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Lobar pneumonia and bacterial pathogens in Vietnamese children.

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Abstract

Background: Pneumonia is one of the leading causes of death in children because of its serious clinical manifestations, rapid progress, and a dangerous condition. lobar pneumonia is more severe, more difficult to determine the etiologies if only based on clinical predictors.

Objectives: To describe the clinical and chest X-ray characteristics of lobar pneumonia; and to determine bacterial pathogens and treatment outcomes in Vietnamese children.

Materials and Methods: A cross-sectional study on 67 patients with lobar pneumonia admitted to Children's Hospital 1, Ho Chi Minh City, Vietnam was conducted. All of nasotracheal aspiration (NTA) specimens of patients were collected and cultured. Real-time PCR was performed to identify bacterial pathogens in NTA specimens.

Results: Lobar pneumonia occurred mainly in children from 3 to 7 years old (46.3%). Clinical manifestations were cough (100%), fever (95.5%), tachypnea (98.5%), lower chest-wall indrawing (53.7%), wheezing (44.8%). Of chest X-ray images, right upper lobe pneumonia was the highest (38.8%), left lower lobe pneumonia (16.4%). The most common bacteria were Mycoplasma pneumoniae (69.7%) and Streptococcus pneumoniae (53%). The original antibiotics mostly used were the 3rd generation cephalosporins (C3G) (50.7%) and C3G + azithromycin (47.8%). 58.2% of cases responded well to the original antibiotics. The successful rate of C3G + azithromycin was 81.2%. The responding of second antibiotics was also high (92.9%), mainly based on the results of real-time PCR. 100% of patients were cured. There were 2 cases with tuberculosis that moved to a tuberculosis hospital for treatment.

Conclusions: Lobar pneumonia can be diagnosed by clinical examination and chest X-ray. Real-time PCR efficient supported in causative pathogens quickly and accurately, guided effective antibiotic therapy, especially in cases of poor clinical responses. Additionally, Mycoplasma pneumoniae was found in a younger group of age than the usual group."

Keywords: Lobar pneumonia, Children, Bacterial pathogens, Vietnam.

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Introduction

Pneumonia is one of the leading causes of death in children because of its serious clinical manifestations, rapid progress, and a dangerous condition [1]. In 2015, an estimated that 900.000 children less than 5 years old died because of pneumonia, with more than 90% of these deaths occurring in low-income and middle-income countries [2]. Between 2000 and 2015, an estimation for children's hospitalization with pneumonia increased by 2.9 times, which is a more rapid increase in the WHO South-East Asia Region than African Region [3]. The majority (>75%) pneumonia- deaths occurred in six countries: Cambodia, China, Laos, Papua New Guinea, the Philippines. and Vietnam [4]. Lobar pneumonia is a clinical form of pneumonia, which is a common pediatric lower respiratory tract infection [5]. According to the World Health Organization (WHO) 2014, the pneumonia case management approach concentrates on basic clinical signs and symptoms [6]. Meanwhile, lobar pneumonia is more severe, more difficult to determine the etiologies if only based on clinical predictors. Besides, it is difficult to ascertain the relative importance of individual pneumonia pathogens in young children because of the low sensitivity and uncertain specificity of microbiological techniques used for pathogen detection [7]. However, despite the fact that the establishment of accurate etiological diagnosis remains a tremendous challenge, the study aims to use the molecular biology techniques supporting early diagnosis to reduce the mortality.

Polymerase chain reaction (PCR) is a modern technique duplicating one fragment of DNA into millions of them, which has a sensitivity of more than 90% [8]. PCR is one of the tops

of methods identifying pathogens and assessing the quantitative of specimens. In Vietnam, however, PCR is still not a common tool in diagnosis because of its high-priced and modernity, which is only used in large hospitals. PCR is an uncommon indication only used in cases that are hard to diagnose and having unresponsive treatment. We, therefore, performed the study to describe the clinical and chest X-ray characteristics of lobar pneumonia; and to determine bacterial pathogens and treatment outcomes in Vietnamese children.

Materials and Methods

Study design

We conducted a cross-sectional study at Children's Hospital 1 from June 2015 to May 2016.

Study population

The study was performed on 67 patients admitted to the Children's Hospital 1 where is a large hospital considered as a national first-class pediatric hospital in Vietnam. In-patient children from 2 months to 15 years of age diagnosed with lobar pneumonia were asked to join the research. Children who entered the research of the ***Children's Hospital 1 met 3 criteria:***

Age: 2 months - 15 years old.

Clinical symptoms: Cough, dyspnea, tachypnea by age ± withdraw chest. Tachypnea by age according to WHO: 2 - <12 months: respiratory rate ≥ 50 breaths/minute; 12 months - <5 years: respiratory rate ≥ 40 breaths/minute; and ≥ 5 years: respiratory rate ≥ 30 breaths/minute.

Chest X-ray image: A typical image of lobar pneumonia (relatively homogeneous blurred image occupies one lobe or lobe of the lung and has an inner bronchial airway image) or atypical (shaded blurs are shaped round at an area of the lung, size about 3-4 cm, clear margin, no calcification nodules).

Exclusion criteria: Children's family refused to join the research group.

$$N = \frac{z^2_{\left(1-\frac{\alpha}{2}\right)} \cdot P(1-P)}{d^2} \approx 62$$

N: the minimum sample; α: confidence level (α=0.05); $z_{(1-\frac{\alpha}{2})}$ Z score, ($z_{(1-\frac{\alpha}{2})}$= 1.96); d: confident limit around the point estimate; P: the rate of lobar pneumonia/pneumonia in Vietnam estimated by Tuan Minh Dao et al. [9] with the P=0.086.

Data collection

Data on demographic, clinical, and subclinical characteristics of inpatients were recorded at the study hospital. NTA specimens were taken by researchers. The children's mother or relatives carried the children in arms and tilt the head back to facilitate the airway opening. Measuring and marking the distance from the ala of the nose to the earlobe and to the thyroid cartilage. Deeply inserting the catheter into the nose until the marking place, there would be no suction on the way down. Suctioning specimens at the moment that the patients were coughing- blushing and when the catheter reaches the marking place. Slowly taking the catheter out, do not twisting and suctioning along the way. Then rinsing out the catheter with saline (5ml). Taking away the catheter and covering by the cap, bringing the NTA to the lab. If for any reason that the specimens cannot be used immediately, they could be stored at the temperature between 2-8°C, but not more than 2 hours.

The NTA specimens were sent to 2 places: Microbiology Department of Children's Hospital 1 for cultivation and Nam Khoa Biotek Laboratory for PCR, where has the high qualified lab in Vietnam got certificate ISO 17025. BIO RAP.CFX96 machine (made in the USA) was used to run Realtime PCR for the NTA specimens.

The quality of NTA was checked at labs according to Bartlett score [10]. The score is derived from a microscopic exam of sputum specimens that looks at 10x field; (1) the number of neutrophils, (2) the presence of mucus strands, and (3) the number of squamous epithelial cells.

10-25 neutrophils: +1

>25 neutrophils: +2

Columnar cell (+): +1

10-25 squamous epithelial cells: -1

->25 squamous epithelial cells: -2

A score of 0 or less indicates unreliable; 1-2: medium reliability; and >=3: high reliability.

Data analysis

All children who met the sampling criteria were included in the study batch. We performed sample medical records and treated according to hospital regimens; proceeded to take NTA (done by the researcher), sent those specimens to the Microbiology Department of Children's Hospital 1 for screening, transplanting, and Nam Khoa Biotek Laboratory for PCR. The cultivation was done in 2 days and the PCR results returned in 24 hours. After microbiological results, if the agent was isolated, we treated according to the agent. If not isolated, we treated according to clinical practice guidelines and based on the local epidemiology of these infections. Evaluating treatment results through the number of days of treatment and whether or not there was death.

Statistical analysis

The data were analyzed with SPSS statistical software for Windows version 18. The differences between patients' characteristics and positions of chest radiograph injury were analyzed by the chi-squared test with a 95% confidence interval. A p-value of less than 0.05 was considered significant.

Ethical approval

Ethical approval followed an assessment by Children's Hospital 1 and Can Tho University of Medicine and Pharmacy.

Results

Supportive cases

In our study, most children do not need breathing support

(accounted for 91.0%). 7.5% of children need breathing through a cannula, 1.5% of children need NCPAP (Nasal Continuous Positive Airway Pressure) and no children need mechanical ventilation.

Demographic, clinical, and subclinical characteristics

67 children enrolled in the study. The average age of the study sample was 60.9 ± 35 months, the smallest was 7 months and the oldest was 136 months. The most common age group was 3-7 years old (46.3%), less common in children <12 months old (6.0%). This difference was statistically significant ($p < 0.001$). The incidence in boys and girls was almost the same ($p=0.903$) (Table 1).

With the clinical findings, the most common symptoms were cough and fever, accounted for 100% and 95.5% of 67 cases. Tachypnea accounted for almost an absolute rate in the group of physical symptoms (98.5%). According to the radiological findings on chest X-rays, single lesions of one lung lobe accounted for the majority (88.0%), the most lesion was in the right lung (64.2%), and especially in the right upper lobe (38.8%). The difference in lesion between positions was statistically significant ($p<0.001$) (Table 2 and Table 3).

Bacterial pathogens

In 67 cases of lobar pneumonia taken NTA samples, 1 NTA sample was not reliable enough for transplanting (Barlett score=0 for screening), the remaining 66 samples were inoculated at the Microbiology Department of Children's Hospital 1 and done Realtime PCR at Nam Khoa Biotek Laboratory. With 66 samples inoculated, 100% cases gave negative results. With 66 samples sent as real-time PCR, there were 2 samples returned negative, the remaining 64 samples are positive, accounting for 97.0%.

In 64 positive PCR samples, there were 2 cases of *Mycobacterium tuberculosis*, transferred to Pham Ngoc Thach Hospital - a hospital specializing in the treatment of pulmonary tuberculosis in Ho Chi Minh City, Vietnam.

The PCR result was called positive when there was 1 agent detected > 10^5 copies/ml. We evaluate the main agent and the co-infection agents in cases of many positive agents on an NTA sample. The main agent is the agent detected with the highest number of copies/ml. Through 66 times of isolation for each agent, we recorded *Mycoplasma pneumoniae* accounted for the highest proportion of 69.7% (both being the main agent in 35 times of isolation and both as a co-infection agent in 11 isolation times), following after were *Streptococcus pneumoniae*, *Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis*, and *Mycobacterium tuberculosis* (Table 4). In 9 cases of *Haemophilus influenzae*, only 1 case was identified as *Haemophilus influenzae* type b. However, in this case, *Haemophilus influenzae* type b was not the main agent. In 18 isolated cases of *Staphylococcus aureus*, there were 11 cases of Methicillin-resistant *Staphylococcus aureus* (5 strains with MecA gene, 3 strains with Nuc and 3 strains carrying FemA gene). But all 11 cases were not the major factor. With 2 cases of tuberculosis detection, the result was both negative firstly, we changed/added antibiotics but clinically still did not respond. We decided to isolate with *Mycobacterium tuberculosis*, a positive result with a high number of copies.

Treatment outcomes

The initial antibiotic was mostly used as the 3rd generation cephalosporin (C3G) (34 cases accounted for 50.7%), followed by C3G + azithromycin 32 cases (47.8%), 1 case of using vancomycin (1.5%), which is for the child admitted after had being treated at FV Hospital, Ho Chi Minh City for 2 days.

Characteristics		Number (N=67)	Percentage (%)	p-value
Age	< 12 months	4	6	p<0.001
	12 – 35 months	15	22.3	
	36 – 84 months	31	46.3	
	> 84 months	17	25.4	
Sex	Boys	34	50.7	p=0.903
	Girls	33	49.3	

Table 1. *Patient characteristics.*

Symptoms	Cases (N=67)	Percentage (%)
Cough	67	100
Fever	64	95.5
Vomiting	29	43.3
Diarrhea	4	6
Abdominal pain	2	3
Headache	1	1.5
Dyspnea	2	3
Tachypnea	66	98.5
Chest in-drawing	36	53.7
Accessory muscle used	25	37.3
Wheezing	30	44.8

Table 2. *Clinical symptoms of patients.*

Traumatic position	Frequency (N=67)	Percentage (%)	Cumulative rate (%)
Right upper lobe	26	38.8	38.8
Right lower lobe	10	14.9	53.7
Middle lobe	2	3.0	56.7
Left upper lobe	10	14.9	71.6
Left lower lobe	11	16.4	88.0
2 lobes on one side of the lungs	5	7.5	95.5
2 lobes of lungs	3	4.5	100
p-value	***p < 0.001***		

Table 3. *Imaging chest trauma.*

Bacterium	Positive isolation			Negative, N (%)	Total (N)
	Main agent (N)	Co-infection agent (N)	Positive, N (%)		
Mycoplasma pneumoniae	35	11	46 (69.7%)	20 (30.3%)	66
Streptococcus pneumoniae	19	16	35 (53%)	31 (47%)	66
Staphylococcus aureus	5	13	18 (27.2%)	48 (72.8%)	66
Haemophilus influenzae	3	6	9 (13.6%)	57 (86.4%)	66
Moraxella catarrhalis	0	5	5 (7.6%)	61 (92.4%)	66
Mycobacterium tuberculosis	2	0	2 (3%)	64 (97%)	66
All pathogens causing lobar pneumonia identified by using real-time PCR					
1. Streptococcus pneumoniae					
2. Streptococcus agalactiae					
3. Streptococcus pyogenes					
4. Mycoplasma pneumoniae					
5. Mycoplasma sp.					
6. Haemophilus influenzae					
7. Haemophilus influenzae type b					
8. Staphylococcus aureus					
9. Staphylococcus aureus has FemA gene					
10. Staphylococcus aureus has Nuc gene					
11. Staphylococcus aureus has MecA gene					
12. Moraxella catarrhalis					
13. Chlamydophila pneumoniae					
14. Chlamydophila psittaci					
15. Chlamydia trachomatis					
16. Legionella pneumophila					
17. Mycobacterium tuberculosis					
18. Nesseria meningitidis					
19. Bordetella pertusis					
20. Bordetella parapertusis					

Table 4. *Bacterial pathogens identified by using real-time PCR.*

There was one case of immediate administration of azithromycin to a child <5 years old (55 months old) because that was the case of a child with an older brother with *Mycoplasma pneumoniae*, who was also in our research samples. That child responded well to antibiotics. Later, the NTA PCR results returned also obtained positive for *Mycoplasma pneumoniae*.

There were 39 cases (accounting for 58.2%) that responded well to the initial antibiotics. The remaining 41.8% needed to change/add antibiotics. With the initial antibiotics, C3G + azithromycin had a relatively good response rate (accounting for 81.2%) that only 6 cases had to change/add antibiotics. The antibiotics used were then based on NTA PCR results. The rate of antibiotic response after changing/adding is quite high (92.9%). There were 25 modified/added antibiotics, 3 empirical cases (1 case of negative NTA PCR result and 2 cases of tuberculosis with initial negative PCR NTA). With 25 modified/added antibiotics by agents, 100% responded well. In 3 cases of modified/added empirical antibiotics, there were 2 unresponsive cases, we had

to exchange/add antibiotics for the second time, which were imipenem+ vancomycin (1 case) and azithromycin (1 case). After having the result of PCR positive with *Mycobacterium tuberculosis*, 2 patients were transferred to Pham Ngoc Thach Hospital for treatment.

All 65 children who continued treatment at Children's Hospital 1 were cured, responding well after exchanging/adding antibiotics once. There were no deaths. The average length of hospital stay was 13.11 ± 4.65 days, the shortest was 6 days and the longest was 24 days. Most patients had a hospital stay <14 days (65.7%).

Discussion

The most common age group was 3-7 years old, less common in children <12 months old. This result was similar to the study of Tuan Minh Dao at the Respiratory Department of National Hospital of Pediatrics, the age of lobar pneumonia was also mostly from 3 to 7 years old (accounted for 61.76%) and rarely seen in children <1 year old (accounted for 5.88%) [9,10]. Thi Yen Dinh's study at Hai Phong Children's Hospital recorded the most common age of lobar pneumonia from 2 to 5 years old (accounted for 69.8%) [11]. Our result was also consistent with the literature on common pneumonia in children >3 years old; while community-acquired pneumonia was generally more common in children <5 years of age, most <3 years old, of which children <12 months of age were the majority [12]. In the study sample, the incidence of boys and girls was almost equal. Many studies of child community-acquired pneumonia generally reported the male:female ratio >1. However, there was not enough evidence to confirm this difference [13].

Cough was the most common symptom found in our research (100% of cases), which is also considered as high sensitivity and specificity for children with pneumonia [14]. Fever was also a common symptom in pneumonia, with a sensitivity of 95.5%. However, fever was a symptom of many diseases, so the specificity was not high. Wheezing symptoms in our study were quite high (44.8%) compared to studies of Levine OS (24.0%) [15], Pio A (25.3%) [16]. With a chest radiograph, in our research sample, the common lesion position was the right upper lobe (38.8%). The result of Minh Tuan Dao also noted mainly inflammation of only one lung lobe (88.24%), where the most common lesion was the right upper lobe (44.29%) [9]. Yen Thi Dinh's study also noted that the right lesion was the majority (81.0%), the most common was the right lung lobe (30.2%) [11]. This was a clear difference in the location of centralized lesions in different lung lobes.

At the Nam Khoa Biotek Laboratory, we performed NTA real-time PCR. The result was 97.0% positive. The sensitivity and specificity of PCR had been proven very high in many studies (>90.0% for both sensitivity and specificity) [8,17]. Whereas screening, transplanting has been used prevalently, in our research, the results returned were not very optimistic, all negative compare to PCR had 64 positive cases. Although this technique was not yet available clinically, PCR showed considerable promise in diagnosing pneumonia pathogens especially atypical pneumonia. Through the results of isolation of bacterial pathogens causing lobar pneumonia, we recorded *Mycoplasma pneumoniae* accounted for the highest proportion of 69.7%. In both the mono-infected and co-infected groups, *Mycoplasma pneumoniae* was still the major pathogen, followed by *Streptococcus pneumoniae*. This result was different from previous studies of lobar pneumonia. According to Yen Thi Dinh's study, the common agent causing lobar pneumonia was *Streptococcus pneumoniae* (50.0%) [11] and to Tuan Minh Dao were *Staphylococcus aureus* (38.09%) and Streptococcus pneumonia (28.57%) [9]. *Streptococcus pneumoniae* was also recognized as the leading agent of lobar pneumonia in many other studies and therefore, lobar pneumonia was also called "pneumococcal pneumonia" [12]. However, to other authors, isolation agents based on the results of culture translated nasopharyngeal, swabbed translation endotracheal [11] or broncho-alveolar lavage fluid by means of bronchoscopy [9]. Our study was based on NTA PCR.

Overall, 67 research samples, 58.2% of children responded well to the initial antibiotic. The failure rate of initial antibiotic treatment for community-acquired pneumonia varied depending on the study, subjects, time, and region. The problems of antibiotics in the Macrolide group were increasingly concerned and its effectiveness was still controversial. According to Ambroggio L, the use of β lactam combined with the Macrolide group on community-acquired pneumonia generally helped to shorten the hospital stay by 20.0% [18]. In Switzerland, it was recommended that additional Macrolide be the next choice for community pneumonia of all ages if there was no response to initial β-lactam antibiotics or severe cases [19]. As for our research, in the initial antibiotics, C3G + azithromycin had a relatively good response rate (81.2%). Only 6 cases have to change/add antibiotics. The rate of antibiotic response after the first changing/adding with 28 cases was quite high (92.9%). With 25 changed/added antibiotics by agents, 100% responded well. This further showed the role of PCR in the diagnosis and treatment of infections, specifically pneumonia.

On the other hand, our study also has some difficulties during the process. NTA specimens can only be stored in the refrigerator after taken if not for instant used, but not for more than 2 hours. Then they were delivered to Nam Khoa Biotek lab, which is then we cannot monitor those specimens' progress. However, Nam Khoa Biotek has the best medical lab in Vietnam that is certified, so the result is trustworthy.

According to the regimen of the Ministry of Health in Vietnam, when we approach children under 5 suspected of having pneumonia, adding antibiotics C3G and azithromycin initially is essential [20]. Usually, the common pathogen causing pneumonia is *Streptococcus pneumoniae*, so the process then continually treats as one. If the patient responded well, the process would keep working out, however, if not, then we check PCR or other clinical. Nevertheless, if the pathogen is *Mycoplasma pneumoniae*, the method of treatment would be completely different, which reduces the time of hospital admission. However, the treatment for *Mycoplasma pneumoniae* is considered for children over 5 years old [20]. Therefore, we were surprised by our result, but research of You-Sook Youn

showing that the age of pneumonia-causing by *Mycoplasma pneumoniae* was also from 4-6 years old, and the age turned to be rejuvenescent. In the world, many pneumonia cases causing by *Mycoplasma pneumoniae* were recorded [21,22] and also having many pieces of research describe [23-25].

Conclusion

Lobar pneumonia can be diagnosed by clinical examination and chest X-ray. Real-time PCR efficient supported in causative pathogens quickly and accurately, guided effective antibiotic therapy, especially in cases of poor clinical responses. Additionally, *Mycoplasma pneumoniae* was found in a younger group of age than the usual group.

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