



ORIGINAL ARTICLE

Risk factors of progressive community-acquired pneumonia in hospitalized children: A prospective study



Ching-Ying Huang^a, Lung Chang^a, Ching-Chuan Liu^c,
Yhu-Chering Huang^d, Luan-Yin Chang^e, Yi-Chuan Huang^f,
Nan-Chang Chiu^{a,b}, Hsiao-Chuan Lin^g, Yu-Huai Ho^h,
Hsin Chi^{a,b,*}, Li-Min Huang^{e,**}, on behalf of the Taiwan
Pediatric Infectious Disease Alliance

^a Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan

^b Mackay Medicine, Nursing and Management College, Taipei, Taiwan

^c Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

^d Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

^e Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

^f Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

^g Department of Pediatrics, China Medical University Hospital, Taichung, Taiwan

^h Division of Infectious Disease, Department of Internal Medicine, Buddhist Tzu Chi General Hospital, Hualien, Taiwan

Received 28 December 2012; received in revised form 22 April 2013; accepted 24 June 2013

Available online 28 August 2013

KEYWORDS

Children;
Community-acquired
pneumonia;
Progressive
pneumonia;
Risk factor

Background: Complications regarding pneumonia occur in children during hospitalization and treatment. The objective of this study is to identify the risk factors of progressive pneumonia in order to institute early appropriate therapy.

Methods: This was a prospective study which involved the pediatric departments of seven medical centers in Taiwan. Children aged from 6 weeks to 18 years old, hospitalized with community-acquired pneumonia (CAP) from January 2010 to August 2011, were enrolled. Progressive pneumonia was defined by the deterioration of discharge diagnosis as compared to

* Corresponding author. Department of Pediatrics, Mackay Memorial Hospital, Number 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.

** Corresponding author. Department of Pediatrics, National Taiwan University Hospital, Number 8, Chung-Shan-South Road, Taipei, Taiwan.
E-mail addresses: chi.4531@ms1.mmh.org.tw (H. Chi), lmhuang@ntu.edu.tw (L.-M. Huang).

admission. Demographic, clinical, and laboratory variables, diagnosis, antimicrobial therapy, and pathogens were compared.

Results: Four hundred and two children were included and 57 (14.2%) had progressive pneumonia. Independent associated factors identified for the development of progressive disease, by multivariate logistic regression analysis, included the following, age < 2 years, pleural effusion as admission diagnosis, Hb < 10 g/dL, WBC count > 17,500/ μ L, tachypnea, and duration to defervescence > 3 days. *Streptococcus pneumoniae* was the main etiology for progressive pneumonia (57.9%). There was no difference in choice of initial parenteral antibiotics between groups of progressive and non-progressive pneumococcal pneumonia.

Conclusion: We found six clinical factors for predicting progressive pneumonia. Further evaluation should be performed in hospitalized pneumonic children with persistent fever not responding to therapy within 72 hours. The initial parenteral antibiotics were not related to the progression of pneumococcal pneumonia.

Copyright © 2013, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.

Introduction

The mortality rate of pneumonia has fallen since effective antibiotic treatment and vaccines for the two most common pneumonia-causing pathogens, *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, became available.^{1,2} Despite a drop in overall mortality cases, pneumonia is still the leading killer and cause of morbidity in children, especially among those < 5 years old.³ Complications of pneumonia occur even when children are hospitalized and receive treatment. Pulmonary complications of pneumonia include pleural or parapneumonic effusion, pneumothorax, acute respiratory distress, empyema, necrotizing pneumonia, bronchopleural fistula, pneumatocele formation, and lung abscess. These complications lead to prolonged hospitalization, surgery, and irreversible sequelae in children.

How long should the physician wait prior to evaluating the failure of treatment? When should the physician take the next step to prevent the complications of pneumonia? Although current treatment guidelines give some suggestions for managing community-acquired pneumonia (CAP),⁴ there is very little information about the risk factors for progressive pneumonia in children. Pneumonia has complex and varying causes, clinical presentation, and severity. Given the variability in the range of clinical response and radiographic resolution, it remains controversial as to when to alter initially empirical therapy for progressive pneumonia.

The purpose of our study was to compare the clinical characteristics and laboratory parameters of children hospitalized with progressive pneumonia, with those of children with non-progressive pneumonia and to identify risk factors for a progressive course. We also wanted to determine when the physician should take the next step to prevent complications, if the patient does not respond well to therapy.

Methods

Study population

We prospectively enrolled pediatric patients, aged from 6 weeks to 18 years, who were admitted to the pediatric

departments of seven medical centers in Taiwan, from January 2010 to August 2011, with the diagnosis of CAP. Children were excluded if they had proven immunodeficiency or immunosuppression in previous medical records. The patients were evaluated at admission and after 1 day to 3 weeks, at which time demographic and clinical data were collected uniformly and laboratory specimens were obtained.

Definition

For purposes of this study, the diagnosis of pneumonia was based on radiographic findings. The severity of pneumonia was categorized according to the radiological confirmation in order of segmental pneumonia, lobar pneumonia, pleural effusion, empyema, necrotizing pneumonia, pneumatocele, and lung abscess. Non-progressive pneumonia was defined by discharge diagnosis being consistent with admission. By contrast, progressive pneumonia was defined by the deterioration of discharge diagnosis as compared to admission.

Study variables

Medical profiles were recorded for age, sex, underlying disease, presenting signs, symptoms, physical examination findings, laboratory data, chest radiography findings, duration of fever prior to hospitalization, time to defervescence, duration of hospitalization, antimicrobial therapy, pathogens, and diagnoses on admission and discharge. Laboratory data including hemoglobin (Hb), white blood cell (WBC) and platelet count, C-reactive protein (CRP), blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, albumin, and Thomsen-Friedenreich antigen (T-antigen) were collected and analyzed. T-antigen was tested using the peanut (*Arachis hypogaea*) lectin agglutination method.

Pathogens were surveyed by: bacterial culture from blood, pleural effusion, and sputum specimen, and rapid antigen assays for *S. pneumoniae*, *H. influenzae* type b, *respiratory syncytial virus*, and influenza virus; throat or

nasopharyngeal viral culture; and serology studies for *Mycoplasma pneumoniae*.

The diagnostic criteria for definite pneumococcal pneumonia infection included: (1) isolation of *S. pneumoniae* from blood and/or sterile body site; (2) *S. pneumoniae* identified from sputum culture plus positive urine pneumococcal antigen; and (3) positive pneumococcal antigen in pleural effusion. The probable diagnostic criteria were positive urine pneumococcal antigen or *S. pneumoniae* identified from sputum culture. *M. pneumoniae* enzyme-linked immunoassays were performed. The assay was considered positive if the immunoglobulin M (IgM) was positive or there was a ≥ 4 -fold rise in immunoglobulin G (IgG) titer.

Statistical analyses

The results are presented as mean \pm standard deviation for continuous variables, and percentages for category variables. Differences between progressive and non-progressive pneumonia groups were calculated using the Student *t* test for continuous variables and Chi-square test for categorical variables. All variables that were statistically significant with $p < 0.05$ were included in a multivariable mode to identify independent predictors for progressive pneumonia. All probabilities were 2-tailed. Odds ratios and their 95% confidence intervals were also determined. All analyses used the SPSS statistical package (SPSS Inc., Chicago, IL, USA).

Results

A total of 410 children hospitalized with CAP were enrolled from January 1, 2010 to August 31, 2011. The diagnoses of the patients included segmental pneumonia (123), lobar pneumonia (201), pleural effusion (65), empyema (13), and necrotizing pneumonia (8). The diagnoses at admission and discharge are listed in Table 1. Eight patients with necrotizing pneumonia at admission were excluded for further analysis because they reached the greatest severity according to our definition. The other 402 children were classified into two groups. A total of 57 (14.2%) children met the criteria of progressive pneumonia and 345 (85.8%) children had non-progressive pneumonia.

Selected clinical characteristics of the patients with progressive versus non-progressive pneumonia are listed in Table 2. Hospitalized children with progressive pneumonia

were younger (average age = 4.0 years vs. 5.7 years; $p < 0.001$) and more likely to be < 2 years old (26.3% vs. 8.6%, $p = 0.005$), and have tachypnea ($p < 0.001$) and abdominal pain ($p = 0.001$) on presentation. There were no differences with regard to the male to female ratio, numbers of siblings, background disease, hospitalization history for respiratory tract disease, vaccination with heptavalent pneumococcal conjugate vaccine (PCV7), or annual influenza vaccine. About one third of children in both groups received PCV7.

Patients with progressive pneumonia were admitted under the following diagnoses: 43.1% with pleural effusion, 35.1% with lobar pneumonia, 21% with segmental pneumonia, and 1.8% with empyema. A higher percentage of children with progressive pneumonia had pleural effusion as an admission diagnosis as compared to children with non-progressive pneumonia (43.1% vs. 11.9%, $p < 0.001$).

The mean duration of fever prior to admission was 5.2 days for the progressive patients versus 4.5 days for the non-progressive patients ($p < 0.001$). The mean time to defervescence after admission for patients with progressive pneumonia was 6.4 days (median = 5 days; range = 0–18 days) versus 2.3 days (median = 2 days; range = 0–14 days) for patients with non-progressive pneumonia ($p < 0.001$). Seventy-three percent of patients in the progressive group continued to have a fever by Day 4 of hospitalization versus 23.2% in the non-progressive group ($p < 0.001$). Children with the progressive clinical course had a longer duration of hospitalization (mean 16.2 days vs. 7.5 days, $p < 0.001$).

Children with progressive disease had a lower Hb count (9.5 g/dL vs. 11.4 g/dL, $p < 0.001$), a higher WBC count ($21.3 \times 10^3/\mu\text{L}$ vs. $14.5 \times 10^3/\mu\text{L}$, $p < 0.001$), higher CRP (24.2 mg/dL vs. 14.3 mg/dL, $p < 0.001$), higher platelet count ($519.8 \times 10^3/\mu\text{L}$ vs. $380.8 \times 10^3/\mu\text{L}$, $p = 0.001$), lower albumin (2.6 g/dL vs. 3.7 g/dL, $p < 0.001$), and a positive rate for T-antigen (50% vs. 0%, $p < 0.001$).

On multivariate logistic regression, age < 2 years, pleural effusion as admission diagnosis, Hb < 10 g/dL, WBC count $> 17.5 \times 10^3/\mu\text{L}$, tachypnea, and days to defervescence > 3 were identified as independent predictors of the subsequent development of progressive disease (Table 3).

An etiologic diagnosis was established in 50 (87.7%) progressive and 169 (48.9%) non-progressive pneumonia patients ($p < 0.001$). The most frequently identified pathogens in progressive and non-progressive groups were *S. pneumoniae* (57.9% and 28.4%, $p < 0.001$),

Table 1 The discrepancies between admission and discharge diagnosis of the hospitalized pediatric patients with community-acquired pneumonia

| Admission diagnosis (Patient No.) | Discharge diagnosis (Patient No.) | | | | |
|-----------------------------------|-----------------------------------|-------------|---------------|--------------|------------------|
| | Segmental (111) | Lobar (187) | Effusion (55) | Empyema (44) | Necrotizing (13) |
| Segmental (123) | 111 | 6 | 6 | | |
| Lobar (201) | | 181 | 8 | 10 | 2 |
| Effusion (65) | | | 41 | 22 | 2 |
| Empyema (13) | | | | 12 | 1 |
| Necrotizing (8) | | | | | 8 |

Effusion = pleural effusion; lobar = lobar pneumonia; necrotizing = necrotizing pneumonia; segmental = segmental pneumonia.

Table 2 Characteristics of children with progressive and non-progressive community-acquired pneumonia during hospitalization

| Characteristics | Mean \pm SD | | p^a |
|---|-----------------------------|----------------------------------|---------|
| | Progressive ($n = 57$) | Non-progressive ($n = 345$) | |
| Demographic | | | |
| Age (year; mean, range) | 4.0 \pm 0.6 | 5.7 \pm 0.4 | < 0.001 |
| Age (year; median, range) | 3.7 (0.4–14.7) | 4.7 (0.3–17.6) | |
| > 2 y | 26.3 | 8.6 | 0.005 |
| \geq 2 y–5 y | 59.6 | 59.1 | 0.894 |
| \geq 6 y | 14.0 | 32.3 | 0.07 |
| Male/female ratio | 0.9 | 1.0 | 0.886 |
| Hospitalization history for respiratory tract disease | 21.1 | 25.7 | 0.512 |
| Previous PCV7 vaccination | 33.3 | 31.8 | 0.879 |
| Annual influenza vaccination | 28.1 | 39.7 | 0.106 |
| Admission radiographic findings | | | |
| Segmental pneumonia | 21.0 | 32.2 | 0.12 |
| Lobar pneumonia | 35.1 | 52.4 | 0.022 |
| Pleural effusion | 43.1 | 11.9 | < 0.001 |
| Empyema | 1.8 | 3.5 | 0.703 |
| Clinical presentations | | | |
| Tachypnea | 80.7 | 31.9 | < 0.001 |
| Abdominal pain | 45.8 | 15.9 | 0.001 |
| Fever prior to admission (days) | 5.2 \pm 0.7 | 4.5 \pm 0.3 | < 0.001 |
| Duration to defervescence (days) | 6.4 \pm 1.2 | 2.3 \pm 0.3 | < 0.001 |
| Duration of hospitalization (days) | 16.2 \pm 2.8 | 7.5 \pm 0.7 | < 0.001 |
| Hematological findings | | | |
| Lowest Hb (g/dL) | 9.5 \pm 0.5 | 11.4 \pm 0.2 | < 0.001 |
| Highest WBC count ($10^3/\mu\text{L}$) | 21.3 \pm 3.1 | 14.5 \pm 0.9 | < 0.001 |
| Highest CRP (mg/dL) | 24.2 \pm 3.2 | 14.3 \pm 1.4 | < 0.001 |
| Highest platelet count ($10^3/\mu\text{L}$) | 519.8 \pm 78.4 | 380.8 \pm 20.0 | 0.001 |
| Lowest albumin (g/dL) | 2.6 \pm 0.3 ($n = 22$) | 3.7 \pm 0.2 ($n = 33$) | < 0.001 |
| Positive T-antigen | 50.0 (10/20) | 0.0 (0/27) | < 0.001 |

^a Presence of progressive pneumonia versus non-progressive pneumonia.

Data are presented as % unless otherwise indicated.

CRP = C-reactive protein; Hb = hemoglobin; PCV7 = 7-valent pneumococcal conjugate vaccine; T-antigen = Thomsen-Freidenreich antigen; WBC = white blood cell.

M. pneumoniae (12.3% and 11.4%), and viral pneumonia (8.8% and 9.3%). The pathogens detected in children with progressive pneumonia are shown in Fig. 1. Pneumococcal pneumonia was found in 33 children with progressive pneumonia. Ten of these were a definite and 23 were a probable diagnosis.

A comparison of initial antibiotic treatment for children with pneumococcal pneumonia is shown in Table 4. Ninety-three point one percent of children with progressive pneumonia started parenteral antibiotics at admission versus 92.9% of children with non-progressive pneumonia ($p = 1.0$). There was no statistically significant difference

Table 3 Independent predictors of the progressive community-acquired pneumonia by multivariate model

| Clinical feature | Patient No. | Progressive (%) | Non-progressive (%) | AOR (95% CI) | p |
|---|-------------|-----------------|---------------------|--------------------|---------|
| Age < 2 y | 44 | 22.8 | 8.9 | 3.48 (1.26–10) | 0.02 |
| Pleural effusion as admission diagnosis | 65 | 43.1 | 11.9 | 14.10 (1.37–145.2) | 0.03 |
| Tachypnea | 156 | 80.7 | 31.9 | 4.24 (1.77–10.16) | < 0.001 |
| Hb < 10 g/dL | 76 | 56.1 | 12.7 | 2.38 (1.00–5.67) | 0.05 |
| WBC > 17500/ μL | 129 | 57.9 | 27.8 | 2.42 (1.08–5.45) | 0.03 |
| Days to defervescence > 3 days | 122 | 73.7 | 23.2 | 3.04 (1.30–7.130) | 0.01 |

AOR = adjusted odds ratio; CI = confidence interval; Hb = hemoglobin; WBC = white blood cell.

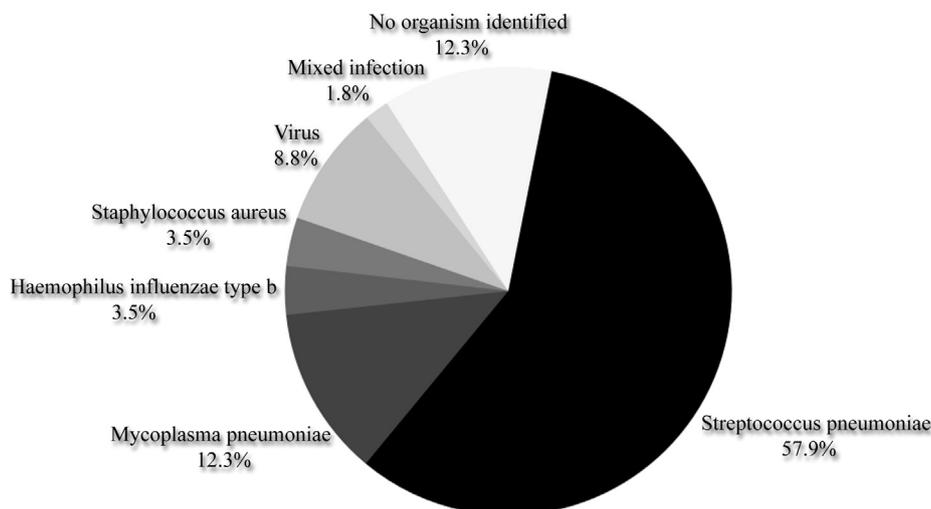


Figure 1. Etiology of progressive community-acquired pneumonia.

in the choice of initial parenteral antibiotics between the two groups.

Discussion

This study identifies key features that can determine children at risk for the development of progressive pneumonia. The initial severity of CAP, in our study, presented with pleural effusion as an admission diagnosis, is an important factor that determines the outcome of the disease and may predict which patients are more likely to fail with regards to empirical treatment, or to have progressive pneumonia.

Tachypnea is also a clue for progressive pneumonia. Guidelines developed by the World Health Organization for the clinical diagnosis of pneumonia in developing countries, highlight tachypnea and retractions as the two best indicators of lower respiratory tract infection (LRTI).⁵ Palafox et al⁶ observed that, in children younger than 5 years of age, of all the clinical signs, tachypnea had the highest sensitivity (74%) and specificity (67%) for radiologically confirmed pneumonia, but it was less sensitive and specific in early disease. This indicates that tachypnea is not only a sign of LRTI, but also a sign to predict acute respiratory distress, which is one of the pulmonary complications of CAP.

We show that children with progressive pneumonia have a greater degree of inflammation, as evidenced by that fact that $WBC > 17.5 \times 10^3/\mu L$ is an independent risk factor of progressive pneumonia. Higher CRP and platelet counts are also associated with the progressive disease in our study, which also reflects a more severe inflammatory response. Similar to other studies, anemia was shown to be a risk factor for developing invasive pneumococcal disease, including pneumonia, and is a marker for increased morbidity and mortality.^{7,8} Children with progressive pneumonia have a higher rate of hypoalbuminemia and positive T-antigen in our study. Hypoalbuminemia is well recognized in severe CAP, as well as being associated with the parapneumonic effusion and empyema. Large effusions are associated with low serum albumin, which might be explained in part by a shift from blood to pleural fluid.⁹ T-antigen presented on erythrocytes, platelets, and glomeruli is exposed by an enzyme produced by the pneumococcal organism. T-antigen positive implies that the patient may have pneumonia caused by *S. pneumoniae*.^{10–12} However, neither positive T-antigen, nor hypoalbuminemia, is statistically different between progressive and non-progressive pneumonia after multivariate logistic regression. This may be related to the reduced case numbers (total 47 patients and 55 patients checked T-antigen and albumin, respectively).

Table 4 Comparison of initial antibiotics for pneumococcal pneumonia

| Antibiotics | Progressive (n = 33) | Non-progressive (n = 98) | p |
|---|----------------------|--------------------------|-------|
| Parenteral antibiotics | 93.9 | 92.9 | >0.99 |
| 1 st line antibiotics ^a ± macrolide ^b | 39.4 | 49.0 | 0.421 |
| 3 rd cephalosporin ^c and/or glycopeptide ^d ± macrolide | 54.5 | 43.9 | 0.318 |

^a Aq. Penicillin, ampicillin, cefuroxime, or augmentin.

^b Azithromycin, erythromycin, or roxithromycin.

^c Cefotaxime or ceftriaxone.

^d Vancomycin or Targocid.

Data are presented as %.

Persistent fever of > 72 hours after admission is another important clinical feature significantly associated with hospitalized children having progressive pneumonia. Current practice guidelines for the management of CAP showed that for children whose condition deteriorates after initiation of antimicrobial therapy, or who show no improvement within 72 hours, further evaluation is needed.¹³ Follow-up chest radiographs should be obtained in patients with complicated pneumonia with worsening respiratory distress of clinical instability, or in those with persistent fever that is not responding to therapy over 48–72 hours.⁴ Our study supports this advice, because 73.7% of children with progressive pneumonia had persistent fever over 72 hours after admission. Repeating a chest radiograph should be considered to identify probable complications in such patients and therapy must be reviewed.

Most of our patients hospitalized with CAP were aged between 2 years and 5 years (59.1%) with a mean age of 4 years, which is similar to previous studies.^{14,15} However, the rate of children < 2 years old in the progressive pneumonia group was significantly higher than in the non-progressive group (26.3% vs. 8.6%, $p = 0.005$). This is not compatible with previous studies for complicated and uncomplicated pneumonia in hospitalized children.^{14–16} Tan et al.¹⁴ found that children hospitalized with complicated pneumonia tended to be significantly older than those with uncomplicated pneumonia (45 months vs. 27 months). There could be several reasons for these differences. Most of their studies focused on patients with pneumococcal pneumonia, whereas ours included all etiologies, although *S. pneumoniae* remained the major cause of progressive pneumonia (57.9% in the progressive group; 60% in children < 2 years old in the progressive pneumonia group). The time span on our study was different from that of Tan et al.¹⁴ Their study covered the time period from 1994 to 1999, during which there was a significant increase in the proportion of their patients with complicated pneumonia (from 22.6% to 53%). It is possible that during this period, the distribution of pneumococcal serotypes may have changed in favor of more virulent subtypes, or subtypes with a propensity for different age groups. Another recent study, conducted by Kunyoshi et al.,¹⁷ supported our findings by showing that the incidence of complicated pneumonia was higher in the 2nd year of life. In addition, a lower rate of PCV7 vaccination (overall 32% in our study) and genetic factors may explain the disparity in the epidemiology of progressive pneumonia in Taiwan, compared to Western countries.

The rate of etiologic diagnosis was higher in progressive than non-progressive pneumonia (87.7% vs. 49.8%, $p < 0.001$). This may be due to the fact that patients with progressive disease have a longer length of stay or more complicated disease; they may also receive more diagnostic tests and have an increased rate of etiologic diagnosis. *S. pneumoniae* remains the most frequently identified pathogen in children hospitalized with CAP, which is similar to a previous study.¹⁸ In our study, bacteria accounted for 79% of infections in children with progressive pneumonia, of which 71% were caused by *S. pneumoniae*.

We further analyzed the initial choice of antimicrobial therapy for pneumococcal pneumonia. Overall, 93.9% patients received parenteral antibiotics in the beginning and

there was no significant difference in the choice of initial parenteral antibiotics between progressive and non-progressive pneumonia patients (whether 1st line antibiotics or 3rd generation cephalosporins). The progression of disease is not related to the initial parenteral antibiotics, as most pediatricians choose antibiotics according to the guidelines.^{4,13,19} Bacterial virulence or host factor is likely to play a more important role in the progression of the disease, as manifested by age < 2 years being an independent risk factor for progressive pneumonia in our study.

Some potential limitations with regards to the present study should be taken into account. As the sample size is limited in relation to some parameters (albumin and T-antigen), those factors that have a weak association with progressive pneumonia might not have been detected. Another potential limitation is that the preadmission treatment was not available, so we could not evaluate the effect of that on children with progressive pneumonia. Finally, the susceptibility of antibiotics to isolated bacteria was not recorded and related detailed analysis was not done.

In conclusion, we identified six independent risk factors for progressive pneumonia including: age < 2 years, pleural effusion as admission diagnosis, tachypnea, Hb < 10 g/dL, WBC count > $17.5 \times 10^3/\mu\text{L}$, and duration to defervescence > 3 days. If the patient has fever for more than 72 hours without evidence of clinical improvement after initial treatment, further evaluation or a follow-up chest radiograph is needed to confirm cases of progressive pneumonia. The initial choice of parenteral antibiotics was not related to the progression of pneumococcal pneumonia.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

This work was supported by the Taiwan National Health Research Institutes. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors wish to thank the Taiwan Pediatric Infectious Disease Alliance (TPIDA) for assistance in case enrollment. The individual authors and affiliations within the TPIDA are the following:

National Taiwan University Hospital/Department of Pediatrics: Li-Min Huang, Luan-Yin Chang, Chun-Yi Lu, Pei-Lan Shao;

Mackay Memorial Hospital/Department of Pediatrics: Nan-Chang Chiu, Hsin Chi, Daniel Tsung-Ning Huang;

Centers for Disease Control, R.O.C. (Taiwan)/Research and Diagnostic Center: Jung-Jung Mu;

Chang Gung Memorial Hospital at Linkou/Department of Pediatrics: Yhu-Chering Huang, Cheng-Hsun Chiu, Yu-Chia Hsieh;

China Medical University Hospital/Department of Pediatrics: Kao-Pin Hwang, Hsiao-Chuan Lin, Ting-Yu Yen;

Taichung Veterans General Hospital/Department of Pediatrics: Po-Yen Chen;

National Taiwan University Hospital Yun-Lin Branch Dou-Liou Region/Department of Pediatrics: Jian-Te Lee;

National Cheng Kung University Hospital/Department of Pediatrics: Ching-Chuan Liu, Shih-Min Wang, Ching-Fen Shen;

Kaohsiung Chang Gung Memorial Hospital/Department of Pediatrics: Yi-Chuan Huang; and

Buddhist Tzu Chi General Hospital, Hualien Tzu Chi Medical Center/Department of Pediatrics: Yu-Huai Ho.

References

- Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C, et al. Randomised trial of *Haemophilus influenzae* type-b tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 1997;349:1191–7.
- Cutts FT, Zaman SMA, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in the Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005;365:1139–46.
- Wardlaw T, Salama P, Johansson EW, Mason E. Pneumonia: the leading killer of children. *Lancet* 2006;368:1048–50.
- Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011;53:e25–76.
- Anon. Serious infections in young infants in developing countries- rationale for a multicenter study. The WHO Young Infants Study Group. *Pediatr Infect Dis J* 1999;18(10 Suppl.):S4–7.
- Palafox M, Guiscarfe H, Reyes H. Diagnostic value of tachypnoea in pneumonia defined radiologically. *Arch Dis Child* 2000;82:41–5.
- Oppenheimer SJ. Iron and its relation to immunity and infectious disease. *J Nutr* 2001;131:616–33.
- Wexler ID, Knoll S, Picard E, Villa Y, Shoseyov D, Engelhard D, et al. Clinical characteristics and outcome of complicated pneumococcal pneumonia in a pediatric population. *Pediatr Pulmonol* 2006;41:726–34.
- Prais D, Kuzmenko E, Amir J, Harel L. Association of hypoalbuminemia with the presence and size of pleural effusion in children with pneumonia. *Pediatrics* 2008;121:e533–8.
- Cochran JB, Panzarino VM, Maes LY, Tecklenburg FW. Pneumococcus-induced T-antigen activation in hemolytic uremic syndrome and anemia. *Pediatr Nephrol* 2004;19:317–21.
- Huang DT, Chi H, Lee HC, Chiu NC, Huang FY. T-antigen activation for prediction of pneumococcus-induced hemolytic uremic syndrome and hemolytic anemia. *Pediatr Infect Dis J* 2006;25:608–10.
- Coats MT, Murphy T, Paton JC, Gray B, Briles DE. Exposure of Thomsen–Friedenreich antigen in *Streptococcus pneumoniae* infection is dependent on pneumococcal neuraminidase A. *Microb Pathog* 2011;50:343–9.
- Devitt M. PIDS and IDSA issue management guidelines for community-acquired pneumonia in infants and young children. *Am Fam Physician* 2012;86:196–202.
- Tan TQ, Mason Jr EO, Wald ER, Barson WJ, Schutze GE, Bradley JS, et al. Clinical characteristics of children with complicated pneumonia caused by *Streptococcus pneumoniae*. *Pediatrics* 2002;110:1–6.
- Francois P, Desrumaux A, Cans C, Pin I, Pavese P, Labarere J. Prevalence and risk factors of suppurative complications in children with pneumonia. *Acta Paediatr* 2010;99:861–6.
- Byington CL, Spencer LY, Johnson TA, Pavia AT, Allen D, Mason EO, et al. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiologic associations. *Clin Infect Dis* 2002;34:434–40.
- Kunyoshi V, Cataneo DC, Cataneo AJ. Complicated pneumonias with empyema and/or pneumatocele in children. *Pediatr Surg Int* 2006;22:186–90.
- Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics* 2004;113:701–7.
- Lee PI, Chiu CH, Chen PY, Lee CY, Lin TY. Guidelines for the management of community-acquired pneumonia in children. *Acta Paediatr Taiwan* 2007;48:167–80.