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Original Article

Radiographic, clinical, and prognostic features of complicated and uncomplicated community-acquired lobar pneumonia in children

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Background and Purpose: The incidence of community-acquired lobar pneumonia in conjunction with either necrosis or empyema in children has rapidly increased in recent years. This study aimed to evaluate the radiographic, clinical, and predicted factors of complicated and uncomplicated lobar pneumonia in children.

Methods: This retrospective study included 131 patients younger than 18 years of age with community-acquired lobar pneumonia treated between January 2002 and March 2005. Multiple logistic regression analysis was performed to demonstrate the risk factors of complicated lobar pneumonia.

Results: The proportion of children with lobar pneumonia in children increased dramatically from 7% in 2002 to 19% in 2004. Analysis revealed the presence of elevated C-reactive protein level (>12 mg/dL) [odds ratio (OR), 3.51; 95% confidence interval (CI), 1.61-7.66], persistent fever for more than 1 week before admission (OR, 1.14; 95% CI, 1.04-1.26), and multilobar (≥2 lobes) confluent lung opacity on chest radiographs (OR, 2.83; 95% CI, 1.27-6.33) were independent predictors of the occurrence of complicated lobar pneumonia. A progressive increase in the number of penicillin-non-susceptible *Streptococcus pneumoniae* isolates was found during the study period. Prolonged fever was a common clinical feature of hospitalized children with lobar pneumonia. Failure of consolidative pneumonia to respond to appropriate antibiotic treatment within 4.4 days was associated with the development of necrosis or empyema.

Conclusions: Complicated and uncomplicated lobar pneumonia are difficult to distinguish based on clinical symptoms at the time of admission. The presence of the above risk factors can help in the early diagnosis of complicated lobar pneumonia.

Key words: Empyema, pneumonia, risk factors, *Streptococcus pneumoniae*

Introduction

Community-acquired pneumonia is a common cause for hospitalization in children with confluent lung opacity or "lobar pneumonia", a particularly serious presentation [1]. Management of pediatric patients with community-acquired lobar pneumonia is challenging because of its broad range of clinical presentations, the potential life-threatening nature of the illness, and the associated high cost of care. Accurate and prompt etiologic diagnosis is limited by inadequate clinical and laboratory diagnostic methods. A rapid antigen assay that accurately detects pneumococcal antigen in the urine of infected patients showed excellent sensitivity and specificity among adults, but studies in children have yielded varying results [2,3]. In the past, penicillin was effective in markedly reducing the development of necrotizing pneumonia and empyema in patients with community-acquired lobar pneumonia. However, beginning in the 1990s, an increase in the prevalence of these conditions was observed among children who received this treatment [4,5]. Many hypotheses were developed for

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the increased prevalence of complicated pneumonia during this period, either focusing on resistant pathogen or enhanced virulence of the pathogen itself [6]. Clinical characteristics of patients might play a crucial role in the development of complicated community-acquired lobar pneumonia. Data on the clinical manifestations in children with community-acquired lobar pneumonia in Taiwan are limited. A rapid increase in the number of patients with community-acquired lobar pneumonia occurring in conjunction with necrosis or empyema has been observed in our hospital in recent years. This study aimed to analyze the demographic and clinical features of children with community-acquired lobar pneumonia as well as to identify laboratory parameters for the prediction of clinical outcome.

Methods

This retrospective study analyzed data from patients younger than 18 years of age who were initially suspected of having lower respiratory tract infection at Taichung Veterans General Hospital (TVGH) from January 2002 through March 2005. TVGH is a referral medical center in central Taiwan; the majority of admissions are children from Taichung, Changhua, Miaoli, and Nantou counties. Two radiologists and two pediatricians retrospectively and independently reviewed the frontal radiographs of 1087 children initially suspected of having lower respiratory tract infection. None of the children had respiratory symptoms lasting for more than 3 months before admission. Lobar pneumonia was established based on the following 3 criteria — clinical symptoms, laboratory and radiographic evidence of unilobar or multilobar pulmonary consolidation with distinctly confined, dense, or a large pleural effusion. Patients were admitted to the intensive care unit because they either required mechanical ventilation or were in an unstable condition requiring intensive medical and nursing care.

Medical records including demographic information, vital signs (initial blood pressure, heart rate, and respiratory rate), radiographic studies, and laboratory data (culture, Gram stain, white blood cell [WBC] count, and C-reactive protein [CRP]) obtained from tests performed within 24 h after admission were collected and analyzed. The duration of fever and hospitalization were regarded as objective measures of recovery. Complicated pneumonia was defined as the presence of necrotizing pneumonia and/or empyema; necrotizing pneumonia was classified based on the finding of multiple radiolucent lesions on chest radiograph or decreased parenchymal contrast enhancement on computed tomography image [7]. Empyema was defined as meeting 1 of the following major criteria or 2 minor criteria. Major criteria included the presence of pus in the pleural space and a positive pleural fluid culture. Minor criteria included pleural fluid pH of ≤7.1, a WBC count of ≥10,000 cells/dL, a glucose level of ≤40 mg/dL, and lactate dehydrogenase concentration of ≥1000 IU/mL [8].

Microbiological studies

Bacterial culture taken at the time of admission was performed according to standard microbiological techniques as reported previously [9]. Gram stain of sputum was evaluated using the following strict criteria. If >25 WBCs and <10 squamous cells per low-power magnification field were present, the predominance of a specific morphologic type of bacterium on microscopy and its subsequent demonstration in abundance on culture indicated a bacterial pathogen. Among the isolated pathogens, *Streptococcus pneumoniae* was routinely screened for penicillin susceptibility using a 1-μg oxacillin disk diffusion method. An inhibition zone diameter <20 mm was defined as non-susceptible to penicillin. The minimal inhibitory concentration (MIC) of penicillin was tested by placing E-test strips (AB Biodisk, Solna, Sweden) on Mueller-Hinton blood agar (BBL Microbiology System, Cockeysville, MD, USA) and then incubating the dishes under 5% CO_2 at 35°C for 18 to 24 h. An isolate with an MIC of penicillin ≤0.06 μg/mL was defined as susceptible to penicillin; an MIC of 0.12 to 1 μg/mL was defined as intermediate; and an MIC of ≥2 μg/mL was defined as highly resistant. Criteria for defining susceptibility and non-susceptibility were based on the National Committee for Clinical Laboratory Standards guidelines [10].

Statistical analysis

Pearson's standard chi-squared test was used to compare proportions between patients with complicated and uncomplicated lobar pneumonia. Fisher's exact test was used when the expected count was <5. Multiple logistic regression analysis was used to identify independent predictors of complicated pneumonia. A value of $p<0.05$ was considered to be statistically significant. All probabilities were 2-tailed. Odds ratios (ORs) and their 95% confidence intervals (CIs) were also determined.

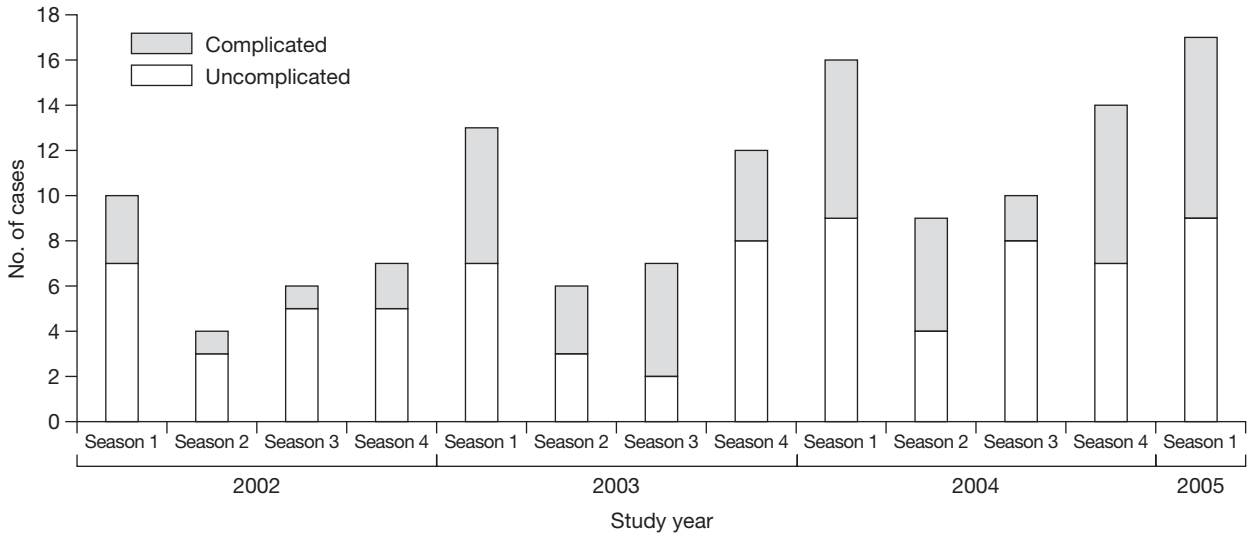

Fig. 1. Distribution of complicated and uncomplicated cases of community-acquired lobar pneumonia from January 2002 through March 2005. Season 1: January to March; Season 2: April to June; Season 3: July to September; Season 4: October to December.

Results

The annual hospitalization rate associated with lower respiratory tract infection ranged from approximately 8.9% to 12.3% during 2002-2005. The proportion of lobar pneumonia in patients with lower respiratory tract infection increased rapidly from 7% in 2002, to 14% in 2003, and to 19% in 2004, and the referral rates for patients with pneumonia were stable during the study period. Community-acquired lobar pneumonia was diagnosed in 134 patients during the study period. Among these patients, 13 were suspected of having atypical infection based on their clinical symptoms and laboratory data. These included 6 patients who had positive nasopharyngeal virus culture results (adenovirus, n = 4; parainfluenza virus, n = 2), 4 patients who were treated with a macrolide, and 3 patients who received supportive treatment without antibiotic agent. None of these patients had complicated pneumonia and all had a short length of hospital stay (<4.5 days). Extrapulmonary conditions developed in 3 patients including 2 who developed hemolytic uremic syndrome and 1 who developed infection-associated hemophagocytic syndrome 1 week after admission. Excluding these 3 patients with severe systemic disease, 54 (45.8%) of the remaining 131 patients had complicated pneumonia, including 29 (53.7%) with empyema and 25 (46.3%) with empyema and necrotizing pneumonia. There were 75 boys and 56 girls. The male-to-female patient ratio was 1.3. The mean age was 4.2 years. A total of 84 patients (64%) were between 2-6 years of age. About 68% of patients developed symptoms between October and March (Fig. 1). Underlying conditions included heart disease (n = 10), failure to thrive (n = 8), mental retardation (n = 8), epilepsy (n = 7), prematurity (n = 4), and metabolic disease (n = 3). None of the patients were receiving steroids or immunosuppressive therapy prior to the onset of pneumonia symptoms. Selection of antibacterial therapy followed the recommendations for the treatment of community-acquired pneumonia in children [11], which have been suggested to be appropriate treatments for pneumonia. All patients were empirically treated with beta-lactam antimicrobial agents after Gram staining of sputum specimens was performed. In all, 14 blood samples (10.7%) and 6 pleural effusion samples (18.8%) had positive results (Table 1); 64 sputum specimens (48.9%) with evidence of bacteria on microscopic examination had positive pathogen results. Among the patients with positive sputum pathogen samples, 12 patients also had bacteremia or pleural effusion. Positive bacterial cultures were found in 55% of patients. The body temperature at admission ranged from 34.6°C to 40.8°C, with a mean of 39.1°C. Hypothermia with shock was noted in 2 patients. Intubation was required in 22 patients (16.8%). Noninvasive nasal continuous-positive airway pressure was required in 14 patients (10.7%), and 44 patients (33.6%) with an unstable condition required intensive medical and nursing care. Inotropic agent support (dopamine and/or dobutrex) was required in 15 patients (11.5%). A total of 7 patients (5.3%) died during the

Table 1. Results of cultures obtained from sterile sites in patients with community-acquired lobar pneumoniae

Results	Complicated (n = 54) No. (%)	Uncomplicated (n = 77) No. (%)	*p*
Blood cultures performed	54 (100)	77 (100)	NS
Positive results	8 (14.8)	6 (7.8)	
Klebsiella pneumoniae	1 (12.5)	0 (0)	
Streptococcus pneumoniae	7 (87.5)	5 (75.0)	
ORSA	0 (0)	1 (25.0)	
Effusion cultures performed	32 (59.3)	0 (0)	
Positive results	6 (18.8)	0 (0)	
Klebsiella pneumoniae	1 (16.7)	0 (0)	
ORSA	1 (16.7)	0 (0)	
Streptococcus pneumoniae	4 (66.7)	0 (0)	

Abbreviations: ORSA = oxacillin-resistant *Staphylococcus aureus*; NS = not significant

[a]Only one case had both positive blood culture and pleural effusion with *K. pneumoniae* isolate. In all, 19 cases had pathogens isolated from sterile sites.

hospital course; 5 due to shock (systolic pressure could not be detected with poor peripheral perfusion) when admitted, and 2 due to nosocomial infection. Six of the seven patients who died had underlying conditions, including heart disease (n = 3), failure to thrive (n = 2), and epilepsy (n = 1). Chest radiographs of these 7 patients showed multilobar consolidation. Five of them had bacteremia (pneumococcal bacteremia, n = 3; *Acinetobacter baumannii* bacteremia, n = 1; pseudomonal bacteremia, n = 1). The average duration of hospital stay of these patients was 14.3 days (1 to 34 days).

Univariate analysis (Table 2) revealed no significant difference at admission between patients with complicated and uncomplicated lobar pneumonia in terms of age, gender, WBC count, or vital signs (including blood pressure, respiratory rate, heart rate) [data not shown]. Multiple logistic regression analysis revealed that the presence of high CRP level (>12 mg/dL) [OR, 3.51; 95% CI, 1.61-7.66], persistent fever for more than 1 week before admission (OR, 1.14; 95% CI, 1.04-1.26), and multilobar (≥2 lobes) involvement on chest radiograph (OR, 2.83; 95% CI, 1.27-6.33) were independent predictors of complicated lobar

Table 2. Univariate analysis of demographic data and clinical characteristics for children with complicated or uncomplicated community-acquired lobar pneumonia

	Complicated (n = 52)	Uncomplicated (n = 69)	OR (95% CI)	*p*
Age (months) [range]	58.7 ± 40.5 (8-216)	46.8 ± 40.0 (1-204)	-	0.11
<24 months (%)	23.0	40.0	-	0.12
>24 months and ≤60 months (%)	52.0	38.0		
>60 months (%)	25.0	22.0		
Gender (male [%])	55.8	55.9	-	
Underlying disease (%)	11.5	5.1	2.12 (0.57-7.94)	
WBC count (x 10^3 cells/mL)	17.6 ± 11.6	15.8 ± 7.9	-	
C-reactive protein level >12 mg/dL (%)	63.5	36.2	3.06 (1.45-6.46)	0.003
Fever before admission (days)	7.64 ± 4.97	5.63 ± 3.97		0.01
Fever clearance after admission (days)	7.5 ± 4.6	4.4 ± 3.6		<0.001
Thoracotomy (%)	61.5	0		
Duration of hospital stay (days)	14.75 ± 11.7	13.81 ± 16.25		
Mortality (%)	7.8	7.2		
Percentage of ever staying in ICU (%)	45.7	31.9		
Duration of ICU stay (days)	12.1 ± 11.8	12.6 ± 13.2		
Respiratory assistance (%)[b]	30.5	13.5	2.96 (1.2-7.4)	0.017

Abbreviations: OR = odds ratio; CI = confidence interval; WBC = white blood cell; ICU = intensive care unit

[a]This table does not include data from 10 of 131 patients since they showed partial or failed antibiotic treatment received in other hospitals.

[b]Respiratory assistance included intubation and noninvasive continuous-positive airway pressure.

Table 3. Univariate analysis of chest radiographic data for children with complicated or uncomplicated community-acquired lobar pneumonia

Location of lobar lung opacity	Complicated (n = 54) [%]	Uncomplicated (n = 77) [%]	OR (95% CI)	*p*
>2 lobes	64.0	37.7	3.04 (1.48-6.29)	0.002
RUL	26.9	54.5	0.32 (0.15-0.68)	0.002
RML	42.3	33.8		NS
RLL	42.3	32.5		NS
LUL	25.0	9.1	3.17 (1.17-8.59)	0.02
LLL	50.0	20.8	3.81 (1.77-8.21)	0.0004

Abbreviations: OR = odds ratio; CI = confidence interval; RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe; NS = not significant

pneumonia. The occurrence of complicated lobar pneumonia was also associated with longer duration until fever clearance after hospital admission ($p<0.001$). Among the patients with complicated lobar pneumonia, 32 (54.2%) had right upper lobe involvement (Table 3), and most of them had sharply defined horizontal margins on the chest radiograph. In the complicated lobar pneumonia group, the basilar lobe was usually involved, on the left and right side of the lower lobe in 50% and 42.3% of patients, respectively. MIC testing was performed in 32 isolates of *S. pneumoniae* (Table 4). There were no significant differences in the MIC for penicillin between isolates from complicated and uncomplicated lobar pneumonia cases, but the prevalence of complicated cases with intermediately susceptible *S. pneumoniae* was significantly higher than that with resistant isolates. *S. pneumoniae* urinary antigen detection was performed in 40 patients with uncomplicated lobar pneumonia and 27 (67.5%) of them had positive results. Among the 27 patients with positive urinary antigen test results, 12 (44.4%) had culture-confirmed pneumococcal infection. *S. pneumoniae* urinary antigen detection was positive in 35 of 48 patients (72.9%) with complicated lobar pneumonia and 17 (48.6%) of these patients had culture-confirmed pneumococcal infection.

Discussion

An increasing incidence of hospitalization with complicated pneumonia has been reported among children in the United States [5]. This has led to an intensified search for the factors responsible for the enhanced severity of pneumonia. The severity of the disease may be related to the virulence and number of organisms causing bacteremia, and to the integrity of specific host defenses with immature immune function [11]. This assumption may partially be supported by the observation in the present study that most cases were between 2 and 6 years of age and most of fatal cases had underlying diseases. In addition to the immune compromised condition, penicillin resistance of *S. pneumoniae* appears to play a crucial role in disease severity. The MIC of penicillin for *S. pneumoniae* progressively increased during the study period (Fig. 2). Whether resistant pneumococci are more likely to induce more severe disease such as complicated lobar pneumonia remains to be established. Hsieh et al [8] showed that a multidrug-resistant *S. pneumoniae* strain of a specific pulsed-field gel electrophoresis pattern and serogroup 14 induced complicated pneumonia in half the children with this isolate. In the present study, no significant difference was found in the penicillin

Table 4. Results of penicillin resistance testing of *Streptococcus pneumoniae* isolates from children with complicated or uncomplicated community-acquired lobar pneumonia[a]

Penicillin resistance (MIC; μg/mL)	No. of isolates (%)		*p*
	Complicated (n = 15)	Uncomplicated (n = 17)	
Susceptible ≤0.06	4 (27)	5 (29)	NS
Intermediately susceptible 0.12-1	9 (60)	9 (53)	
Resistant >2	2 (13)	3 (18)	

Abbreviations: MIC = minimum inhibitory concentration; NS = not significant

[a]In the uncomplicated group, 1 isolate had an MIC of penicillin of 6 μg/mL, 2 others had MIC of penicillin of 8 μg/mL. In the complicated group, 2 patients had MIC of penicillin of 4 μg/mL.

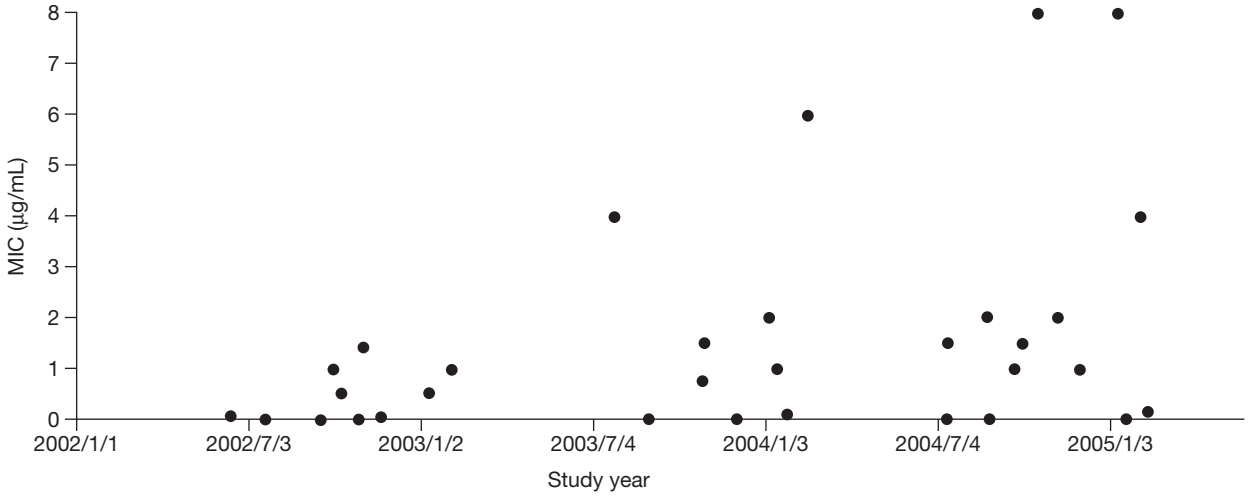

Fig. 2. Distribution of the minimum inhibitory concentration (MIC) of penicillin to *Streptococcus pneumoniae* during January 2002 through March 2005.

resistance of *S. pneumoniae* between isolates from patients with complicated and uncomplicated community-acquired lobar pneumonia. Whether there is a relationship between increasing prevalence of community-acquired lobar pneumonia and an increasing MIC of penicillin remains unclear. The prevalence of penicillin non-susceptible *S. pneumoniae* (PNSSP) in patients admitted to our hospital has increased dramatically, from 5.6% (1990-1994) to 74% (1995-2000) [12]. In the present study, the prevalence rate of PNSSP (71.9%) was similar to that recently reported in Taiwan (42.4%-95.5%) [13,14]. Most (68%) cases of community-acquired lobar pneumonia in children occurred during the cold season (from October to March), which was also reported in other studies [12,15]. A high CRP level (>12 mg/dL) was a significant predictor of necrosis and empyema complications. CRP is an acute-phase protein that allows for recognition of foreign pathogens, activation of the complement system, and mediation of inflammation [16]. A severe inflammatory response could induce tissue necrosis or abscess formation. Thus, elevated CRP levels can help in predicting complicated lobar pneumonia at an early stage.

This study had a few limitations; the causative etiology was not thoroughly investigated unless patients had bacteremia or pleural empyema. In order to increase the likelihood of identifying the probable etiology, the Gram-stained sputum with large numbers of polymorphonuclear neutrophils (PMNs) and very few epithelial cells (PMN/epithelial cell ratio, approximately 10:1 to 20:1) were cultured immediately to identify a potential pathogen. A previous study found that complicated lobar pneumonia most commonly occurred in the right upper, right lower, and left lower lobes [17]. In the present study, the right lung was involved 3 times as often as the left lung. Patients with complicated lobar pneumonia had 50% of confluent lung opacity occurring in the left lower lobe, a phenomenon which seemed to be related to terrestrial gravitation. More than half the patients with left lobe involvement had multilobar (≥2 lobes) involvement (Table 3). Multilobar (≥2 lobes) confluent lung opacity was found more often in complicated than in uncomplicated lobar pneumonia (64% and 37.7%, respectively). Among the 67 positive bacterial pathogens identified in the patients in this study, 20 were from a sterile site (blood and pleural effusion); the most common bacterial pathogens isolated from either sterile or non-sterile sites were *S. pneumoniae* (n = 40, 59.7%), *Staphylococcus aureus* (n = 11, 16.4%), and *Klebsiella pneumoniae* (n = 6, 8.9%). In the past decade, *Haemophilus influenzae* was the most common cause of bacterial pneumonia in children from Taiwan [18,19]; however, the use of conjugated *H. influenzae* type b vaccines has reduced the frequency of this infection since the late 1980s [20]. Many studies have shown a reduction in the proportion of parapneumonic effusion due to *S. aureus* in the United States and Canada [21,22]. However, such a reduction in frequency of staphylococcal pneumonia and empyema over the last decade has not occurred in other parts of the world [23]. In this study, there was a significant difference in the duration of hospital stay and the use of respiratory assistance between complicated and uncomplicated groups (Table 2), reflecting the higher cost of care for

patients with complicated lobar pneumonia. Prolonged fever was another important clinical feature significantly associated with hospitalized patients who had complicated, consolidated, lobar pneumonia that did not respond to appropriate antibiotic treatment within 4.4 days ($p<0.001$). Ultrasound should be performed to identify probable complications in such patients.

In summary, this study has demonstrated that the proportion of community-acquired lobar pneumonia in children increased dramatically during these 3 years. Children with complicated lobar pneumonia had a prolonged hospital course that led to a higher cost of care. It was difficult to distinguish between complicated and uncomplicated lobar pneumonia based on clinical symptoms at the time of admission. High CRP level (>12 mg/dL), persistent fever for more than 1 week before admission, and multilobar (≥2 lobes) confluent lung opacity on chest radiograph can help predict complicated lobar pneumonia early.

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