirus (4) Enterovirus (3)
Atypical bacterial infection	None	*Mycoplasma pneumoniae* (8) *Chlamydia trachomatis* (4) *Simkania negevensis* (1) *Chlamydia pneumoniae* (1)
Typical bacterial infection	*Streptococcus pneumoniae* (10) *Moraxella catarrhalis* (1)	*Streptococcus pneumoniae* (13) *Heamophyilus influenzae* (10) *Moraxella catarrhalis* (2)

This table presents the absolute number of etiological agents, which could be found in co-infections.

detected in 29 (32%) patients. Overall, 23 (26%) patients had evidence of pneumococcal infection. Six of these patients had pneumococcal invasive disease (PID) – 4 detected by blood culture and 2 by PCR. Seventy-five (84%) children became afebrile within 48 h of aqueous penicillin G treatment. Fig. 2 presents the distribution of etiologies between patients who became or did not become afebrile within 48 h of treatment. Table 3 depicts the frequency of the etiological agents found among patients who became or did not become afebrile within 48 h of treatment. Pneumococcal infection was more common in children who remained febrile after 48 h of treatment (71% vs 17%; $P < 0.001$) (Fig. 2). Moreover, 10 (44%) patients out of all 23 cases with pneumococcal infection were febrile after 48 h of treatment. In the subgroup who remained febrile beyond 48 h of treatment, among 10 patients with bacterial infection, all of them had pneumococcal infection and one had *M. catarrhalis* co-infection.

Median (IQR) serum PCT level (ng/ml) in all patients on admission was 0.8 (0.1–2.8). PCT concentrations were lower in children who became afebrile within 48 h after commencing antibiotic treatment compared to those who remained febrile (0.6[0.1–2.2] vs 2.1[0.8–3.7], respectively; $P = 0.025$).

Serum PCT concentrations (ng/ml) were higher in children with pneumococcal infection compared to those with non-pneumococcal pneumonia (2[0.7–4.2] vs 0.5[0.08–2.1]; $P = 0.002$). When the analysis was repeated comparing the pneumococcal infection group with each of the other groups, serum PCT continued higher in the pneumococcal group (viral 0.6[0.1–2.2], $P = 0.009$; atypical bacteria

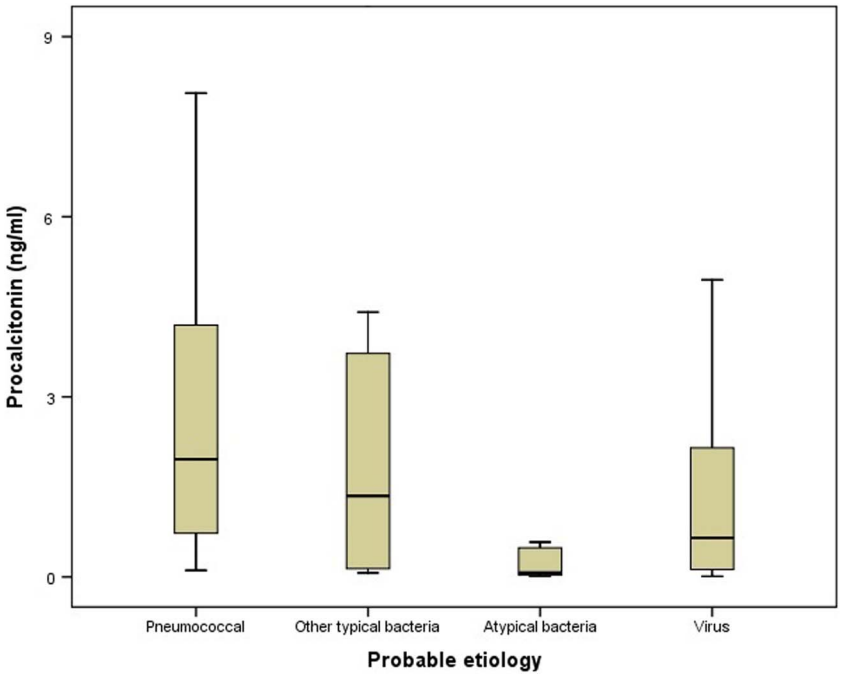

Fig. 3. The distribution of serum PCT levels upon admission in distinct etiological subgroups.

Table 4
Comparison on admission and on 3rd day of treatment of clinical characteristics of children hospitalized with community-acquired pneumonia with or without fever after 48 h of treatment.

Characteristics	On admission			On 3rd day of treatment		
	Fever after 48 h of treatment		P[a]	Fever after 48 h of treatment		P[a]
	Yes (n = 14)	No (n = 75)		Yes (n = 14)	No (n = 75)	
Cough	12 (85.7)	42 (56.0)	NS	10 (71.4)	38 (50.7)	NS
Tachypnea	12 (85.7)	49 (65.3)	NS	10 (71.4)	22 (29.3)	0.005
Difficulty breathing	9 (64.3)	51 (68.0)	NS	9 (64.3)	23 (30.7)	NS
Malaise	1 (7.1)	5 (6.7)	NS	4 (28.6)	3 (4.0)	0.01
Chest indrawing	2 (14.3)	18 (24.0)	NS	2 (14.3)	6 (8.0)	NS
Vomiting	7 (50.0)	28 (37.3)	NS	2 (14.3)	–	0.02
Thoracic recession	3 (21.4)	25 (33.3)	NS	–	5 (6.7)	NS
Grunting	–	6 (8.0)	NS	–	1 (1.3)	NS

Results n (%).
[a] χ^2 test or Fisher's Exact test.

0.07[0.03–0.6], P < 0.001; other typical bacteria 1.4 [0.1–4.4], P = 0.2) (Fig. 3). Clinical characteristics on admission and on the third day of hospitalization of children who did or did not become afebrile within 48 h of treatment are compared in Table 4.

The area under the receiver-operating-curve (ROC) for PCT to predict pneumococcal infection was 0.71 (95%CI: 0.6–0.82) (Fig. 4). Diagnostic characteristics of serum PCT level ≥ 0.25 ng/ml to diagnose pneumococcal infection are presented in Table 5. None of the patients who remained febrile beyond 48 h of treatment had serum PCT < 0.25 ng/ml upon admission.

In multivariate analysis, neither age (OR [95%CI]: 1.1[0.7–1.8]; P = 0.6) nor length of disease (OR[95%CI]: 1.1[1.0–1.2]; P = 0.08) were predictors for pneumococcal infection. On the other hand, the OR of PCT level ≥ 0.25 ng/ml was 9.4(1.8–48.4), P = 0.007.

To address generalizability, serum PCT level ≥ 0.25 ng/ml was further evaluated to diagnose pneumococcal infection with the inclusion of all 159 cases which had serum PCT level measured upon admission. In such analysis, cases with undetected etiology were labeled as non-pneumococcal infection. Cases treated with antibiotics besides aqueous penicillin G, or with pleural effusion but with pneumococcal infection were labeled as pneumococcal infection. Table 5 depicts the results of this analysis. The negative predictive value was 91% (95%CI: 81%–97%).

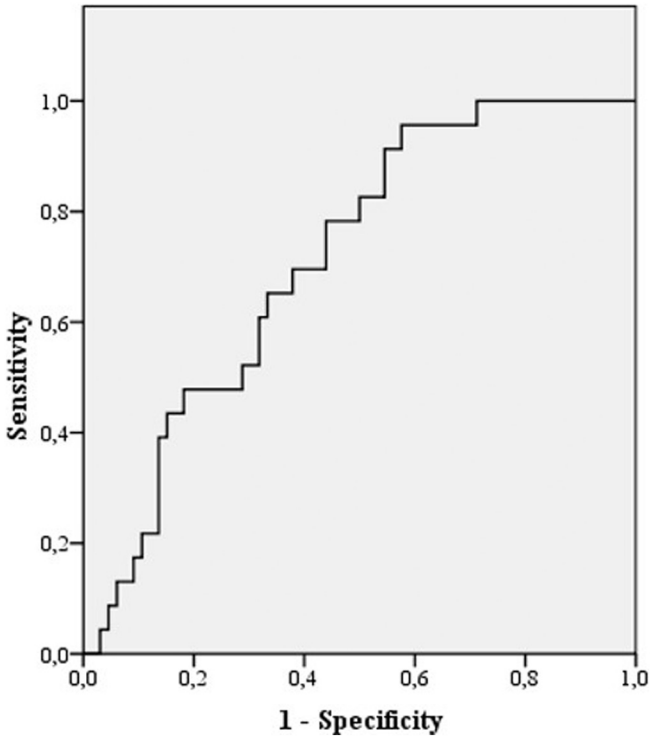

Fig. 4. ROC curve for serum PCT levels upon admission and pneumococcal infection in children hospitalized with community-acquired pneumonia.

4. Discussion

Our observations show that 84% of the children hospitalized due to

Table 5
Diagnostic characteristics of serum PCT levels ≥ 0.25 ng/ml to diagnose pneumococcal infection among children hospitalized with community-acquired pneumonia: all cases with or without determined etiology.

		All cases with determined etiology					
		Yes[a]			No[b]		
		Pneumococcal infection		Total	Pneumococcal infection		Total
		Yes	No		Yes	No	
PCT ≥ 0.25 ng/ml	Yes	21	38	59	29	74	103
	No	2	28	30	5	51	56
Total		23	66	89	34	125	159

[a] Sensitivity: 91% (95% CI: 74–99%). Specificity: 42% (95% CI: 31–55%). Positive predictive value: 36% (95% CI: 24–48%). Negative predictive value: 93% (95% CI: 80–99%).
[b] 85% (95% CI: 70–94%). 41% (95% CI: 32–50%). 28% (95% CI: 20–37%). 91% (95% CI: 81–97%).

CAP in a developing country become afebrile within 48 h after commencing penicillin treatment. Serum PCT level on admission < 0.25 ng/ml predicts rapid response to treatment and also predicts non-pneumococcal infection. The high negative predictive value of PCT < 0.25 ng/ml was confirmed when all children with PCT measured in serum collected upon admission were included in the analysis. This finding suggests that PCT may be useful at the point of care in children hospitalized with CAP in identifying patients who will not benefit from antibiotic therapy.

S. pneumoniae has been recognized as the most frequent bacterial causative pathogen of CAP [2,6,7]. However, during recent years, the importance of respiratory viruses infection in children with CAP has been increasingly recognized [5]. Actually, the guidelines by the Pediatric Infectious Disease Society and Infectious Diseases Society of America and by the British Thoracic Society have already recommended that antimicrobial should not be routinely prescribed to young children unless bacterial disease is suspected [6,7]. However, the description of these cases is rather subjective, which leaves the decision to prescribe antimicrobials or not at the discretion of the attending pediatrician. Based on our results, children with serum PCT levels < 0.25 ng/ml on admission are not prone to have pneumococcal infection. In 2015, Bivona et al. reviewed the available literature and showed that PCT is the diagnostic marker with the best performance, especially in terms of detection of a pneumococcal infection [25]. Additionally, these authors concluded that further studies were needed for a better understanding of PCT's role [25]. Our study adds to this data by finding that serum PCT level < 0.25 ng/ml is a potential biomarker to identify children who will not benefit from receiving antimicrobials. In a randomized clinical trial of CAP conducted in Italy, all of 155 (100%) children received antimicrobials at the discretion of the attending pediatrician when PCT testing was not undertaken. On the other hand, 86% of 155 patients were given antimicrobials when a serum PCT level was measured; the algorithm used to guide treatment decisions in the intervention group used a threshold of serum PCT level ≥ 0.25 ng/ml. No difference in recurrence of respiratory symptoms and new antibiotic prescription in the month following enrollment was reported for those patients not treated with antimicrobials [11].

Interestingly, children who remained febrile after 48 h of treatment also had tachypnea, malaise, and vomiting more frequently on the third day of treatment when compared with children who became afebrile within the first 48 h of treatment (Table 4). It is important to recall that the vast majority (71%) of patients who remained febrile had pneumococcal infection (Fig. 2). Despite the fact that appropriate antimicrobial is given, some patients with pneumococcal infection may respond slowly to therapy. In fact, 44% of children with pneumococcal infection detected in our study remained with fever after 48 h of treatment. It contrasts with the previous information that 94% of children with bacteremic pneumococcal pneumonia became afebrile within 48 h of treatment [8]. It is important to stress essential clinical differences observed between both studies: our patients had longer and more intense disease, based on more severe symptoms and signs on admission, which may be attributable to difficult access to the health care system in a developing country [26]. In fact, CAP in children in developed countries is not a serious disease, with a rapid recovery after starting antimicrobials [27]. It is possible to infer that patients with longer and more intense disease occurring among children in developing countries may respond more slowly. We also unexpectedly observed that children with apparent viral infection improved quickly after starting antimicrobial therapy. This finding may be due to the long duration of disease before admission. These children were probably hospitalized late, in the course of disease resolution.

Our study has some limitations: etiology was established based on probability, supported by the best investigations available, as lung tissue was not studied for ethical reasons. To try to decrease the chance of error, several microbiological techniques were used to identify the same pathogen. PCT was not measured in serum collected upon admission from all included patients due to lack of enough serum sample, after the performance of the tests to investigate etiology. However, the included sample size was appropriate to detect the differences found.

5. Conclusion

PCT concentration < 0.25 ng/ml in children hospitalized with CAP predicts rapid response to antibiotic treatment and predicts non-pneumococcal infection. Children with pneumococcal pneumonia in a developing country may respond slower to treatment than those in a developed country.

Acknowledgments

The authors thank the pediatricians of the Emergency Room of the Federal University of Bahia Hospital, in Salvador, Brazil. This study was supported by the Bahia State Agency for Research Funding (FAPESB) and the Brazilian Council for Scientific and Technological Development in Brazil and the Foundation for Pediatric Research, in Finland.

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