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NATIONAL INSTITUTE OF MALARIOLOGY – PARASITOLOGY AND ENTOMOLOGY

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STUDY OF SEVERAL EPIDEMIOLOGICAL, CLINICAL CHARACTERISTICS AND EVALUATION OF PNEUMOCOCCAL PNEUMONIA IN CHILDREN AT THE VIETNAM NATIONAL CHILDREN'S HOSPITAL (2015- 2018)

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INTRODUCTION

Streptococcus pneumoniae is the leading reason of pneumonia in children under 5 years of age [45], [63], the pneumococcal pneumonia cases occupy 27% to 61.7% pneumonia cases diagnosed by mammography [20], [28], [34]. Pneumococcal pneumonia is the most serious form of pneumonia in children who must receive first aid in hospital [75], [76]. The death cases caused by pneumococcal pneumonia occupy 55.8% death cases caused by pneumonia [40] and 81% death cases caused by Streptococcus pneumoniae in children less than 5 years of age [66]. In 2015, the Streptococcus pneumoniae caused around 12.4 million pneumonia cases and 318,000 death cases in children less than 5 years of age [66]. Streptococcus pneumoniae is becoming less and less sensitive and becomes completely resistant to penincillin, gradually appears the species against one or more kinds of different vaccines [74].

In Vietnam, the disease burden of pneumonia is still high, it was ranked the 9th position among 15 nations which had the highest disease burden of pneumonia in 2008, and it was estimated 2.9 million cases and 0.35 pneumonia seasons / children less than 5 years of age/ year [59]. Streptococcus pneumoniae is the top-ranking reason of pneumonia in children less than 5 years of age in Vietnam [6], [9], [17].

We conduct the thesis's title: "Study of several epidemiological, clinical characteristics and evaluation of pneumococcal pneumonia in children at the Vietnam National Children's Hospital" aiming at the research targets, as follows:

1. Identifying several epidemiological, clinical characteristics and associated factors of children with pneumococcal pneumonia treated at the Vietnam National Children's Hospital (2015 – 2018).

2. Describing the clinical, paraclinical characteristics and antibiotic resistance of streptococcus pneumoniae in children with pneumococcal pneumonia.

3. Evaluating the pneumococcal pneumonia treating results in children.

STRUCTURE OF THESIS

The thesis covers 123 pages, including: Introduction of 2 pages; Overview of 36 pages; Research method of 23 pages; Research results of 33 pages; Discussion of 26 pages; Conclusion of 2 pages; Petition of 1 page. The thesis includes 20 figures, 39 datasheets, 201 references, including 65 documents for 5 recent years.

SCIENTIFICITY, NOVELTY, APPLICABILITY

Scientificity

The research thesis is designed according to standard scientific research methods applied broadly in Vietnam and over the world. This is the method describing the series of concurrent cases, apalyzing, evaluating the treatment intervention solutions.

The signs and clinical standards are evaluated by the Ph.D student and pediatricians with major of respiration at the Vietnam National Children's Hospital.

The testing technologies applied to identify the research index are modern technologies and laboratories satisfying ISO standard.

The thesis uses the standard and reliable encoding methods, data importing and processing methods bcased on specialized statistical software, such as Epidata, SPSS, STATA, consequently the results have high reliability.

Novelty, applicability

The result of thesis is the first time of researching sufficiently and systematically the pneumococcal pneumonia in children in Vietnam, including the epidemiological, clinical, paraclinical characteristics and associated factors and evaluating the treatment and intervention results. The research results are the scientific foundation to help diagnose timely, treat and prevent from disease, in order to decrease the patient prevalence and death ratio of streptococcus pneumonia in children.

Identifying the sensitiveness of streptococcus pneumoniae against antibiotic by identifying MIC, MIC50, MIC90, which is the base to select antibiotic and directions for use it in treating streptococcus pneumonia in children.

Chapter 1:
OVERVIEW

Streptococcus pneumoniae is discovered and promulgated in 1881 by Louis Pasteur (in France) and Gorge Miller Sternberg (in America), it is the gram positive diplococcus in form of egg, scimitar blade or candle, immobile and dimension of 0.5 to 1 μm. Streptococcus pneumoniae has the polysaccarid cover, specific characteristics in each type are the decisive factor of antigen and virulence of bacteria [74], currently 100 serum types of streptococcus pneumoniae have been discovered. Sensitive to optochin and soluable in bile salt are two basic properties to distinguish streptococcus pneumoniae with other streptococci viridians [5]. Streptococcus pneumoniae is a bacterium residing permanently in nose and throat of human without symptoms, however, it is able to penetrate and cause diseases thanks to virulent factors as cover, wall, pneumolysin, autolysin, surface proteins, feather, hydrolytic enzymes and able to create its biological film.

Pneumococcal pneumonia is a popular disease and is the top-ranking death reason in children under 5 years of age over the world. The clinical manifestations of pneumococcal pneumonia in children happen suddenly and animatedly. They frequently have high fever and admit poorly. Their whole states are changed. When radiographing, the injuries of lung appear late, thus it is difficult to diagnose and treat. There are complications as Pleural Empyema, lung abscess, pleural effusion, septicemia and leading to death if they are not diagnosed early and treated timely [52], [73]. On the other hand, the streptococcus pneumoniae is reducing the sensitiveness and totally resistant to penicillin, the species resistant to one or more other antibiotic kinds gradually appear [74]

Chapter 2:
RESEARCH OBJECT AND METHOD

2.1. Research object and method of target 1: Identifying several epidemiological, clinical characteristics and associated factors of children with pneumococcal pneumonia treated at the Vietnam National Children's Hospital (2015 – 2018).

2.1.1. Research object, place and time

- Research object: Pediatrics with pneumococcal pneumonia from 1 year to 5 years of age.
- Research place: Respiratory Department of Vietnam National Children's Hospital.
- Research time: from January 2015 to December 2018.

2.1.2. Research method

2.1.2.1. Research design

The descriptive research of concurrent case series in researching the epidemiological, clinical characteristics and the cross-sectional descriptive research with analysis in identifying the associated factors of pneumococcal pneumonia in children.

- *Size of research sample:* Applied for descriptive research to identify the current pneumococcal pneumonia prevalence in children [10], [11].

$$n = Z^2_{1-\alpha/2} \frac{1-p}{p.\varepsilon^2}$$

In which:

n: is the minimal research sample's size required; $Z_{(1-\alpha/2)}$: is the reliability factor depending on statistical meaning level of selected α. We select α =0,05, the value of $Z_{1-\alpha/2}$ =1,96, with reliability 95%; p: current prevalence of pneumococcal pneumonia (%) estimated at the research time. In this study, we use the value p = 0,313 (p = 31,3%), according to the study of Dao Minh Tuan and al et., in 2012 [14]; ε: is the relative error desired. We select ε = 0,15. Applying the formula stated above, we have n = 374

In the study, 375 children with pneumonia are researched.

Way of selecting samples into study: Taking all children with pneumonia qualified to select into research sample based on daily hospital admission records.

- Research contents

+ Identifying the prevalence of patients, the distribution of epidemiological characteristics of pediatrics, as age, sex, ethnic group, geography, vaccination history, antibiotic using history and etc.

+ Among associated factors of pneumococcal pneumonia, we only analyze and compare the simple pneumococcal pneumonia and pneumonia caused by other popular bacteria discovered by positive culturing method (other bacteria) including pneumonia caused by simple *Haemophilus influenza* and pneumonia caused by simple *Moraxella catarrhalis.*

2.2. Research object and methods

2.2.1. Research object, place and time

- Research object: The pneumonia children are identified as caused by *Streptococcus pneumoniae* by Realtime PCR method of pleural solution, growing and cultivating bacteria by identification colony's morphology and properties, from 1 month to 5 years of age.

- Research place: Respiratory Department of Vietnam National Children's Hospital.

- Research time: From January 2015 to December 2018.

2.2.2. Research method

- Research design: The descriptive research of concurrent case series in researching the epidemiological, clinical characteristics of pneumococcal pneumonia in children. Non-control intervention study aims at evaluating the pneumococcal pneumonia treating results in children.

- Size of research sample: Selecting all pediatrics objects diagnosed as pneumococcal pneumonia, treated according to protocol of Ministry of Health.

- Research contents

+ Study of clinical characteristics: Identifying the distribution of symptoms of disease.

+ Study of paraclinical characteristics: Testing and analyzing the peripheral blood cells, CPR, X-ray of hear and lung, having the ultrasound scan of pleura, microbiological test, molecular biological test of several infectious diseases, identifying the antibiotic sensitiveness of streptococcus pneumoniae.

+ Evaluation of treatment results

Appointing the initial antibiotic according to protocol of Ministry of Health, changing antibiotic according to Antibiotic susceptibility test or according to happenings of disease.

Supervising the clinical, paraclinical manifestations during the process of treating and re-evaluating the time ò being discharged from hospital.

Treatment time and disease prognosis time…

2.3. Techniques used in researching

- Clinical examination technique for pediatrics: The clinical examination is done according to standard procedure, identified by at least 2 doctors of pediatric respiration.

- Identifying the hematological and biochemical index: Testing and analyzing the peripheral blood cells and C reactive protein (CRP).

- Hear and lung radiography: Scanned by Care Tream X-ray machine.

- Ultrasound scanning of lung, pleura: Philips ultrasound machine when having any doubts of pleural effusion.

- Computed tomography scan: Siemens 128 computed tomography scan machine.

- Growing and cultivating bacteria from nasopharyngeal solution by quantitative cultivating method.

+ The specimens are taken according to technical procedure, taking the nasopharyngeal solution for testing at the Vietnam National Children's Hospital (QTKT.ĐD.001.V1.0 and QTKT.ĐD.001.V2.0)

+ The nasopharyngeal solution is cultivated according to QTXN.VS.007.V3.0 procedure, staining Gram according to Gram staining procedure QTXN.VS.024, identifying bacteria by automatic system VITEK MS according to QTXN.VS.160 procedure.

- Blood culture for finding bacteria.

+ The specimens are taken according to blood taking procedure QTKT.ĐD.025.V1.0

+ Result identifying and cultivating technique follows the procedure QTXN.VS.010.V3.0.

- Antibiotic susceptibility testing technique: is done according to procedure QTXN.VS.161

- Real time PCR technique aims at finding bacteria in plenral solution: According to procedure of Department of Molecular Biology Researching for infectious diseases (HDSD.PT.002.V1.0).

2.4. Research index

2.4.1. Researching the epidemiological characteristics

Exploiting the epidemiological factors; Obstetrical history, feeding history, vaccinating history, developing history: spirit, exercise, history of diseases, history of using drugs before being hospitalized, history of family, time of disease before being hospitalized.

2.4.2. Identifying several factors related to pneumococcal pneumonia

- Relation between diseases associated and pneumococcal pneumonia

- Relation between nutrition and vaccination situations and pneumococcal pneumonia

- Relation between being infected by virus at the same time and pneumococcal pneumonia

2.4.3. Researching the clinical characteristics

- Signs of whole body: situation of consciousness, weight, height, breathing rate, pulse, temperature, oxygen saturation level through skin (SpO2).

- Symptoms of respiratory organs: cough, fast breathing, rale in lung, sound shaking changes, thorax concave.

- Signs apart from respiration: anemia, gastrointestinal disorder, cardiovascular disorder, nervous manifestations (nape stiffness, stimulus or fast asleep, lethargic)

- Disease happening evaluation index: Time of disease, antibiotics used before being hospitalized, antibiotics used during the process of hospitalization, disease progress (recovering totally from illness, recovering with complications, death)

2.4.4. Researching the paraclinical characteristics

- Peripheral blood cell analysis, CRP

- Hear and lung radiography

- Ultrasound scanning of lung, pleura: pulmonary solidification, pleural effusion.

- Computed tomography scan for thorax

- Identification of bacteria

+ Cultivating quantitatively the positive nasopharyngeal solution, identifying by automatic machine.

+ Cultivating the positive blood, cultivating the positive nasopharyngeal solution, and then identifying by automatic machine.

+ RealTime PCR test for identifying whether positive with streptococcus pneumoniae

- Sensitiveness of streptococcus pneumoniae is read on automatic antibiotic susceptibility testing machine.

2.4.5. Evaluating the treating results when discharged from hospital

Based on signs of whole body as awareness, temperature, food absorbing ability and respiratory symptoms as breathing rate, breathing hard, pulling the respiratory muscles, oxygen using demand, SpO_2, and based on diphtheria tests, CRP, lung radiography.

- Recovering from illness: The pediatrics is of sound mind, eating and drinking well, no fever for at least 3 days, breathing normally, no cough, normal white blood cells and normal CRP, lung radiography becomes normal, no antibiotics when discharged from hospital, no after-effect.

- The disease reduces when improving the clinical and paraclinical symptoms, but does not belong to standard of recovering from illness, the pediatrics is of sound mind, eating and drinking well, he can be supervised and cared at home, continuing to use antibiotic in form of drinking when discharged from hospital, no after-effect.

- The after-effect of thick pleura when discovering by ultrasound scanning of pleura.

- Death: During the treating process, the pediatrics is dead.

- Classification of results according to treatment time and several factors related to treatment time $\geq$ 14 days.

2.5. Tools used in researching

Clinical records researched and software EpiData, Stata 10, SPSS 20.

2.6. Errors and constraining methods

They include the measurement errors, identifying symptoms, sample selecting errors, symptom identifying errors, recalling errors and interfering factors as seriousness degree and treatment time of disease, age of pediatrics. Error limitation: Complying with patient selecting standards, sample sizes according to calculation….

2.7. Date processing and analyzing methods

The data are inputted and analyzed by modern and reliable software, as: Stata 16.0, SPSS, using audits χ^2, Fisher exact test used to compare the ratios. The statistical audits are done with meaningful level 5%; Odds Ratio- OR; Exact test Fisher's

2.8. Ethics in researching

- The researched objects are informed and explained clearly about purposes, rights and responsibilities when participating into research, they are entitled to withdraw from research; Ensuring all secrets of patients, only researching the voluntary participants.

- Ensuring secrets of information providers and treatment results.

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- The study implementation has been approved by the council of detailed draft examination and ethics in research by National Institute of Malariology – Parasitology and Entomology and Medical Ethics Council of Vietnam National Children's Hospital.

Chapter 3:
RESEARCH FINDINGS

3.1. Epidemiological characteristics and associated factors of pneumococcal pneumonia

3.1.1 Epidemiological and clinical characteristics of children with pneumococcal pneumonia

- Among 375 cases diagnosed as pneumococcal pneumonia by clinical and mammography, there are 165 pneumonia cases caused by simple streptococcus pneumoniae, occupying 44%, pneumonia cases caused streptococcus pneumoniae suffered simultaneously with virus occupy 4%.

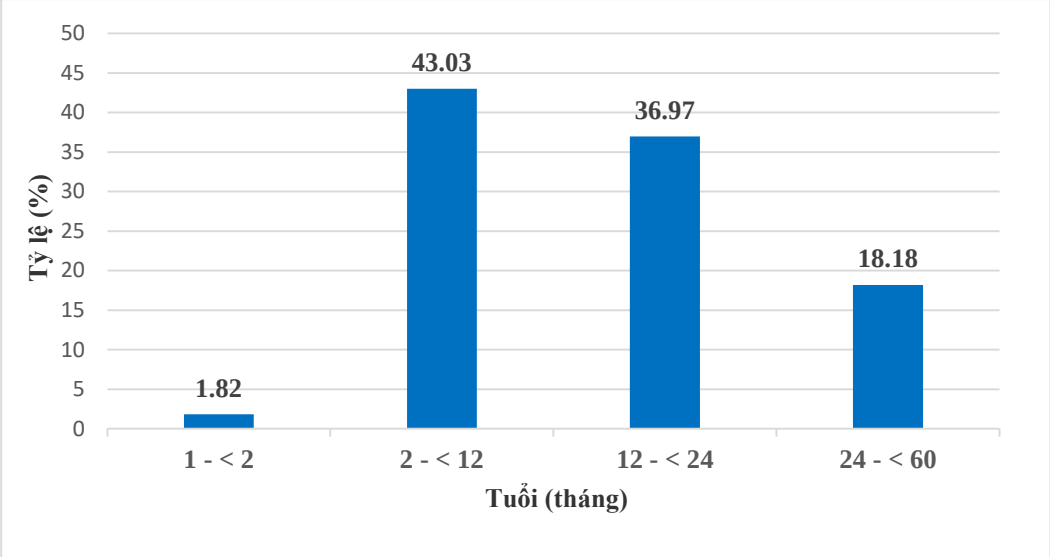

Figure 3.1: Distribution of children with pneumococcal pneumonia based on age (n=165)

- The pneumococcal pneumonia ratio is highest in the group of children from 2 months to less than 12 months of age, and then it decreases gradually.

- The number of male children with pneumococcal pneumonia are higher than female, the male occupies 65%, the female occupies 35% (male/ female ratio is 1.89/1).

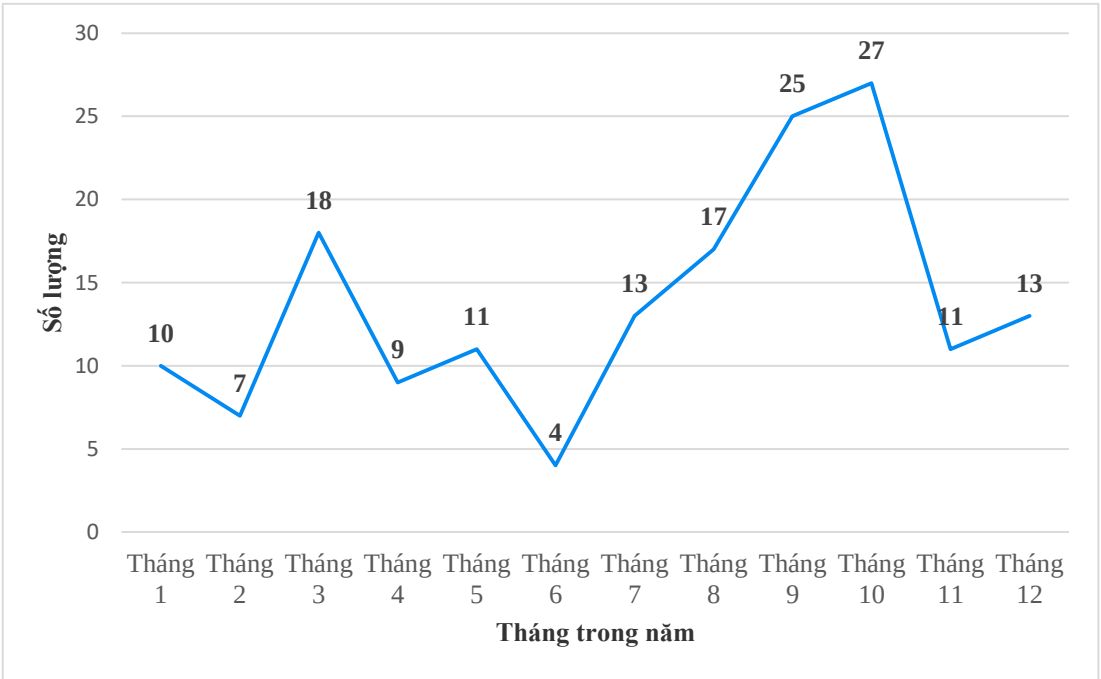

Figure 3.3: Distribution of pneumococcal pneumonia based on months in year (n=165)

Children are infected by pneumococcal pneumonia the most easily in October, and then in March, from April to July, this disease is more difficult to infect.

The children in urban areas are easier to catch pneumococcal pneumonia than children in rural areas; the ratio between urban/ rural is 2.8/1.

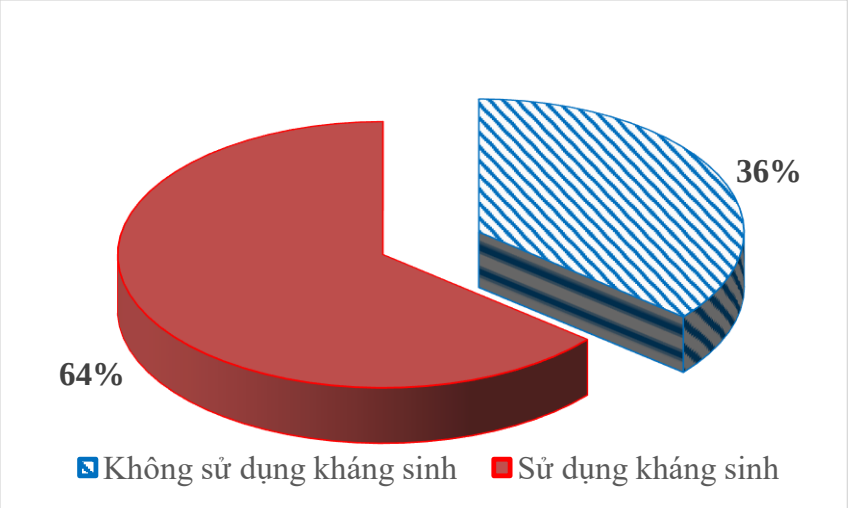

Figure 3.5: Ratio of antibiotic using before being hospitalized (n= 165)

Among children with pneumococcal pneumonia admitted to hospital for treating, there are 64% children used antibiotic before being hospitalized.

Table 3.10: History of immunization (n=165)

Kind of vaccine		VPPC	
		Number	Ratio (%)
Expanded immunization	Sufficient	108	65,45
	No	57	34,55
Streptococcus pneumonia conjugate vaccine	Yes	9	5,45
	No	156	94,55

Children with pneumococcal pneumonia with insufficient immunization ratio are still high, occupying 34.55%, only 5.45% children are immunized by streptococcus pneumonia conjugate vaccine.

3.1.2. Several factors associated with pneumococcal pneumonia in children

Table 3.16: Relation of several environmental factors and pneumococcal pneumonia

Factors	Pneumococcal pneumonia		Other pneumonia		OR; 95%CI	p
	Number	Ratio %	Number	Ratio %		
Smoke & dust						
Yes	51	30,91	15	24,59	1,37; 0,72-2,73	0,321
No	114	69,09	46	75,41		
Tobacco						

Yes	90	54,55	24	39,34	1,85; 1,11- 3,34	**0,043**
No	75	45,45	37	60,66		
Breeding dogs and cats						
Yes	72	43,64	15	25,00	2,32; 1,18- 4,41	**0,013**
No	93	56,36	45	75,00		
Contacting with collective environment						
Yes	52	31,52	21	34,43	0,88; 0,57- 1,96	0,855
No	113	68,48	40	65,57		
Cooking by gas stove						
Yes	149	90,30	48	78,69	2,52; 1,09- 5,34	**0,025**
No	16	9,70	13	21,31		

- The factors associated with pneumococcal pneumonia include: Contacting with tobacco smoke OR = 1,85 (95%CI: 1,11- 3,34, p < 0,05). Families breed dogs/ cats OR = 2,32 (95%CI: 1,18- 4,41, p < 0,05); Cooking by gas OR = 2,52 (95%CI: 1,09- 5,34, p< 0,05).

3.2. Clinical and paraclinical characteristics and antibiotic resistance in children with pneumococcal pneumonia

3.2.1. Clinical characteristics of pneumococcal pneumonia in children

Table 3.18: Mechanical energy symptoms of pneumococcal pneumonia

Mechanical energy symptom		Pneumococcal pneumonia	
		Number	Ratio (%)
Fever		148	89.70
Fever degree	Slight	15	9,09
	Medium	64	38,79
	High	69	41,82
Cough		157	95,15
Runny nose		150	90,91
Cyanosis		21	12,73
Rale breath		8	4,85
SpO_2 (%)	< 90	9	5,45
	90 - 93	11	6,67
	≥ 94	145	87,88

Cough is the symptom occupying the highest ratio (95.15%), fever (89.70%), runny nose (90.91%), cyanosis 12.73% and rale breath occupies 4.85%. SpO_2 under 90% occupies 5.45%, from 90% - 93% occupying 6.67%.

Table 3.20: Actual symptoms of pneumococcal pneumonia

Symptom	Pneumococcal pneumonia	
	Number	Ratio (%)
Moist/ dry rales	133	80,61

Rhonchus	85	51,52
Sibilant rale	23	13,94
Chest concave withdraw	103	62,42
Solidification syndrome	6	3,64
3 reduction symptom	3	1,82

When examining lung, we recognize the moist/ dry rales as actual symptom occupying the highest ratio (80.61%), chest concave withdraw (62.42%), rhonchus (51.52%), solidification syndrome (3.64%) and 3 reduction symptom occupies 1.82%.

3.2.2. Paraclinical characteristics of pneumococcal pneumonia in children

Table 3.21: White blood cell, CRP results of pneumococcal pneumonia (n=165)

Blood testing		**Pneumococcal pneumonia**	
		Number	**Ratio (%)**
White blood cell	Normal	13	7,88
	Increase	152	92,12
CRP	Normal	54	32,73
	Increase	111	67,27

For pneumococcal pneumonia in children, the increase of white blood cell in blood occupies very high ratio (occupying 92.12%), the increase of CRP occupies 67.27%.

Table 3.22: Image of damage on lung radiography

Image of damage on lung radiography	**Pneumococcal pneumonia**	
	Number	**Ratio (%)**
Image of bronchopneumonia	132	80,00
Image of lobar pneumonia	33	20,00
Image of pleural effusion	8	4,85

The image of damage on lung radiography for pneumococcal pneumonia in children include the images of bronchopneumonia occupy the highest ratio, the images of lobar pneumonia occupy 20%. The images of pleural effusion are the complication images of pneumococcal pneumonia only occupy 4.85%.

3.2.3. Antibiotic resistance of streptococcus pneumoniae

Table 3.24: Antibiotic sensitiveness of streptococcus pneumoniae

Antibiotic group	**Antibiotic name**	**Number**	**Sensitive**	**Intermediate**	**Resistant**
			Number (%)	**Number (%)**	**Number (%)**
Penicillin	Penicillin G	132	58 (43,9)	74 (56,1)	0 (0)
	Penicillin V	132	5 (3,8)	30 (22,7)	97 (73,5)
	Amoxicillin	40	38 (95)	1 (2,5)	1(2,5)
Cephalosporin	Cefotaxim	162	93 (57,4)	43 (26,5)	26(16,1)
	Ceftriaxon	162	99 (61,1)	30 (18,5)	33 (20,4)
Macrolid	Azithromycin	154	3 (1,9)	1 (0,7)	150(97,4)
	Clarithromycin	68	1 (1,5)	0 (0)	67 (98,5)
	Erythromycin	159	5 (3,1)	0 (0)	154 (96,9)
Sulfamid	TMP/SMX	100	9 (9)	1 (1)	90 (90)

Rifampin	Rifampycin	45	45 (100)	0 (0)	0 (0)
Phenicol	Chloramphenicol	100	81 (81)	0 (0)	19 (19)
Cyclin	Tetracyclin	64	17 (26,6)	0 (0)	47(73,4)
Glycopeptid	Vancomycin	162	162 (100)	0 (0)	0 (0)
Oxazolidinon	Linezolid	62	62 (100)	0 (0)	0 (0)
Quinolon	Levofloxacin	162	161 (99,4)	0 (0)	1 (0,6)
	Ofloxacin	98	98 (100)	0 (0)	0 (0)
Lincosamid	Clindamycin	64	3 (4,7)	0 (0)	61 (95,3)

streptococcus pneumoniae is able to:

Resist antibiotic of macrolid group (94.4% with azithromycin, 98,53% with clarithromycin and 96,86% with erythromycin), 89.8% resist trimethoprim/sulfamethoxazon, 95.31% resist clindamycin, 73.44% resist tetracyclin, 19% resist chloramphenicol;

Nonsensitive with penincillin G, 73.48% resist penicillin V; 95% are sensitive with amoxicillin, 100% are sensitive with rifampycin, linezolid, vancomycin. The sensitiveness decreases for cephalosporin antobiotics, the third generation (C3G):

3.3. Treatment intervention results

3.3.1. State of pediatrics after treatment

Table 3.32: State of pediatrics when being discharged from hospital (n=165)

Result	Number	Ratio (%)
Recovering	138	83,64
Reducing	23	13,94
Pleural after-effect	4	2,42
Total	165	100

Treatment result: 2.42% pleural after-effect; 13.94% reduction, 83.64% complete recovery. In our study, there is no dead pediatrics or withdrawing.

3.3.2. Treatment time

Table 3.33. Treatment time

Time		Slight pneumococcal pneumonia	Serious pneumococcal pneumonia	p
		Number (%)	Number (%)	
Average treating days ± SD		10,23 ± 5,81		
		8,56 ± 4,11	11,04 ± 6,34	**0,009**
Median		7	9	
Treatment time (week)	< 1	24 (45,28)	22 (19,64)	**0,003**
	1 - < 2	25 (47,17)	67 (59,82)	
	2 - < 3	4 (7,55)	14 (12,50)	
	≥ 3	0 (0)	9 (8,04)	

The difference has the statistical meaning between serious pneumococcal pneumonia and slight pneumococcal pneumonia groups (11.04 ± 6,34 days in comparision with 8,56 ± 4,11 days with $p < 0,05$).

3.3.3. Several factors related to long-time treatment results ≥ 14 days

Table 3.37: Paraclinical results and long-time treatment time

Paraclinical results		Treating ≥ 14 days	Treating < 14 days	P	OR; 95%CI
		Number (Ratio)	Number (Ratio)		
Number of white blood cell	Increase	30 (19,74)	122 (80,26)	0,41	-
	Normal	3 (23,08)	10(76,92)		
Aneamia	Yes	18(26,87)	49(73,13)	**0,03**	2,03; 1,09-5,14
	No	15 (15,31)	83 (84,69)		
CRP (mg/l)	≥ 60	8 (21,62)	29 (78,38)	0,99	-
	< 60	25 (19,53)	103 (80,47)		
Lung radiography	Lobar pneumonia	9(27,27)	24 (72,73)	0,35	-
	Bronchopneumonia	24 (18,18)	108 (81,82)		
	Pleural effusion	6 (75,00)	2 (25,00)	**0,0003**	14,4; 1,8-60,55
	No pleural effusion	27(17,20)	130(82,80)		

The children with pneumococcal pneumonia who have the images of pleural effusion on lung radiography have the risks of long-time treatment ≥ 14 days, 14.4 times as high as children with pneumococcal pneumonia without images of pleural effusion on lung radiography (95%CI: 1,8- 60,55, p= 0,0003).

Table 3.38: Antibiotic resistance and treatment time

Antibiotic	Treatment time ≥ 14 days	Treatment time < 14 days	P	OR; (95%CI)
	Number (Ratio)	Number (Ratio)		
Ceftriaxon				
Resistant	12 (33,66)	21(63,64)	**0,002**	4,33 (1,71-10,99)
Intermediate	9 (30,00)	21 (70,00)	**0,01**	3,25 (1.21- 8,71)
Sensitive	11 (11,11)	88 (88,89)		
Cefotaxim				
Resistant	11 (42,31)	15 (57,69)	**0,001**	5,73 (2,11-15,58)
Intermediate	11 (25,58)	32 (74,42)	**0,03**	3,69 (1,06- 6,81)
Sensitive	10 (10,75)	83 (89,25)		
Multi-bntibiotic resistance of streptococcus pneumoniae				
Yes	22 (20,37)	86 (79,63)	0,913	-
No	11 (19,30)	46 (80,70)		

The pneumococcal pneumonia resistant to ceftriaxon has the treatment time ≥ 14 days, it is 4.33 times as high as pneumococcal pneumonia sensitive to ceftriaxon (95% CI: 1,71-

10,99; p< 0,005); The pneumococcal pneumonia resistant to cefotaxim has the treatment time ≥ 14 days, it is 5.73 times as high as pneumococcal pneumonia sensitive to cefotaxim (95% CI: 2,11-15,58; p< 0,005).

Chapter 4:
DISCUSSION

4.1. Epidemiological, clinical characteristics and associated factors of children with pneumococcal pneumonia

4.1.1 Epidemiological, clinical characteristics

- Ratio of pneumococcal pneumonia in children

Through analyzing the collected data, we recognize that among 375 cases diagnosed as pneumonia by clinical and lung radiography, there are 165 cases with pneumonia caused by simple streptococcus pneumoniae, occupying 44%, it is the leading reason of pneumonia in children under 5 years of age. The prevalence of pneumococcal pneumonia in children from 2 months to 12 months of age is 50%, it in children from 12 months to 24 months is 48.41% and it in children from 2 months to 24 months of age is 49.25%.

Nguyen Van Bang and et al (2009), study of pneumonia in children treated at Department of Pediatrics, Bach Mai Hospital, showing that pneumococcal pneumonia in children occupies 58.8% [4].

Dao Minh Tuan and et al (2012), study of cause and antibiotic resistance degree of bacteria causing pneumonia in children from 1 month to 5 years of age at the Vietnam National Children's Hospital, the ratio of pneumococcal pneumonia is 31.3% [14].

Thomas Bénet and el at, the case-control, multi-center prospective study identifies the microorganisms related to pneumonia in children < 5 years in developing countries and emerging countries with low PCV covering ratio from May 2010 to June 2014, it shows that the pneumococcal pneumonia occupies the highest ratio (42.4%), in which the children from 2 months to 12 months of age with pneumococcal pneumonia occupy 50%, the children from 12 months to 24 months of age with pneumococcal pneumonia occupy 48.8% [23].

In pneumonia in children, streptococcus pneumoniae is the reason occupying the highest ratio in different studies at different times and places over the world. In our country and other countries with very low conjugate streptococcus pneumoniae vaccine coverage, the prevalent of pneumococcal pneumonia is still high, in vice versa, in countries where the streptococcus pneumoniae preventing vaccine is put in expanded immunization program, the prevalence of pneumococcal pneumonia in children decreases, the ratio of streptococcus pneumoniae in community decreases and the ratio of infectious diseases caused by streptococcus pneumoniae, including pneumonia, bacterial contamination of blood and purulent meningitis [32]. Our research findings are lower than almost research findings inside country, equivalent to research findings of author Thomas Bénet and et al., in developing and emerging countries the PCV covering ratio is low.

- Distribution of pneumococcal pneumonia

The research findings show that the pneumococcal pneumonia in children from 2 months to 1 year of age occupies the highest ratio, occupying 43.03%, it in children from 1 to 2 years of age occupies 36.97%, in children from 2 to 5 years of age, cases occupy 18.18%. Therefore, the pneumococcal pneumonia in children in our study decreases gradually according to age.

Zhao W. and et al., study from January to December 2018 in Shanghai, China had collected that among 243 children with pneumococcal pneumonia, there are 20.2%

children under 1 year, 27.2% children from 1 year to 2 years of age, 43.2% children from 2 years to 5 years of age and 9.5% children from 5 years of age and above. All of these pediatrics have been not immunized the conjugate streptococcus pneumoniae vaccine [69].

The data collected from Institute for Health Metrics and Evaluation (America, 2016), show that pneumococcal pneumonia occupies the highest ratio in children less than 1 year of age and it decreases gradually to 14 ages [78].

Our research findings are suitable to research findings of Institute for Health Metrics and Evaluation in America.

Streptococcus pneumoniae is a germ exploiting the hosts with underdeveloped, weakened or declined immune system. Thus, the the ratio of children with pneumococcal pneumonia is higher, weakened immune system and old people [25]. Awareness of immune system changed under age is important in providing the disease prevention methods to prevent from invation and pathogenic of streptococcus pneumoniae.

- *Distribution based on sex*

Through result analysis, we see that the male children with pneumococcal pneumonia are higher than female, male children occupy 65%, female children occupy 35% (ratio of male/ female is 1.89/1).

Our research findings are suitable to many studies on sex in pneumococcal pneumonia in children, the authors conclude that the prevalance of pneumococcal pneumonia in boys is higher than girls. The study of author Zhao W and al et., shows that the boys occupy 55.6%m girls occupy 44.4% [69]. The other study of Kang Cai and al et., was conducted from 2008 to 2018 in Lanzhou and Shanghai on pneumococcal pneumonia in children showed that boys occupied 72.5%, girls occupied 27.5^ (male/ female = 2.6/1) [27]. For explaining why the prevalence of pneumococcal pneumonia in boys higher than girls, Gubbels Bupp M. R. thinks that the concentration of genital hormone can affect the sensitiveness with infectious diseases. The estrogen receptors are found in many immune cell kinds, including cell T, cell B, dendritic cell and macrophage. In addition, the behaviors related to sex, contact with infants and children in school age are able to be infected with streptococcus pneumoniae [41]. However, we could research more deeply about role of genital hormone for immune system, behaviors and contacts with environment of children can increase the sensitiveness with pneumococcal pneumonia.

- *Distribution based on seasons, months in year*

The research fidings show that the pneumococcal pneumonia in children is highest in Autumn in October, lower in Winter (November, December and January), it increases in March and lowest in Summer (May, June and July).

According to Zhao and al et., in the study in Shanghai, China, the cases diagnosed in Summer (from June to August) occupies 20.1% lower than other seasons, highest in Spring, occupying 28.4%. This difference has no statistical meaning p=0,992 [69]. Our research findings are suitable to research findings of other authors in which the children are frequently infected from pneumococcal pneumonia in cool seasons, lower in hot seasons and suitable to climate characteristics of Northern Vietnam.

- *Geographic characteristics*

Our research findings present 74% children with pneumococcal pneumonia coming from urban areas, the ratio of urban/ rural is 2.8/1.

The author Cardoso M. R. and al et., study of pneumococcal pneumonia discovered by cultivating blood shows that 90% children with pneumococcal pneumonia come from urban areas [19].

The multinational drug resistance supervision network researches the antibiotic resistance Streptococcus pneumoniae carrying situation in 11 Asian and Middle East countries shows

that the ratio of children carrying Streptococcus pneumoniae insensitive with penicillin in Vietnam is 70.4%, in which living in urban areas is the risk factor with OR=3,75, 95%CI: 2,02-6,94, p<0,005 [51]. In several countries including Vietnam, the ratio of children carrying antibiotic resistance Streptococcus pneumoniae in urban areas is higher than in rural areas.

In urban area, the density of population is denser, they move more thus the capacity of spreading germs through respiratory ways is higher, consequently the prevalence of diseases caused by Streptococcus pneumoniae [26]. On the other hand, the air pollution in urban areas is higher than in rural areas, because the exhaust gas from traffic vehicles cause injuries fro protection barrier, creating good conditions for Streptococcus pneumoniae to reside permanently in respiratory way, invade and cause diseases, it can explain why the prevalence of children with pneumonia in urban areas is higher in rural areas.

- *Antibiotic using state before being hospitalized*

Through surveying the antibiotic using situation, we recognize that the ratio of pediatrics using antibiotic before being hospitalized is 64%, in which macrolid occupy 31%, zinnat 12%, augmentin 10%, and do not memorize names of antibiotic.

According to Nguyen Thi Van Anh and al et., study of children with pneumonia treated inpatient in Department of Pediatrics, Bach Mai Hospital shows that 63% children using antibiotic before being hospitalized [3]. The author Tran ThangTu and et al., study of children with pneumonia caused by *H. influenza* treated in Vietnam National Children's Hospital shows that 72% children using antibiotic before being hospitalized [13]. The other study of author Tran Thi Anh Tho in pneumonia children from 2 months to 5 years of age, the ratio of children using antibiotic before being hospitalized is only 33,1% [12].

- *Characteristics of feeding and immunization history*

+ Thanks to survey of breast feeding, we can see that the ratio of children fed by breast milk totally for 6 first months, the obstetrics with pneumococcal pneumonia only occupy 18.79%. Breast feeding does not only provide the necessary nutrition demand for children's development, but it also provides the antibodies to help children to prevent from infectious diseases. According to the World Health Organization, the ratio of children fed totally by breast feed for six first months is 36%. In Vietnam, this ratio depends on each locality: Rural areas of Thanh Hoa (17%) [38], Hoi An (22.3%) [2].

+ In our study, the result of children fed totally by breast milk for 6 first months is similar to research results inside country, but it is lower than common result of whole world, which has negative impacts on developing the constitutions and immune systems of children and able to increast the risks of pneumococcal pneumonia in children.

+ When surveying the immunization history, we recognize that the ratio of children immunized insufficiently is still high, occupying 34.55%. The ratio of children immunized to prevent from Streptococcus pneumoniae is very low, only 5.45% children immunized by conjugate streptococcus pneumoniae vaccine.

According to UNICEF- Vietnam, the expanded immunization program has succeeded in protected 6.7 million children of Vietnam and preventing 42,000 dead cases caused by fatal diseases in children as diphtheria, whooping cough, paralytic and tetanus. Insufficient expanded immunization leads to risks of pneumonia 1.83 times as high as (95%CI: 1,32-2,52) [43].

4.1.2. Several factors associated with pneumococcal pneumonia

- *Relation of disease history and pneumococcal pneumonia*

Survey of disease history ≥ 03 wheezing stages (recurred wheezing) in infants, asthma in juvenliles, we recognize that the children with history of recurred wheezing, asthma have

the risks of pneumococcal pneumonia 2.09 times as high as children without history of recurred wheezing or asthma (95%CI: 1,10- 4,63, p = 0,04).

The authors over the world, when researching the invasive pneumococcal diseases, we see that asthma is the risk factor of disease: Tamar Pilishvili and et al. (OR: 1.8; 95%CI: 1.5–2.2, p= 0,001) [58]. Stephen I Pelton and et al., the risks of invasive pneumococcal diseases in children under 5 years of age are 3.5 times (95%CI:3.0–4.0) [57]. Byung Ok Kwak and et al., (OR: 2,08; 95%CI: 1,25-3,45, P = 0,005, in 2010 and OR: 3,26; 95%CI: 1,74-6,11; P <0,001, in 2011) [48]. Derek Weycker and et al. (OR: 1,5; 95%CI: 1,1-2) [68].

The authors explain that asthma is the chronic inflammation of respiratory tract, causes the injury of natural immunity barrier of children, creating good conditions for Streptococcus pneumoniae to reside permanently in nose and throat to invade and cause diseases. On the other hands. Using corticoit in forms of drinking or spraying for prevention in long time is the risk factor of invasive pneumococcal diseases. [29].

- *Relation of several environmental factors and pneumococcal pneumonia*

+ In our study, contacting with smoke and dust has the risk of pneumococcal pneumonia 1.37 times, however this relation has no statistical meaning with p >0,05.

The author Zheng Zhou and et al., the study on relation between NO2 in air polution and pneumococcal pneumonia in children, concludes that the threshold risk of NO2 for pneumococcal pneumonia in children is 13,31% (95%CI: 3,12- 24,51%, P = 0,001) in model of a pollutant. If increasing $\mu g/m^3$ NO_2 exposure, 23,30% risks of pneumococcal pneumonia in children will increase (95%CI: 2,02- 49,02%; P = 0,03) according to model of multi pollutant. It means that the exposure of No2 in air relates to pneumococcal pneumonia in children [70].

The author Matteo Bonato and et al., proves that contact with air pollution makes the expression IFN-β of epithelium of respiratory track in children before school age [24], which leads to the increase of virus number, makes the damage of respiratory track and creates good conditions for streptococcus pneumoniae to invade and cause diseases.

Our study is only done on pediatrics hospitalized, thus the findings does not reflect sufficiently the relation of streptococcus pneumoniae and air pollution, consequently it should research more in community.

+ Contact with tobacco smoke: Thanks to analysis of research results, we recognize that the children living in families have the risks of pneumococcal pneumonia 1.85 times as high as children living in family where no member smokes (95% CI: 1,11- 3,34; p < 0,05).

The author Chien-Chang Lee and et al., (2010), study of relation between exposure of tobacco smoke bearing streptococcus pneumoniae and invasive pneumococcal diseases, we see that children with exposure of tobacco smoke has risks of invasive pneumococcal diseases 1,21 times (95% CI: 0,69- 2,14, p > 0,05) and risks of bearing streptococcus pneumoniae on throat 1,66 times (95%CI: 1,33- 2,07, p < 0,05) [50].

The author JP Nuorti and et al. (2000), study on adults from 18 years to 64 years of age with normal immune capacity, we see that smoking has the risk of invasive pneumococcal diseases 4.1 times (95%CI: 2,4- 7,3, p < 0,001) and exposure with tobacco smoke has the risks of invasive pneumococcal diseases 2.5 times (95%CI: 1,2- 5,1, p = 0,01) [54].

Exposue with tobacco smoke is taken much care about children health, it is the risk factor of pneumonia in children. However, the studies of impacts of tobaccosmoke on streptococcus pneumoniae invasion and infection as premiss of pneumococcal pneumonia in children are still limited. Recently, the author Daichi Murakami and et al., has studied on the model of rats and confims that contact with tobacco smoke impulses he invasion and infection of streptococcus pneumoniae in model of rat [18]. Tobacco smoke also

reduces the reactions of hosts in nose for streptococcus pneumoniae, makes the pre-inflammation environment in noise and throat to decline by streptococcus pneumoniae, which obstructs the attraction of necessary cells to prevent from pneumonia, consequently it increases the risk of pneumococcal pneumonia [60].

+ Breeding dogs, cats in families: Survey of breeding dogs, cats in families with children with pneumococcal pneumonia, we see that the children living in families breeding dogs, cats have the risk of pneumococcal pneumonia 2.32 times as high as children living in families without any dog and cat (95% CI: 1,18- 4,41; p< 0,05).

+ Cooking by gas: the children living in families cooking by gas cookers have the risk of pneumonia 2.52 times as high as children living in families do not cook by gas cookers (95% CI: 1,09-5,34; p< 0,05).

Long ago, many studies have confirmed that using solid fuels as fossil coal and living masses to cook makes air pollution in house and it increases the risk of pneumonia in children [36]. TJ O'Dempsey and et al., the study of risk factors of pneumococcal diseases in children in rural areas in Western America shows that the risk factors of cooking solid fuels for pneumococcal diseases (pneumonia, meningitis, blood infection; 79% pneumonia) in children under 5 years of age 2.55 times (95%CI: 0,98–6,65) [55]. The recent study of author Yang Zhuge and et al., researches the risk factors of residential areas for pneumonia in children at 8 Chinese cities, it shows that using natural gas for cooking is the risk factor of pneumonia in children [71]. Eric S Coker and et al., researches the gas cooker using ways and pneumonia in children under 5 years of age in Ameria, the study shows that using gas cookers to cook with ventilation has the risks of pneumonia in children 2.31 times (95%CI: 1,67- 3,19), p <0,01), whereas using gas cookers to warm without ventilation system has the risks of pneumonia in children 6.83 times 6,83 (95%CI: 3,74- 12,14) [33].

When setting gas on fire, NO_2 and dusts with dimension from 2,5- 10 µm (PM_{10}),, the risk of pneumonia increases 30% and 76% equivalent to increase of 10 ppb NO 2 and PM_{10} [53].

The studies on toxicity mechanism of NO_2 shows when the epithelium cells of respiratory track contact with NO_2, it will create the excessive oxidation reaction [31], producing the pre-inflammation molecular [35], inhibiting the response of innate immune [21], reducing the activation of macrophage [22], and changing the functions of protein operating on surface which play an important role in the inflammation and phagocyte processes [31]. These impacts reduce the defending capacity of hoists against spreading, invading and causing pneumococcal pneumonia [21]. A epidemiological study shows that children of mothers cooking by gas cookers have a risk for liberating TNF-α (OR = 17,1, 95%CI: 3,0-98,1) [37]. A separate study on children under 24 months of age shows that the presence of gas cookers indoor relates to increase 46,5% (p <0,01) cytokine T-helper 2 [39], in vivo experiments shows that the increase of T-helper 2 cells relate to increase of sensitiveness of pneumococcal pneumonia on the model of rats [44].

4.2. Clinical, paraclinical characteristics and antibiotic resistance of streptococcus pneumoniae in children with pneumococcal pneumonia

4.2.1. Clinical characteristics of pneumococcal pneumonia in children

- Respiratory symptoms

Through analyzing data, we recognize that the popular symptoms of pneumococcal pneumonia are cough (95.15%), runny noise (90.91%), moist/ dry rales (80.61%). Subsequently, the symptoms of chest concave withdraw (62.42%), rhonchus (51.52%). The unusual symptoms are rale breath (4.85%), solidification symptom (3.64^), 3 reduction symptom (1.82%).

Tan T. Q. and et al., (1998), the retrospective study for 3 years from 1/9/1993 to 31/8/1996 in 8 children hospitals in US. Consequently, there are 257 cases with pneumococcal pneumonia, in which 93% cases diagnosed by blood culture and 7% cases diagnosed by culturing the pleural solution, with respiratory symptoms as cough (72%), reduction of rustling noise of alveolus (55%), moist/ dry rales (42%), runny noise (41%), chest concave withdraw (30%), breath difficulty (26%), rale breath (24%), bronchi rale (20%), rhonchus (29%), dull sound (12%) and chest pain (11%) [62].

Pia Toikka and et al., (1999), the retrospective study on the whole of Finland about pneumococcal pneumonia in children from 1985 to 1994 by blood culture. Consequently, there are 85 cases with pneumococcal pneumonia having the respiratory symptoms as cough (55%), runny noise (49%), breath difficulty (11%), chest pain (8%), rhonchus (42%), moist/ dry rales (14%), reduction of rustling noise of alveolus (11%) [63].

- *Symptoms of whole body and expressions except lung*

+ Fever is a expression of whole body reaction with infection. Children with pneumococcal pneumonia have high fever, poor tolerance combined with whole state's change. In this study, fever occupies 89.7% in which fever from $39^0$5C and above occupies 41.82%. The study of Le Thi Hong Hanh and et al., (2013) about lobar pneumonia in children 2 – 15 years of age in the Department of Respiration - Vietnam National Children's Hospital, children with pneumococcal pneumonia having fever occupy 95.5%.

+ Symptoms of appetite loss, eating refusal or non-drinkability are the symptoms with prognosis value. In our study, the ratio of these symptoms is 59.97%, our findings are much higher than researching findings on pneumococcal pneumonia in Finland, poor eating and drinking only occupies 21% [63].

+ The central cyanosis is a symptom of serious pneumococcal pneumonia in children. It is the consequence of oxidative Inflammation in alycolum which obstructs the gas exchange process between alycolum and capilary. In out study, the central cyanosis occupies 12.73%, out result is higher than research result of author Pia Toikka and et al., (6%)

+ The nervous symptoms as stimulus occupying 16.97%, fast asleep occupying 4.24%, convulsion caused by fever 2.42%. Streptococcus pneumoniae is able to cause purulent meningitis in children, however children with pneumococcal pneumonia can have the false symptoms of meningitis, thus we should examine carefully to avoid vomit, in case of difficult distinction, we should poke the cerebrospinal fluid to avoid purulent meningitis. Thanks to our research study's results, the ratio of nervous symptoms is much lower than research results of other authors over the world: Tan T. Q. and et al., fast asleep or stimulus occupying 39%.

+ The digestive symptoms as vomit, stomachache, diarrhea can met for pneumococcal pneumonia in children. In this study, the ratio of diarrhea symptoms is 18.79%, whereas the study of Tan T.1. and et al., stomachache occupying 21% and study of Poa Toikka and et al., the ratio of diarrhea is only 2% [63].

4.2.2. Paraclinical characteristics of pneumococcal pneumonia in children

- *Peripheral blood testing results of pneumococcal pneumonia*

The ratio of anemia in children with pneumococcal pneumonia occupies 59.39%. Our research findings are similar to research findings of Pham Ngoc Han (2007), the ratio of anaemia in children from 2 months and 5 years of age with pneumonia is 79.3% and according to Hoang Ngoc Hung (2010) it is 55% in children with pneumonia from 6 – 24 months of age, higher than researching findings of Ho Do Vinh and et al., (2015), the ratio of anaemia is 33.2% [16].

The result analysis shows that the ratio of increase of white blood cell in blood is high (92.12%), the ratio of CRP increase is 67.27%. The study of author Pia Toikka and et al.,

(1999), the ratio of white blood cell's increase is 95% and CPR increase occupies 85% [63]. Mono cell is the predecessor of macrophage helping the pneumococcus phagocyte and damaged cells. CRP is a protein of acute inflammation, it frequently increases highly in pneumococcus infection, reduces the infection process, recognizing and connecting with streptococcus pneumoniae surface, activating complements in the classic pathway to destroy streptococcus pneumoniae [25].

- Lung radiography's images of pneumococcal pneumonia

The images of bronchopneumonia occupy 80%, the images of lobar bronchitis occupy 20%, the images of pleural effusion occupy 4.85%. According to Tan T. Q. and et al. (1998), the images of bronchopneumonia occupy 29.21%, the images of lobar bronchitis occupy 50.79%, the images of pleural effusion occupy 28.74% [62]. Iin the study of Pia Toikka on pneumococcal pneumonia in children with blood infection, damages on chest radiography are described more specifically with image of alveolus invasion (84%), interstitial organization invasion (9%), medium invasion of alveolus and interstitial organization (7%). In which, lobar solidification of small lobe (41%), solidification of pulmonary lobe (38%), pleural effusion (20%).

The research fidings of authors inside country about pneumonia in children show that the damages of lung radiography are mainly the images of bronchopneumonia: Quach Ngoc Ngan and et al., in Can Tho, bronchopneumonia (99%), lobar bronchitis (1%) [7], Huynh Van Tuong and et al., in Ho Chi Minh City, bronchopneumonia (82.7%), lobar bronchitis (15.9%) [15].

Our research findings are suitable to research findings of authors inside country, the X-ray images of pneumococcal pneumonia in children are mainly the images of bronchopneumonia, it is not similar to classic model in which the pneumococcal pneumonia is emphasized as model of lobar bronchitis, consequently the children with pneumococcal pneumonia having images of bronchopneumonia can be diagnosed incorrectly [56].

4.2.3. Antibiotic resistance of streptococcus pneumoniae

Very high resistance ratio to macrolid group (97,4% to azithromycin, 98,5% to clarithromycin and 96,9% to erythromycin), resistant 90% to trimethoprim/sulfamethoxazon, resistant 95,3% to clindamycin, resistant 73,4% to tetracyclin, 19% resistant to chloramphenicol. The sensitiveness of streptococcus pneumoniae reduces to penicillin G, only 3.8% streptococcus pneumoniae sensitive 100% to rifampin, linezolid, vancomycin. The streptococcus pneumoniae reduces its sensitiveness to antibiotics cephalosporin of generation 3 (C3G): 57.4% sensitive to cefotaxim and 61,1% sensitive to ceftriaxon. Streptococcus pneumoniae is resistant to important antibiotics levofloxacin (resistant 0.6%).

Jae-Hoon Song, Pham Hung Van and et al., (2004), the study of antobiotoc resistance situation of streptococcus pneumoniae in 14 centers and 11 countries of Asia and Middle East from January 2000 to June 2001, consequently there are 685 streptococcus pneumoniae species (64 species in Vietnam), 23% is intermediate (MIC =0,12-1µg/ml), 29,4% resistant to (MIC =0,12-1µg/ml); 29,4% resistant to penicillin (MIC $\geq$ 2 µg/ml),, (In Vietnam, 20.6% is intermediate and 71.4% is resistant to penincillin). The ratio of streptococcus pneumoniae intermediate and resistant to erythromycin is 1,8% and 53,1% (In Vietnam, it is 92,1% and 1,6%) [61].

Torumkuney D., Van P. H. and et al., study the situation of antibiotic resistance of streptococcus pneumoniae from 2016 to 2018 in four countries of South East Asia including Vietnam, consequently there are 161 streptococcus pneumoniae species in Vietnam. The streptococcus pneumoniae resistant to 93.8% clarythromycin, resistant 95,7% to erythromycin, resistant 78,3% to TMP/SMX. Only 62.1% streptococcus

pneumoniae species are sensitive to ceftriazon. There are 12% and 30.4% streptococcus pneumoniae intermediate and resistant to penicillin G, only 1.2% sensitive to penicillin V. There are 10% streptococcus pneumoniae species resistant to important antibiotic levofloxacin [64].

Our researh findings also show that the streptococcus pneumoniae resistant to 3 antibiotic groups occupy the hgihest ratio (32.93%), a case resistant to 6 antibiotic groups (occupying 0.61 %). Multi-resistant streptococcus pneumoniae (resistant to at least 3 antibiotic gourps) occupy 64%.

The author Mattias Larsson and et al., the study of multi-antibiotic resistance of rural areas of Ba Vi in years 1999, 2007 and 2014 shows that the multi-antibiotic resistance ratio of streptococcus pneumoniae is 31%, 60% and 80% successively [42-49]. The study of author Wang C. Y. And et al., in 10 hospitals in China in 2016 shows that the multi-antibiotic resistance ratio of streptococcus pneumoniae is 46.1% in pediatrics with invasive pneumococcal diseases [67]. The drug resistance agent supervision network of Asia has implemented the concurrent supervison study in 60 hospitals in 11 countries of Asia from 2008 to 2009, the multi-drug resistance invasive streptococcus pneumoniae occupy 59.3%, in which it is 83.3% in China and 73.3% in Vietnam [46].

The ratio of multi-antibiotic resistance streptococcus pneumoniae in our study is equivalent to research results of Asian drug resistance agent supervision network, higher than research results of author Wang C. Y., but lower than research results of author Mattias Larsson, because this author considers the breaking point pK/pD of antibiotic penincillin and cefotaxim (new standard, breaking point pK/pD of antibiotic penicillin G is 2-8µg/ml, penicillin V is 0,06-2µg/ml and cefotaxim is 1-4µg/ml). Although the multi-antibiotic resistance ratio of streptococcus pneumoniae is not similar depending on researching times and places, but this ratio is almost more than 50% and is increasing more and more, it is a big risk for medicine of whole world.

The multi-antibiotic resistant streptococcus pneumoniae is described at the first time in 1977 in Southern Africa, and then it spreads broadly over the world. Penicillin antibiotic resistant streptococcus pneumoniae is simultaneously resistant to antibiotics of groups macrolid, clindamycin, chloramphenicol, trimethoprim/sulfamethoxazon and tetracyclin. However, streptococcus pneumoniae is also sensitive to antibiotics vancomycin, rifampin, imipenem. Consequently, it breaks the principle of using antibiotic as using ceftriaxon, clindamycin to treat meningitis [46]. It increases the selection pressure, because using antibiotic broadly and continuously lead to the status of antibiotic resistance. According to National Center for data on streptococcus pneumoniae of France, since applying the national strategy on managing and using antibiotic (2001) and since putting streptococcus pneumoniae prevention vaccine into expanded immunization program (2003), the ratio of streptococcus pneumoniae reducing sensitiveness to penicillin decrease gradually from 52% in 2003 to 21% in 2014 [72].

4.3. Treatment intervention findings

4.3.1. Treatment findings

Our research findings show 2.42% pleural after-effect. 13/94% illness reduction and 93.64% complete recovery from illness. There is no dead pediatrics.

Hoang Ngoc Anh and et al., the study of 36 children with lobar pneumonia at Department of Respiration - Vietnam National Children's Hospital, from January to December 2015, there are 16 children indentified the bacterium reason, in which 9 pediatrics with streptococcus pneumoniae. After treating, 97.2% children are recovered from illness, 2.8% children are not improved and they must be moved to upper line, there is no dead pediatrics. The average treating time is 15,41 ± 4,35 days [1].

Pia Toikka and et al., study from January 1985 to December 1994 in Finland, there are 85 pediatrics with blood culture positive to streptococcus pneumoniae and damaged by pneumonia on Lung radiography. After treating, there is no dead pediatrics, 6% children recur new period of pneumonia within 1 month (only supervising 48 children), a pediatrics with blood culture is positive to streptococcus pneumoniae after 4 treatment stopping weeks but there is no infection expression [63].

Our research findings are similar to research findings of Hoang Ngoc Anh and al et., about high recovery ratio and there is no dead pediatrics. However, the average treatment time in our study is shorter, because the children are discharged from hospital earlier when they have not recovered completely from pneumonia and they continue taking antibiotic at home, thus in our study, the ratio of recovery is lower, it is replaced by ratio of children reduced from illness. Whereas, the study of author Be Van Cam, the ratio of dead children is 6.2%, because at this time, children are hospitalized late. On the other hand, the satisfaction capacity of local medical system is limited, which has impacts on treating results.

Report of Global disease burden, the ratios of dead cases caused by pneumococcal pneumonia in children under 5 years are different depending on each area, highest in South East Asia, occupying 61.2% in total death cases caused by pneumonia at same age, lowest in developing area of North America, occupying 46.6% [40].

4.3.2. Treating time

The research findings show that the average treating time is 10,23 ± 5,81 (days), for slight pneumococcal pneumonia group, it is 8,56 ± 4,11, for serious pneumococcal pneumonia group, it is 11,04 ± 6,34. The treating time is longer in serious pneumococcal pneumonia group has the statistical meaning with $p < 0.05$. The treating time is lengthened ≥ 2 weeks occupying 20% total children with pneumococcal pneumonia**.** The author Yu-Chia Hsieh and et al., (2004), the retrospective study on pneumococcal pneumonia in children in Taiwan shows that the treating time of pneumococcal pneumonia without complication and with complications as Pleural Empyema and pulmonary necrosis is 12,6 ± 6,8 days and 25,2 ± 12,0 days [77]. The average hospitalizing time is considered as a indicator on efficiency and the average hospitalizing time is shorter, which will reduce the economic burden of families and society.

4.3.3. Factors related to treatment findings

- Relation of pulmonary damages on chest radiography and treating time

When analyzing the paraclinical results, we see that the pneumococcal pneumonia with complications of pleural effusion, Pleural Empyema have the statistical meaning related to lengthened treating time, OR = 14,4, p< 0,05.

The author Yu-Chia Hsieh and et al., (2004), study of pneumococcal pneumonia in Taiwan shows that the average treating times of pneumococcal pneumonia without complication and pneumococcal pneumonia with complications are 12.6 ± 6.8 days and 25.2 ± 12.0 days successively, this difference has the statistical meaning with p< 0,005 [77].

- Relation of aneamia and treating time

Aneamia and nutrition lack are frequently met in pneumonia in children, it is the consequency and the risk factor of pneumonia in children. The author Nguyen Thi Hong Nhan and et al., research the relation of iron aneamia and pneumonia in children under 5 years of age examined and treated in Saint Paul General Hospital in 2017, it shows that 72.2% pediatricses with aneamia and iron lack is the risk factor of pneumonia in children under 5 years of age (OR = 4,33, 95%CI: 1,72-9,52, p < 0,05) [8].

The author Do Ho Vinh and et al., (2015), the study of aneamia in children from 2 months to 5 years of age at the Department of Pediatrics, Hue Central Hospital shows that the degree of aneamia has the statistical meaning related to seriousness of pneumonia p <0,01 [16].

Through analysis of research findings, we see that aneamia is the risk factor of long-time treatment ≥ 14 days (OR =2,03; 95%CI: 1,09- 5,14, p = 0,03).

- *Relation of antibiotic resistance and treating time*

Thanks to analysis of antibiotic resistance and treating time, we see that the antibiotic resistance of streptococcus pneumoniae with cefotaxim and ceftriaxon have the statistical meaning with long-time treatment p < 0.05. In details, the children with pneumonia caused by intermediate streptococcus pneumoniae with ceftriaxon have the treating time ≥ 14 days 3.69 times as high as children with pneumococcal pneumonia sensitive to (95% CI: 1,21-8,71; p< 0,05). The children with pneumococcal pneumonia intermediate to cefotaxim have the treating time ≥ 14 days 3.69 times as high as children with pneumococcal pneumonia sensitive to cefotaxim (95% CI: 1,06-6,81; p< 0,05). The children with pneumococcal pneumonia resistant to cefotaxim have the treating time ≥ 14 days 5.73 times as high as children with pneumococcal pneumonia sensitive to cefotaxim (95% CI: 2,11-15,58; p< 0,005). However, in this study, we do not see any relation between multi-antibiotic resistance of streptococcus pneumoniae and long-time treatment, it has the statistical meaning with p>0,05.

Streptococcus pneumoniae has the low sensitiveness ratio with cephalosporin antibiotics of generation 3 (58,4% with cefotaxim and 62% with ceftriaxon) and having MIC_{90} high (4 µg/ml), whereas the breaking point pK/pD of these antibiotics is 1- 4 µg/ml, therefore it can reaches the treatment efficiency, we must increase the dose and increase the antibiotic using times in day, this is difficult to implement for children.

CONCLUSION

1. Epidemiological, clinical characteristics and associated factors of children with pneumococcal pneumonia

- Epidemiological, clinical characteristics: the pneumococcal pneumonia cases occupy pneumonia cases in children, the male/ female ratio = 1.89/1, concentrating mainly in ages from 2 months of age occupying 80% pneumococcal pneumonia cases, 74% children from urban areas, only 5.45% immunized by streptococcus pneumoniae vaccine, 64% children use antibiotic before being hospitalized, serious pneumonia cases occupy 68%.

- The factors related to pneumococcal pneumonia in children include: history of asthma in juveniles, or ≥ 3 wheezing periods in infants OR = 2,09 (95%CI: 1,10- 4,63, p < 0,05); Children living in families with smoking people OR = 1,85 (95%CI: 1,11- 3,34, p< 0,05); Breeding dogs, cats OR = 2,32 times (95%CI: 1,18- 4,41, p< 0,05). Children living in families using gas cookers OR = 2,52 (95%CI: 1,09- 5,34, p< 0,05)

2. Clinical, paraclinical characteristics and antibiotic resistance of streptococcus pneumoniae in children with pneumococcal pneumonia

- Fever cases occupy 89.70%, in which high fever cases occupy 41.82.%. Cough (95.15%), runny noise (90.91%), cyanosis (12.73%), moist/ dry rales (80.61%), chest concave withdraw (62.42%).

- White blood cell increase cases occupy 92,12%, CRP increase (67,27%), aneamia (40,61%), lobar pneuminia (20%), pleural effusion (4.85%).

- Streptococcus pneumoniae has very high resistance ratio, over 95% for macrolid antibiotic groups, resistant 90% to cotrimoxazol, resistent 95,3% to clindamycin. The streptococcus pneumoniae is sensitive 43.9% to penicillin G (MIC_{90}=4 µg/ml), sensitive 57,4% to cefotaxim (MIC_{90} = 4 µg/ml), sensitive 61,1% to ceftriaxon (MIC_{90} = 4 µg/ml), sensitive 95% to amoxicillin (MIC_{90} = 2 µg/ml), sensitive 100% to rifampycin, linezolid, vancomycin. Multi-antibiotic resistant streptococcus pneumoniae occupies 64%.

3. Treatment intervention findings

- Complete recovery cases occupy 83.64%, illness reduction cases occupy 13.94%, after-effect of thick pleura is 2.42%, there is no dead pediatrics.

- The average treating time is 10,23 ± 5,81 days.

- The factors related to treating time ≥ 14 days include: streptococcus pneumoniae resistant to ceftriaxon (p = 0,002; OR = 4,33), intermediate to ceftriaxon (p = 0,01; OR = 3,25); streptococcus pneumoniae resistant to cefotaxim (p = 0,001; OR = 5,73), intermediate to cefotaxim (p = 0,03; OR = 3,69); Pleural Empyema (p = 0,0003; OR= 14,4); Anaemia of pediatrics (p = 0,03; OR= 2,03).

PETITION

1. Preventing from factors increasing the risks of pneumococcal pneumonia in children as avoiding tobacco smoke, preventing children from contacting with dogs, cats, especially children with allergy, controlling well asthma, recurred wheezing. Do not cook by gas cookers in closed room. It should have means to circular air well.

2. Using the diagnosing means to improve the ability of discovering pneumococcal pneumonia in children as culturing quantitatively nasopharyngeal solution, culturing blood should be done in all children with pneumonia and testing Realtime PCR for pleural solution. Based on clinical and paraclinical characteristics, the antibiotic resistance model, several factors related to long-time treatment, we can build a private guideline on diagnosing and treating pneumococcal pneumonia in children.

3. Managing antibiotic, improving awareness of community by providing information in order to change habit of excessive antibiotic using in hospital and also in community.

LIST OF THESIS-RELATED PUBLICATIONS OF THE AUTHOR

1. Nguyen Dang Quyet, Dao Minh Tuan, Bui Quang Phuc, Truong Thi Viet Nga (2021). Situation of antibiotic resistance of streptococcus pneumoniae and pneumococcal pneumonia treatment results in children at the Vietnam National Children's Hospital. Magazine of Pediatrics Research and Practice, 5(4), 27 – 34.

2. Nguyen Dang Quyet, Dao Minh Tuan, Bui Quang Phuc (2021). Clinical and paraclinical characteristics of pneumococcal pneumonia in children at the Vietnam National Children's Hospital. Maganize of Malaria and parasitic diseases, 5 (125), 33-40.

3. Nguyen Dang Quyet, Dao Minh Tuan and Bui Quang Phuc (2022). Several epidemiological, clinical characteristics and associated factors of children with pneumococcal pneumonia treated at the Vietnam National Children's Hospital. Magazine of Malaria and parasitic diseases, 1 (126).