RESEARCH PAPER

Clinical Patterns and Risk Factors for Pneumonia Caused by Atypical Bacteria in Vietnamese Children

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Objectives: To investigate clinical characteristics and risk factors for atypical community-acquired pneumonia (CAP) in children. **Methods**: Multiplex polymerase chain reaction and specific IgM determination were used to detect atypical bacteria in 661 hospitalized children aged 1-15 years with CAP. Clinical and epidemiological patterns were compared between typical and atypical CAP. **Results**: Children in atypical CAP group manifested significantly lower rates of wheezing, bronchial rales, and interstitial pneumonia and showed higher rates of asthma history, headache, chest pain, and lobar pneumonia . Age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings were the significant risk factors for atypical CAP on multivariate logistic regression analysis. **Conclusions**: The clinical characteristics and risk factors can be used to identify a child at high risk of atypical CAP.

Keywords: *Asthma, Evaluation, Identification, Lower respiratory tract infection*.

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Childhood pneumonia is a considerable public health problem worldwide [1]. Atypical pathogens are increasingly being recognized as important causes of community acquired pneumonia (CAP) [2-4]. Since these atypical bacteria cannot be cultured using standard methods [5] and microbiological diagnosis of atypical CAP has been limited due to inadequate laboratory diagnostic facilities in developing countries, the clinical practice guidelines highlight the importance of signs suspicious for atypical CAP in children to help guide antibiotic selection [6,7]. However, such signs have not been well defined yet. The aforementioned problems prompted us to conduct the study to identify clinical characteristics of atypical CAP and the important risk factors which help pediatricians predict children with atypical CAP.

METHODS

The study was conducted at the National Hospital of Pediatrics from July, 2010 through March, 2012. The study proposal was approved by the Research Ethics Committee of the hospital. The detailed methodology has been previously reported [4]. In summary, the socio-demographic characteristics and potential risk factors were collected on standardized questionnaires by interviewing the patient's parents. After evaluating clinical manifestation and chest *X*-ray, bronchoalveolar lavage and two blood samples were taken from all the recruited patients for laboratory diagnosis. Multiplex polymerase chain reaction [8-10] and IgM/IgG antibody-based enzyme-linked immunosorbent assay were used to detect *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila* [4]. Of the total 722 children aged 1-15 years with CAP, 661 children without mixed typical and atypical pneumonia were the study subjects.

Statistical analysis: Multivariate logistic regression analyses with backward stepwise method were performed to test several models for identifying risk factors of atypical CAP. The final model presented the most significant risk factors for atypical CAP. The area under a receiver operating characteristic curve (AUC) was calculated [11]. The selection of an optimal threshold was based on the Youden index [12], and the sensitivity and the specificity of the model were calculated. The nomogram for identifying an individual with high risk of atypical CAP was constructed based on the variable estimates from the final model. A *P* value of less than 0.05 was considered statistically significant. The statistical procedures were performed using SPSS version 16.0 (SPSS, Chicago, USA) and R statistics version 3.5.3 [13].

RESULTS

There was no statistical difference between atypical and typical CAP in socioeconomic status except for age group and season of disease onset (**Web Table I**).

Table I shows the clinical and laboratory characteristics among children with atypical and typical CAP. Fever (or high fever), cough, sore throat, and tachypnea were the most common signs and not different between atypical and typical CAP. Children showed significantly lower rates of wheezing, bronchial breathing, leukocyte counts, and interstitial pneumonia and higher rates of asthma history, headache, chest pain, and lobar pneumonia in atypical CAP compared to typical CAP.

The potential risk factors for atypical CAP were analyzed using multivariate logistic regression including factors found significant on univariate analysis. The final model involved the most significant risk factors for atypical CAP including age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings (**Table II**). Based on parameter estimates of the final model, the prediction nomogram was constructed for individualizing the probability of atypical CAP (**Web Fig. 1**). The final model had AUC of 0.736 (95% CI 0.691-0.781), the optimal cut-off value of 17.8%, sensitivity of 79.9% and specificity of 57.0%.

Table I Clinical Pattern and Laboratory Values in Vietnamese Children With Pneumonia (*N*=661)

Characteristics	*Community-acquired pneumonia*	
	Typical (n=507)	*Atypical (n=154)*
Clinical		
Fever	476 (93.9)	145 (94.2)
High fever (≥38.5°C)	345 (68.0)	113 (73.4)
Cough	498 (98.2)	151 (98.1)
Sore throat	404 (79.7)	123 (79.9)
Tachypnea	406 (80.1)	128 (83.1)
Wheezing[c]	392 (77.3)	97 (63.0)
Moist rales	364 (71.8)	98 (63.6)
Bronchial breathing[d]	334 (65.9)	86 (55.8)
Headache[c]	79 (15.6)	48 (31.2)
Chest pain[d]	69 (13.6)	32 (20.8)
Chest indrawing[b]	177 (38.7)	38 (35.5)
Diarrhea	178 (35.1)	49 (31.8)
Skin rash	51 (10.1)	24 (15.6)
Radiological findings		
Interstitial pneumonia[b,e]	95 (18.7)	14 (9.1)
Lobar pneumonia[d]	128 (25.2)	54 (35.1)
Asthma[c]	24 (4.7)	24 (15.6)
C-reactive protein (mg/L)[a]	18 (6-36)	24 (10-36)
Anemia	229 (45.2)	82 (53.2)
Count		
Leukocytes ($X10^9$/L)[a]	14 (10-19)	12 (8.5-18.5)
Neutrophils (%)[a]	58 (43-69)	56 (43-67)
Lymphocytes (%)[a]	30 (20-43)	31 (21-43)
Eosinophils (%)[a]	0 (0-1)	1 (0-2)
Platelets ($X10^9$/L)[a]	328 (259-399)	334 (259-422)

Data shown as no. (%) or [a]median (IQR); [b]In children aged<5 y; [c]P<0.001; [d]P<0.05; [e]P=0.005.

DISCUSSION

The present study depicted the clinical patterns of atypical CAP compared with typical CAP. The risk factors and nomogram for identifying a child with high risk of atypical CAP were also reported.

To date, there have not been many reports on clinical signs suggestive of atypical CAP. In adults, the guidelines set up parameters and criteria for the differential diagnosis of atypical pneumonia and bacterial pneumonia based on clinical symptoms, physical signs and laboratory data [14]. In children, such parameters and criteria have not been well defined yet. We previously reported the clinical patterns of 52 children with atypical pneumonia caused by *M. pneumoniae* [15]. In agreement with our finding, a study in Thailand [16] reported that lobar pneumonia was associated with atypical CAP in children. Age has also been found as an important risk factor for atypical pneumonia in several studies [16,17].

The strength of the study was prospective recruitment of a large sample of children with CAP through four seasons of the year. Moreover, the investigations combining serologic and molecular tests were performed to maximize the diagnostic yield of atypical CAP. The study limitations were no urine test for detection of *L. pneumophila* antigen, and low sensitivity and specificity of the prediction model.

Table II Risk Factors on Multivariate Logistic Regression for Atypical Pneumonia in Vietnamese Children (*N*=661)

Independent risk factor	*OR (95% CI)*	*P value*
Age group		
1 - <2 y	1.0	-
2 - <5 y	1.50 (0.96-2.36)	0.07
5 - <10 y	5.63 (3.14-10.1)	<0.001
≥10 y	2.65 (0.94-7.48)	0.06
Season		
Spring	1.0	-
Summer	0.59 (0.34-1.03)	0.06
Fall	0.46 (0.27-0.77)	0.004
Winter	0.40 (0.22-0.72)	0.002
Asthma	4.63 (2.39-8.99)	< 0.001
Radiological findings		
Interstitial pneumonia	1.0	-
Broncho-alveolitis	2.00 (1.03-3.87)	0.04
Lobar pneumonia	2.48 (1.23-5.01)	0.01
Pleuropneumonia and others	2.80 (0.86-9.15)	0.09
Duration between symptom onset and hospital admission		
<1 wk	1.0	-
1-2 wk	1.84 (1.21-2.78)	0.004
>2 wk	0.51 (0.25-1.03)	0.06

WHAT THIS STUDY ADDS?

- Age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings identify a child at high risk of atypical community-acquired pneumonia.

Further independent studies should be conducted to validate and evaluate the performance of the prediction model.

In conclusion, the study indicated the clinical characteristics of atypical CAP in comparison with typical CAP. Age group, season of disease onset, asthma history, duration of symptom onset to hospital admission, and radiological findings were the independent risk factors for atypical CAP in children. The nomogram constructed from the risk factors may be used to identify a child at high risk of atypical CAP; although, confirmation of the findings from studies in various regions are required.

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Ethics clearance: Research Ethics Committee Vietnam National Children's Hospital; No. 1124/HDDD, dated 2 June, 2010.

Contributors: PLTH: conceptualized and designed the study, designed and performed laboratory analyses, drafted the initial manuscript, reviewed and revised the manuscript; PTH: recruited patients, collected and entered data, follow-up patients; NTPL: participated in laboratory analyses, reviewed the manuscript; DMT: designed the study, recruited patients, follow –up patients, participated in discussion and interpretation of the findings; DDA: had a substantial contribution in experimental design and interpretation of ELISA and multiplex PCR, critically reviewed the manuscript; TQB: cleaned data, supervised data collection, performed statistical analyses and interpretation of findings, critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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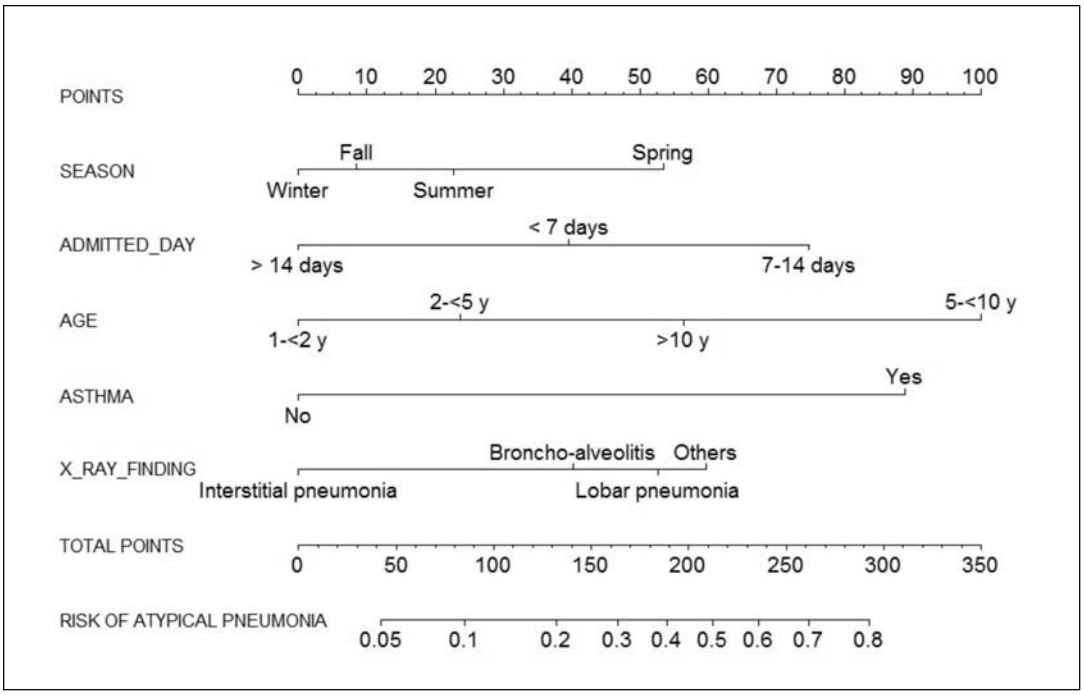

Instructions for usage: *Locate an individual value on each variable axis (season, admitted day, age, asthma, X-ray finding). Draw a vertical line from that value to the top "points" scale to determine the number of points assigned by variable value. Sum the points from each variable value. Mark the sum on the "total points" scale. Draw a vertical line down to meet the "risk of atypical pneumonia" axis to obtain a personalized risk of atypical pneumonia.*

Web Fig. 1 Nomogram to identify an individual at high risk of atypical pneumonia.

Web Table I Socio-Demographic Characteristics of Study Groups

Characteristics	*Community-acquired pneumonia*	
	Typical (n=507)	*Atypical (n=154)*
Age group		
1- <2 y	276 (54.4)	53 (34.4)
2- <5 y[a]	181 (35.7)	54 (35.1)
5- <10 y	38 (7.5)	40 (26.0)
>10 y	12 (2.4)	7 (4.5)
Season of disease onset[a]		
Spring	97 (19.1)	46 (29.9)
Summer[b]	119 (23.5)	37 (24.0)
Fall	180 (35.5)	43 (27.9)
Winter	111 (21.9)	28 (18.2)
Female gender	216 (42.6)	69 (44.8)
Residence		
Rural	235 (46,4)	60 (39.0)
Mountain	43 (8.5)	16 (10.4)
Urban	229 (45.2)	78 (50.6)
Mother education		
Elementary and intermediate	120 (23.7)	47 (30.5)
Secondary	240 (47.3)	62 (40.3)
Post-secondary	147 (29.0)	45 (29.2)
Mother occupation		
Unemployed	122 (24.1)	31 (20.1)
Farmer	116 (22.9)	45 (29.2)
Office staff	192 (37.9)	59 (38.3)
Other	77 (15.2)	19 (12.3)
Income level[b]		
First quartile (lowest)	170 (33.5)	61 (39.6)
Second quartile	79 (15.6)	22 (14.3)
Third quartile	175 (34.6)	45 (29.2)
Fourth quartile (highest)	83 (16.4)	26 (16.9)
Having air-conditioning	231 (45.6)	71 (46.1)
Living condition polluted by dust	216 (42.6)	70 (45.5)
Contact with tobacco smoke	169 (33.3)	54 (35.1)

Data are shown as no. (%). [a]P<0.001; [b]P=0.03. [a]North Vietnam has 4 different seasons in a year: spring (February, March, and April); summer (May-July); fall (August-October) and winter (November-January). [b]Average income per person/month in the previous year was calculated and classified into 4 categories based on IQR: first quartile (<1 mil VND), second quartile (1-1.8 mil VND), third quartile (1.8-3.0 mil VND), and fourth quartile (>3.0 mil VND).