RESEARCH PAPER

Differences in Evolution of Children with Non-severe Acute Lower Respiratory Tract Infection With and Without Radiographically Diagnosed Pneumonia

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Objective: To identify differences in the evolution of children with non-severe acute lower respiratory tract infection between those with and without radiographically diagnosed pneumonia.

Design: Prospective cohort study.

Setting: A public university pediatric hospital in Salvador, Northeast Brazil.

Patients: Children aged 2-59 months.

Methods: By active surveillance, the pneumonia cases were prospectively identified in a 2-year period. Each case was followed-up for changes in various clinical symptoms and signs. Demographic, clinical and radiographic data were recorded in standardized forms. Exclusion was due to antibiotic use in the previous 48 hours, signs of severe disease, refusal to give informed consent, underlying chronic illness, hospitalization in the previous 7 days or amoxicillin allergy. Chest *X*-ray (CXR) was later read by at least 2 independent pediatric radiologists.

Main Outcome Measures: Radiographic diagnosed pneumonia based on agreed detection of pulmonary infiltrate or pleural effusion in 2 assessments.

Results: A total of 382 patients receiving amoxicillin were studied, of whom, 372 (97.4%) had concordant radiographic diagnosis which was pneumonia (52%), normal CXR (41%) and others (7%). By multivariate analysis, age (OR=1.03; 95% CI: 1.02-1.05), disease ≥ 5days (OR = 1.04; 95% CI: 1.001-1.08), reduced pulmonary expansion (OR = 3.3; 95% CI: 1.4-8.0), absence of wheezing (OR = 0.5; 95% CI: 0.3-0.9), crackles on admission (OR = 2.0; 95% CI: 1.2-3.5), inability to drink on day 1 (OR = 4.2; 95% CI: 1.05-17.3), consolidation percussion sign (OR = 7.0; 95% CI: 1.5-32.3), tachypnea (OR = 2.0; 95% CI: 1.09-3.6) and fever (OR = 3.6; 95% CI: 1.4-9.4) on day 2 were independently associated with pneumonia. The highest positive predictive value was at the 2nd day of evolution for tachypnea (71.0%) and fever (81.1%).

Conclusion: Persistence of fever or tachypnea up to the second day of amoxicillin treatment is predictive of radiographically diagnosed pneumonia among children with non-severe lower respiratory tract diseases.

Key words: *Acute respiratory infection, Children, Fever, Lower respiratory tract disease, Lung disease, Respiratory discomfort.*

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Pneumonia has been identified as a leading killer of children in developing countries and a cause of significant morbidity worldwide [1]. In order to control childhood deaths in resource poor settings, the World Health Organization (WHO) proposed the use of a standardized management based on the detection of simple signs in the 1990s [2]. Such approach and its improvements were assessed taking into account clinical and chest *X*-ray (CXR) findings on admission [3]. The major difficulty in diagnosing pneumonia promptly, particularly in first-level health care settings, is the absence of an easily feasible and definitive gold-standard diagnostic criteria [4]. In the emergency room (ER), it is mandatory to distinguish between children with and without pneumonia and the CXR evaluation is a fundamental tool for accomplishing this goal [5]. To the best of our knowledge, clinical aspects of the evolution of clinical symptoms and signs in children with and without radiographically diagnosed non-severe pneumonia remains poorly described.

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In this study, we aimed to identify differences in evolution of children with non-severe acute lower respiratory tract infection between those with and without radiographically diagnosed pneumonia receiving amoxicillin. The results on clinical failure are presented elsewhere [6].

METHODS

Participants: Children aged between 2 and 59 months seen in the ER of Professor Hosannah de Oliveira Pediatric Center, in Salvador, North-east Brazil, from November 2006 to October 2008, who underwent CXR for suspicion of pneumonia were prospectively identified. The study protocol was approved by the Ethics Committee of the Federal University of Bahia. For recruitment purpose, pneumonia was defined as report of respiratory complaints and detection of lower respiratory tract findings plus presence of pulmonary infiltrate on CXR taken on admission and read by the pediatrician on duty. Children were excluded if there were lower chest indrawing, danger signs (inability to drink, convulsions, somnolence, central cyanosis, grunting in a calm child), underlying chronic diseases (anatomic abnormalities of the respiratory tract, chronic pulmonary illness besides asthma, immunological defects, progressing neurological disorders, psychomotor retardation, heart disease with clinical repercussion, hemoglobinopathy, liver or kidney disease), severe malnutrition, other concurrent infection, hospitalization during the previous 7 days, amoxicillin or similar antibiotic use during the last 48 hours, allergy to amoxicillin or history of aspiration. Nutritional evaluation was performed by using the software "Anthro" (WHO) and severe malnutrition was defined as Z-score for weight-for-age under -3.00. Written informed consent was obtained from parents or legal guardians before enrolment. One trained medical student from the research team was in the study setting every morning and afternoon. A thorough examination was performed and data on demographics, clinical history, and physical examination were recorded at admission. The child's respiratory rate was assessed by observing the thorax for 60 seconds when the child was awake, calm and without fever; if the child presented with fever, an antipyretic was given and the temperature was lowered before the respiratory rate was assessed. Fever was defined as axillary temperature >37.5º C [7], and tachypnea as respiratory rate ≥50 breaths/min in children aged 2-11 months and ≥40 breaths/min in children from 12 months of age onwards [8]. Amoxicillin was given at a daily dosage 50 mg/kg.

Evolution follow-up: Patients were evaluated in the hospital twice a day, for up to 5 days and a senior pediatrician personally checked each evaluation. The patients stayed in the observation ward for children without signs of severity with their respective caregiver so that they could be carefully followed-up by the research team, who also assisted the drug administration. Amoxicillin for up to the tenth day of treatment and the telephone number of the surveillance coordinator were supplied to the guardian adult at discharge and a phone call was advised if the patient developed any new complaint. Each child was discharged from hospital when there was no more fever and respiratory discomfort. At the fifth day of treatment, a telephone call was made to the caregiver to enquire for symptoms and interventions. Cure was recorded when the caregiver informed of absence of all the presenting symptoms. A follow-up examination was performed 2 to 4 weeks after recruitment. Every patient received a telephone call on the day before the scheduled outpatient visit to remind them. All clinical data were collected without knowledge about the final CXR assessment.

Radiological studies: For the purpose of this study, CXR were read by two pediatric radiologists who were unaware of the patients' clinical history and evolution. Each pediatric radiologist gave his assessment independently. In case of disagreement regarding diagnosis of pneumonia, CXR was read by a third pediatric radiologist without knowledge on the previous evaluations. Radiographic findings were recorded in a standardized form according to previously published recommendation [9]. The pediatric radiologist looked for the presence of pulmonary infiltrate, consolidation, pleural effusion, atelectasis, hyperinflation, abscess, peribronchial thickening, pneumatocele and pneumothorax. The pulmonary infiltrate was characterized as alveolar, interstitial or alveolar-interstitial. Pneumonia was radiographically diagnosed if there was agreement on presence of pulmonary infiltrate or pleural effusion in 2 independent assessments.

Data management and analysis: Epi-Info (version 6.04) was used for data entry, Statistical Package for the Social Sciences (SPSS 9.0) and STATA (version 9.0) were used for statistical analysis. The presence of a symptom or sign at least once during the two daily evaluations was considered as presence of that finding on that day of evolution. Differences in proportions were assessed by using the Pearson chi square or Fisher's exact tests and continuous variable by the Student t or Mann-Whitney U tests, as appropriate. Bivariate and multivariate analyses, using logistic regression models, were performed to identify association between radiographically diagnosed pneumonia on admission and findings during evolution. The 95% confidence intervals were calculated.

Sensitivity, specificity and predictive values were calculated. The positive and negative likelihood ratio (LR) were estimated. The study protocol was approved by the Ethics Committee of the Federal University of Bahia.

RESULTS

Overall, 630 patients were evaluated, out of whom 239 were excluded [antibiotic use in the previous 48 hours (*n*=95), signs of severe disease (*n*=92), refusal to give informed consent (*n*=18), underlying chronic illness (*n*=17), hospitalization in the previous 7 days (*n*=10) or amoxicillin allergy (*n*=7)]. Moreover, 6 families refused to continue in the study, 3 children had poor quality on CXR at the evaluation of the first 2 pediatric radiologists and there was no agreement between 2 of 3 participant radiologists in the reading of CXR of 10 patients. Therefore, the study group included 372 patients.

The median (Inter quartile range, IQR) age was 26 (13-40) months. Seventy five (20.2%) children were younger than 1 year. There were 201 (54.0%) males and 14 (3.8%) malnourished patients. The median (IQR) duration of disease was 6 (4-10) days and the most frequent complaints were cough (98.7%), fever (94.1%), difficulty breathing (68.8%), vomiting (47.6%) and wheezing (29.8%). Rales (70.7%), crackles (62.4%), tachypnea (50.8%) and fever (36.3%) were the most common findings. None presented with cyanosis, abdominal distension or stridor. Only 5 (1.3%) patients presented with chest retraction, but nobody showed lower chest indrawing.

Agreement was found between the first 2 pediatric radiologists in 284 (74.3%) cases. By adding the evaluation from the third pediatric radiologist, agreement was found in 372 (97.4%) cases. The final radiographic diagnosis was pneumonia (*n* = 192; 51.6%), normal CXR (*n* = 152; 40.9%) and other diagnosis (*n* = 28; 7.5%) which comprised peribronchial thickening (2.9%), atelectasis (2.4%), hyperinflation (1.6%), peribronchial thickening plus atelectasis (0.3%) or plus hyperinflation (0.3%). Abscess, pneumatocele and pneumothorax were not described. ***Table* I** shows the comparison of baseline

TABLE I BASELINE CHARACTERISTICS ACCORDING TO RADIOGRAPHIC DIAGNOSIS

Characteristic	*Pneumonia (n = 192)*	*Normal CXR (n = 152)*	*Other diagnosis (n = 28)*	*P value#*
History				
Age (mo)*	32 (17-45)	22 (12-36)	19 (10-29)	<0.001
Duration of disease (d)*	7 (4-10)	5 (4- 8)	5 (3-8)	0.01
Duration of fever (d)*	4 (2.5-7)	3 (2-5)	3 (2-5)	0.03
Age ≥1 year	164 (85.4)	115 (75.7)	18 (64.3)	0.02
Disease ≥5 days	141 (73.4)	96 (63.2)	18 (64.3)	0.04
Male sex	106 (55.2)	79 (52.0)	16 (57.1)	0.6
Malnutrition	5 (2.6)	7 (4.6)	2 (7.1)	0.3
Cough	189 (98.4)	151 (99.3)	27 (96.4)	1.0
Fever	187 (97.4)	138 (90.8)	25 (89.3)	0.008
Difficulty breathing	132 (68.8)	102 (67.1)	22 (78.6)	0.7
Vomiting	88 (45.8)	79 (52.0)	10 (35.7)	0.3
Wheezing	57 (29.7)	49 (32.2)	5 (17.9)	0.6
Physical examination				
Fever	76 (39.6)	50 (32.9)	9 (32.1)	0.2
Tachypnea	104 (54.2)	69 (45.4)	16 (57.1)	0.1
Irritability	11 (5.7)	18 (11.8)	1 (3.6)	0.04
Chest retraction	5 (2.6)	0	0	0.07
Prolonged expiration	22 (11.5)	26 (17.1)	9 (32.1)	0.1
Reduced pulmonary expansion	42 (21.9)	9 (5.9)	1 (3.6)	<0.001
Rales	130 (67.7)	114 (75.0)	19 (67.9)	0.1
Wheezing	46 (24.0)	54 (35.5)	12 (42.9)	0.02
Crackles	126 (65.6)	83 (54.6)	23 (82.1)	0.04
Tubal murmur	4 (2.1)	0	1 (3.6)	0.1
Hepatomegaly	7 (3.6)	1 (0.7)	0	0.08
Splenomegaly	2 (1.0)	0	0	0.5

*CXR-Chest X-ray; * Results are reported as median (IQR), Other results are reported in n (%); #Pneumonia vs Normal CXR.*

characteristics according to the radiographic diagnosis subgroup.

Among 344 patients with pneumonia or normal CXR, 337 (98.0%) were hospitalized. The median (25th-75th percentile) duration of hospitalization was 1 day (1-2, range 1-21 days). Amoxicillin was substituted with another antibiotic in 12 (3.2%) inpatients at the first (*n*=1), second (*n*=2), third (*n*=5), fourth (*n*=2) or fifth (*n*=2) day of treatment because of clinical deterioration (*n*=5), concurrent infection (sinusitis or otitis) diagnosed during follow-up (*n*=3), persistent vomiting (*n*=2), persistence of symptoms (*n*=1) or immediate allergic reaction (*n*=1). All patients were discharged after improvement. ***Table* II** presents the significant differences on evolution in a univariate analysis and ***Table* III** depicts the significant differences on admission or evolution in a multivariate analysis between children with radiographic diagnosis of pneumonia and normal CXR on admission. ***Table* IV** shows the validation of tachypnea and documented fever on admission and up to the second day of evolution. The positive LR of tachypnea or fever on the second day of evolution was 1.88 (95% CI: 1.27-2.78) and 3.29 (95% CI: 1.49-7.28), respectively. On the contrary, the negative LR of both characteristics was 0.80 (95% CI: 0.70-0.88) and 0.88 (95% CI: 0.81-0.94), respectively.

Successful telephonic contact, between the fourth and seventh day of treatment (median=5 days, IQR = 5-5 days), was obtained with 336 (98.2%) families who

TABLE II DIFFERENCES IN EVOLUTION BETWEEN CHILDREN WITH PNEUMONIA AND NORMAL CHEST RADIOGRAPH ON ADMISSION

Characteristic	*Pneumonia (n=192)*	*Normal CXR (n=152)*	*P value*
Inability to drink[$]	13 (6.8)	3 (2.0)	0.04
Percussion sign of consolidation[*] on			
Day 1	29 (15.1)	2 (1.3)	<0.001
Day 2	24 (12.6)	2 (1.4)	<0.001
Day 3	15 (22.1)	0	0.002
Tachypnea on			
Day 1	112 (58.3)	72 (47.4)	0.04
Day 2	66 (34.7)	27 (18.5)	0.001
Fever on			
Day 1	108 (56.3)	62 (40.8)	0.004
Day 2	30 (15.8)	7 (4.8)	0.001
Hospital length[†] (d)	1 (1-2)	1 (1-1)	0.02

CXR indicates chest x-ray. Day 1 is the first day after staying over 1 night in the hospital, day 2 is the second day after staying over 2 nights in the hospital, and so on. The number of hospitalized patients with pneumonia on day 1,2 or 3 was 192, 190 and 68, respectively. The number of hospitalized patients with normal CXR on day 1, 2 or 3 was 152, 146 and 32, respectively. Results are reported in n (%) Except [†] Results are reported as median (IQR); [$]on Day 1.

TABLE III MULTIVARIATE ANALYSIS OF CLINICAL FINDINGS ON ADMISSION OR EVOLUTION BETWEEN CHILDREN WITH PNEUMONIA OR NORMAL CHEST RADIOGRAPH ON ADMISSION (*N=336)**

	OR (95% CI)	
Characteristic	*Unadjusted*	*Adjusted*
On admission		
Age	1.03 (1.01-1.04)	1.03 (1.02-1.05)
Disease ≥5 days	1.03 (1.00-1.07)	1.04 (1.001-1.08)
Reduced pulmonary expansion	4.4 (2.1-9.5)	3.3 (1.40-7.98)
Wheezing	0.57 (0.36-0.91)	0.53 (0.30-0.94)
Crackles	1.59 (1.03-2.46)	2.01 (1.17-3.46)
On evolution		
On Day 1		
Inability to drink	3.61 (1.01-12.90)	4.25 (1.05-17.26)
On Day 2		
Consolidation percussion sign	10.41 (2.42-44.80)	7.05 (1.54-32.34)
Tachypnea	2.35 (1.40-3.92)	1.97 (1.09-3.58)
Fever	3.72 (1.58-8.74)	3.59 (1.37-9.40)

*Day 1 is the first day after staying over 1 night in the hospital, day 2 is the second day after staying over 2 nights in the hospital. *8 children had been discharged on the first day.*

TABLE IV VALIDATION OF TACHYPNEA AND DOCUMENTED FEVER ON ADMISSION AND UP TO SECOND DAY OF EVOLUTION FOR THE DIAGNOSIS OF PNEUMONIA

Characteristics	Sensitivity	Specificity	Positive Predictive Value %	Negative Predictiv Value %
Tachypnea				
On admission	54.2	54.6	60.1	48.5
On Day 1	58.3	52.6	60.9	50.0
On Day 2	34.7	81.5	71.0	49.0
Fever				
On admission	39.6	67.1	60.3	46.8
On Day 1	56.2	59.2	63.5	51.7
On Day 2	15.8	95.2	81.1	46.5

Day 1 is the first day after staying over 1 night in the hospital, day 2 is the second day after staying over 2 nights in the hospital.

WHAT IS ALREADY KNOWN?

- WHO criteria to diagnose pneumonia in children (cough or difficulty breathing plus tachypnea) are sensitive to identify pneumonia cases among children with upper respiratory infection. The criteria are not sensitive to distinguish pneumonia from other lower respiratory tract infections.

WHAT THIS STUDY ADDS?

- Persistence of fever or tachypnea up to the second day of amoxicillin treatment is predictive of radiographically diagnosed pneumonia among children with non-severe lower respiratory tract infections.

informed that the child had complete resolution of symptoms (75.2%), improvement with persistence of at least one initial complaint (24.2%), absence of improvement (n = 1; 0.3%) or worsening (n = 1; 0.3%). At this moment, report of complete resolution of symptoms was more frequent among those with normal CXR (80.7% *vs*. 70.7%; P = 0.04). Ambulatory follow-up evaluation occurred between 11 and 38 days after recruitment (median 21; IQR= 17-23) among 337 (98.0%) patients; mean duration of amoxicillin administration was 10 ± 1 day among 323 users. No clinical difference at this time was found by comparing patients with pneumonia or normal CXR (data not shown).

DISCUSSION

We observed differences among simple signs like tachypnea and fever during the evolution, specifically on the second day, between children aged 2-59 months with and without radiologically diagnosed pneumonia. Although the implementation of the standardized management for children with respiratory complaints recommended by WHO has resulted in decreased childhood mortality in developing countries [10], the recognition that the proposed diagnostic criteria by WHO, that is, cough or difficulty breathing plus tachypnea [8], are not always sensitive indicator of pneumonia has been published [11]. In a clinical trial of different doses of amoxicillin in the treatment of non-severe pneumonia conducted in Pakistan, children were included by applying WHO criteria and out of 891 cases only 6.8% had radiographic pneumonia [12]. In the 1990s, several studies examined the validity of the WHO guidelines for diagnosing pneumonia in children under 5 years of age and the presented sensitivity range between 59-81% [13-17]. In these investigations, children with radiographic pneumonia were compared with those with upper respiratory tract infection.

The necessity to improve WHO case management of childhood pneumonia especially due to the clinical overlap of pneumonia with other lower respiratory tract diseases has been reported [18]. In this study, the inclusion criteria comprised subjects aged 2-59 months who underwent CXR for suspicion of pneumonia after undergoing a clinical examination by the pediatrician on duty in the emergency room (ER). By using this strategy, children with a clinical diagnosis of lower respiratory tract infection compromising were selected while there was no association of tachypnea at admission with radiographic pneumonia there was an association of radiographic pneumonia with older age (for each additional month on age the risk for pneumonia increases 3%) with absence of wheezing. These findings might be explained by the overlap on clinical presentation of children with bronchiolitis and pneumonia: bronchiolitis predominates in children under 12 months of age and presents with fast breathing and wheeze [19]. By calculating the validity of simple signs independently associated with radiographic pneumonia, the highest positive predictive value was at the 2nd day of evolution for tachypnea (71.0%) and fever (81.1%). Another Brazilian investigation recently showed that the addition of fever to cough and tachypnea on admission greatly enhances the ability to identify pneumonia cases among children with different lower respiratory tract diseases [20]. From the results presented herein, it is possible to observe that persistence of fever or tachypnea on the second day of treatment enhances the chance of children with acute lower respiratory tract disease to have radiographically diagnosed pneumonia (that is, the positive LR X the Adjusted odd ratio).

The frequency of reported cure was significantly higher on the fifth day telephone call survey for those with normal CXR on admission. This suggests that the resolution of the clinical findings of patients with radiographic pneumonia is slower than that among children with other lower respiratory tract diseases. Although this result might have been expected, it raises worry about the length of antibiotic administration to treat pneumonia. The WHO has recommended antibiotic use for 3-5 days to children with non-severe pneumonia [21], and this recommendation comes from studies in which children were included by using WHO diagnostic criteria [22,23]. A recent meta-analysis recognizes that

more well-designed randomized clinical trials are needed to support such recommendation [24]; we now add addition evidence. We did not investigate the etiology and this is a limitation. However, this study was carried out in a scenario that is similar to many ERs, all over the world. In this study, the duration of amoxicillin administration was 10 days to be in accordance with the national Brazilian guidelines, for ethical reason [25].

In this investigation, the final radiographic diagnosis was based on the agreement of 2 independent assessments by trained pediatric radiologists using a standard evaluation form previously validated [9]. The use of such strict criteria was meant to control the subjective bias that may occur in CXR reading [4]. In addition to that, the close evaluation on admission and evolution by a senior pediatrician, the low rate of loss to follow-up and the implementation in only one pediatric center contribute to the reliability of our results.

To conclude, this study, to the best of our knowledge, is the first prospective study enrolling and following children with non-severe CAP treated with amoxicillin, where detailed clinical and radiographic aspects on admission and evolution were registered. From our data, persistence of fever or tachypnea up to the second day of amoxicillin treatment is predictive of radiographically diagnosed pneumonia among children with non-severe lower respiratory tract diseases.

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Contributors: M-SHF, ARM, CCS, MCS, MNB, FO, BBB, and the PNEUMOPAC-Efficacy Study Group collected the clinical data and drafted the manuscript; CAAN, SCA and RVB read the chest *X*-rays, filled the radiographic forms out, took part in the interpretation of the results and criticized the manuscript; M-RA Cardoso took part in the analysis and revised the manuscript; CMNC conceived the research question and designed the study protocol, analyzed the data and revised critically the manuscript. All authors approved the submitted version.

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Competing interests: None stated.

APPENDIX I

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