Journal of Tropical Pediatrics, 2019, 65, 224–230
doi: 10.1093/tropej/fmy037
Advance Access Publication Date: 12 July 2018
Original paper

OXFORD

Underlying Diseases and Causative Microorganisms of Recurrent Pneumonia in Children: A 13-Year Study in a University Hospital

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ABSTRACT

Pneumonia is a significant cause of death for children, particularly those in developing countries. The records of children who were hospitalized because of pneumonia between January 2003 and December 2015 were retrospectively reviewed, and patients who met the recurrent pneumonia criteria were included in this study. During this 13-year period, 1395 patients were hospitalized with pneumonia; of these, 129 (9.2%) met the criteria for recurrent pneumonia. Underlying diseases were detected in 95 (73.6%) patients, with aspiration syndrome (21.7%) being the most common. Rhinovirus (30.5%), adenovirus (17.2%) and respiratory syncytial virus (13.9%) were the most frequent infectious agents. These results demonstrate that underlying diseases can cause recurrent pneumonia in children. Viruses are also commonly seen in recurrent pneumonia. Appropriate treatments should be chosen based on an analysis of the underlying disease, the patient's clinical condition and the laboratory and radiological data.

KEYWORDS: children, recurrent pneumonia, respiratory virus, underlying disease

INTRODUCTION

Pneumonia is the most common cause of death of children in developing countries, where mortality rates are 10 times higher than in industrial countries [1]. Worldwide, 922 000 children <5 years old died from pneumonia in 2015. The majority of those deaths occurred in South Asia and Saharan Africa [2].

Recurrent pneumonia is defined as two or more episodes of pneumonia in a year or at least three episodes of pneumonia during a lifetime. Recurrence is seen in 7–9% of children who have suffered from pneumonia [3]. In this study, we reviewed the records of children admitted to our hospital with recurrent pneumonia to determine their underlying

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diseases, identify the causative microorganisms of their infections and evaluate the distribution of these factors according to the patient's age and the season of admittance. After statistical analysis, our results were compared with previous studies.

MATERIAL AND METHODS

This retrospective study reviewed the records of children who were admitted to our pediatric infectious disease hospital between January 2003 and December 2015 and diagnosed with pneumonia. A pneumonia diagnosis was defined as cough, dyspnea, absence of wheezing at auscultation, fever and indications of lobar infiltration or bronchopneumonia on a chest X-ray and tachypnea (as defined by the World Health Organization) [2]. Patients of age between 0 and 18 years who met the criteria for recurrent pneumonia (at least two episodes of pneumonia within a year or at least three episodes during a lifetime) were included in this study. Patients with a normal chest X-ray and no radiological examination were excluded. The demographic characteristics of the study patients and their clinical, laboratory and imaging results were collected from the data system using ICD-10 codes.

In our hospital, real-time polymerase chain reaction (RT-PCR) has been available for the detection of causative pathogens isolated from respiratory tract secretions since November 2012. For the pneumonia patients included in this study, respiratory specimens (nasopharyngeal aspirates) were obtained within the first 48 h of hospitalization. The responsible pathogens were detected by RT-PCR, which included a panel of the following 20 viruses and 6 bacteria: rhinovirus, enterovirus, respiratory syncytial virus (RSV) A and B, parainfluenza virus (PIV)-1, PIV-2, PIV-3, PIV-4, bocavirus, coronavirus 229E, coronavirus NL63, coronavirus HKU1, coronavirus OC43, influenza A virus, influenza A H1/N1 virus, influenza B virus, metapneumovirus A and B, parechovirus, adenovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*, *Legionella pneumophila*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. In addition, tracheal aspirate culture samples were collected from patients with tracheostomies.

The patients who were diagnosed as having recurrent pneumonia were categorized in terms of their underlying diseases. In addition to standard laboratory and imaging tests, the following tests were optionally used to facilitate diagnosis: sweat chloride tests; immunoglobulin (Ig)G, IgA, IgM, serum total IgE and specific Ig levels; lymphocyte subsets; esophagus–stomach–duodenum X-rays; reflux scintigraphy or esophageal pH manometry; and transthoracic echocardiography. If patients remained undiagnosed after these results, additional tests were administered, including the tuberculin skin test, acid fast stain, tuberculosis PCR and tuberculosis culture from gastric aspirate, computed tomography of the thorax, respiratory function tests, laryngoscopy and flexible bronchoscopy. Those patients with an underlying disease were divided into three groups according to the occurrence of their underlying disease: before the first pneumonia episode, during the first pneumonia episode and after diagnosis of recurrent pneumonia.

Statistical analyses were performed using the SPSS version 18.0 (Chicago, IL, USA). The Chi-square test was used for univariate analysis. Differences between groups were identified with the Mann–Whitney U test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

During the study period, 1395 patients were hospitalized with pneumonia. Of these, 129 (9.2%) met the criteria for recurrent pneumonia. Fifty (38.8%) patients were female. The median age was 14 (range 1–204) months. The median number of pneumonia episodes was 3 (range 2–30). Fifty-one (39.5%) patients had two pneumonia episodes within 1 year, and 78 (60.5%) patients had three or more pneumonia episodes during their lifetime. The median age of the patients at the time of the recurrent pneumonia diagnosis was 22 (range 1–206) months. The median hospitalization length was 7 (range 1–28) days. Underlying diseases were detected in 95 (73.6%) patients. The most prevalent underlying diseases were as follows: 28 (21.7%) aspiration syndrome, 26 (20.2%) asthma, 15 (11.6%) CHD and 7 (5.4%) gastroesophageal reflux. There was no underlying disease in eight patients who had history of prematurity.

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Of these, seven (87.5%) needed mechanical ventilation in neonatal intensive care. Six premature patients were diagnosed with respiratory distress syndrome, and one had congenital lung disease. The underlying diseases are summarized in Table 1.

The occurrence of the underlying disease diagnosis was as follows: 27 (28.4%) before the first pneumonia episode, 6 (6.3%) during the first pneumonia episode and 62 (65.3%) after the recurrent pneumonia diagnosis. While all asthmatic patients with recurrent wheezing were diagnosed after repeated radiographic imaging (because of a recurrent pneumonia attack), most of the CHD patients were diagnosed before their first pneumonia episode. The relationships between the underlying disease and pneumonia episodes are summarized in Table 2.

Respiratory tract samples were obtained during 151 pneumonia episodes. At least one type of virus or bacteria was detected in 111 (73.5%) samples. The coinfection rate was 26.5% (40 of 151) as microbiologically documented by RT-PCR. One microorganism was detected in 65 patients; two microorganisms were detected in 29 patients, three microorganisms were detected in 10 patients and four microorganisms were detected in 1 patient. The most prevalent causative agents in the respiratory samples were rhinovirus (30.5%), adenovirus (17.2%), RSV (13.9%) and bocavirus (7.9%). Tracheal aspirate samples were obtained from six (13%) patients with tracheostomies. *Pseudomonas aeruginosa* was isolated by culture in six patients who had no positive RT-PCR results.

The seasonal distribution of recurrent pneumonia episodes was as follows: 43 (28.5%) in winter, 50 (33.1%) in spring, 32 (21.2%) in summer and 26 (17.2%) in autumn. Influenza A virus, RSV and

Table 1. Demographic and clinical characteristics of children hospitalized with recurrent pneumonia

Characteristic	*n*		
Total number of patients	129		
Age, median (range), months	14 (1–204)		
Gender	79 M/50 F		
Number of pneumonia, median (range), episode	3 (2–30)		
Age at the diagnosis, median (range), months	22 (1–206)		
Median hospitalization length, median (range), days	7 (1–28)		
Underlying disease	*n* (%)	Underlying disease	*n* (%)
Unknown	34 (26.4)	Gastroesophageal reflux	7 (5.4)
Aspiration syndrome	28 (21.7)	Lung and airway abnormalities	5 (3.9)
Cerebral palsy	6	Laryngomalacia, bronchomalacia	3
Metabolic diseases	3	Diaphragmatic hernia	1
Neurodegenerative diseases	7	Congenital bronchiectasis	1
Congenital hypotonia	4	Immune disorders	4 (3.1)
Congenital muscle disease	4	Severe combined immunodeficiency	2
Swallowing dysfunction	1	Transient hypogammaglobulinemia	2
Cleft lip or palate	3	Bronchopulmonary dysplasia	4 (3.1)
Asthma	26 (20.2)	Cystic fibrosis	3 (2.3)
Congenital heart disease	15 (11.6)	Hydatid cyst	2 (1.6)
Ventricular septal defect	5	Foreign body aspiration	1 (0.8)
Atrioventricular septal defect	3		
Ventricular septal defect + single atrium	1		
Atrial septal defect	2		
Patent ductus arteriosus	4		

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Table 2. The relationship between underlying diseases and pneumonia episodes

Underlying disease	Diagnosed before the first pneumonia episode	Diagnosed during the first pneumonia episode	Diagnosed after pneumonia recurrence	Total
Aspiration syndrome	4	2	23	29
Asthma	0	0	26	26
Congenital heart disease	13	1	1	15
Gastroesophageal reflux	3	0	4	7
Lung and airway abnormalities	1	1	3	5
Immune disorders	1	0	3	4
Bronchopulmonary dysplasia	4	0	0	4
Cystic fibrosis	1	0	2	3
Hydatid cyst	0	2	0	2
Total	27	6	62	95

coronavirus were detected more frequently in winter than in other seasons ($p < 0.001$, $p < 0.001$ and $p < 0.05$, respectively). There was no seasonal difference in the frequency of rhinovirus, enterovirus, PIV-1, PIV-3, PIV-4, bocavirus, adenovirus and *M. pneumoniae* ($p > 0.05$).

RSV was detected significantly more frequently in children <1 year ($p < 0.01$). There was no difference between the age groups in terms of the other viral agents. A summary of the RT-PCR analyses of the bacteria and viruses detected in the respiratory samples is provided in Table 3.

DISCUSSION

Pneumonia is a significant childhood disease. Although previous studies have identified the etiology of recurrent pneumonia, not enough data have been reported on the causative microorganisms [3–7]. We believe that this is the first study to identify the responsible pathogens in children hospitalized because of recurrent pneumonia (Table 3). A comparison of this study with previously published results is summarized in Table 4. When comparing the two studies conducted at our hospital, we found that the frequency of recurrent pneumonia did not change over the years. As in our previous study, 9% of all children hospitalized with pneumonia met the criteria for recurrent pneumonia [4].

In our study, the majority of hospitalized patients with recurrent pneumonia (73.6%) had an underlying disease. Similarly, Hoving *et al.* [3] reported that 70% of hospitalized patients with recurrent pneumonia had an underlying disease.

In accordance with other studies, we found that aspiration syndrome was a frequent underlying disease [8–11]. Neurological diseases and anatomical disorders are the primary causes of aspiration syndromes [8]. In our previous study, the most common underlying disease was asthma, while aspiration syndrome was seen less frequently [4]. This difference may be explained by the increased life expectancy and improved treatment options for patients with neurological diseases.

Asthma is an important risk factor for recurrent pneumonia in children [12–14]. However, asthma was not diagnosed as an underlying disease in the study by Hoving *et al.* They suggested that it was difficult to exclude pneumonia in asthmatic patients because of overlapping symptoms such as cough, tachypnea and dyspnea [3]. In our study, asthma was a frequent underlying cause of recurrent pneumonia. We determined that asthmatic patients were hospitalized during pneumonia episodes because they had lung infiltrations on their chest X-rays and because wheezing cases were excluded. For these reasons, our patients were accepted as having pneumonia, not asthmatic exacerbation. In addition, the asthma diagnosis was confirmed after the recurrent pneumonia episode.

Immune disorders are another risk factor for recurrent pneumonia. Unlike previous studies, we found a low frequency of immune disorders in our study group [5–7].

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Table 3. Summary of the RT-PCR analysis of the bacteria and viruses detected in the respiratory specimens

	0–12 months (%)	13–59 months (%)	60+ months (%)	*p*	Winter (%)	Spring (%)	Summer (%)	Autumn (%)	*p*	Total
Rhinovirus	17 (37)	26 (56.5)	3 (6.5)	0.664	9 (19.6)	15 (32.6)	14 (30.4)	8 (17.4)	0.211	46
RSV	14 (66.7)	5 (23.8)	2 (9.5)	0.001	13 (61.9)	8 (38.1)	0 (0)	0 (0)	<0.001	21
PIV-1	1 (50)	1 (50)	0 (0)	0.819	2 (100)	0 (0)	0 (0)	0 (0)	0.165	2
PIV-2	0 (0)	2 (100)	0 (0)	0.522	0 (0)	0 (0)	0 (0)	2 (100)	0.021	2
PIV-3	4 (57.1)	3 (42.9)	0 (0)	0.299	0 (0)	2 (28.6)	2 (28.6)	3 (42.9)	0.163	7
PIV-4	1 (33.3)	2 (66.7)	0 (0)	0.886	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	0.672	3
Mycoplasma pneumonia	1 (50)	1 (50)	0 (0)	0.819	0 (0)	1 (50)	1 (50)	0 (0)	0.595	2
Bocavirus	3 (25)	8 (66.7)	1 (8.3)	0.870	0 (0)	5 (41.7)	4 (33.3)	3 (25)	0.147	12
Enterovirus	2 (50)	2 (50)	0 (0)	0.667	1 (25)	0 (0)	3 (75)	0 (0)	0.053	4
Coronavirus	2 (18.2)	8 (72.7)	1 (9.1)	0.502	4 (36.4)	2 (18.2)	0 (0)	5 (45.5)	0.028	11
Influenza A virus	5 (45.5)	5 (45.5)	1 (9.1)	0.544	11 (100)	0 (0)	0 (0)	0 (0)	<0.001	11
Influenza B virus	0 (0)	1 (100)	0 (0)	0.724	0 (0)	1 (100)	0 (0)	0 (0)	0.565	1
Bordetella pertussis	1 (100)	0 (0)	0 (0)	0.340	0 (0)	0 (0)	1 (100)	0 (0)	0.291	1
Legionella pneumophila	0 (0)	1 (100)	0 (0)	0.724	0 (0)	0 (0)	0 (0)	1 (100)	0.184	1
Adenovirus	5 (19.2)	21 (80.8)	0 (0)	0.053	8 (30.8)	10 (38.5)	5 (19.2)	3 (11.5)	0.807	26
Metapneumovirus	2 (40)	2 (40)	1 (20)	0.443	1 (20)	4 (80)	0 (0)	0 (0)	0.136	5

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Table 4. Comparison of our results with previous studies in the literature regarding the underlying diseases of recurrent pneumonia in children

	Owayed *et al.* [5]	Lodha *et al.* [6]	Hoving *et al.* [3]	Çelebi *et al.* [7]	Çiftci *et al.* [4]	Our study
Number of patients (*n*)	220	70	62	185	71	129
Causes (%)						
Unknown	7.6	15.7	30.6	33	15	26.4
Aspiration syndrome	47.9	11.4	25.7	14.5	3	21.7
Asthma	8	14.2	0	8.6	32	20.2
Cardiac defects	9.2	0	5	17.2	9	11.6
Gastroesophageal reflux	5.4	12.8	0	16.7	15	5.4
Lung-airway anomalies	7.6	8.6	16	3.2	6	3.9
Immune disorder	14.3	15.7	16.1	5.4	10	3.1
Cystic fibrosis	0	7.1	0	6.4	3	2.3
Others	0	14, 5	6, 6	4.8	6	5.4

CHD, particularly ventricular septal defect, is also a frequent underlying disease of recurrent pneumonia. More children with CHD have been referred to our hospital in recent years; therefore, we found a higher rate of CHD compared with our previous study [4]. In this study, the majority of CHD patients were diagnosed before their first pneumonia episode, likely because current diagnostic methods like fetal echocardiography have improved CHD diagnosis.

The onset age of recurrent pneumonia in children can suggest potential underlying diseases. Congenital lung and airway abnormalities should be considered in early onset recurrent pneumonia. However, in our study, laryngomalacia, bronchomalacia, diaphragmatic eventration and congenital bronchiectasis were primarily diagnosed after episodes of recurrent pneumonia.

In our clinic, the causative microorganisms for all children hospitalized with pneumonia are detected by RT-PCR. The treatment is chosen according to the patient's general condition, the presence of underlying diseases and the patient's laboratory and radiologic results. Although causative microorganisms leading to pneumonia have been reported in many studies, there are limited data on the causative agents in children with recurrent pneumonia. In our study, rhinovirus, RSV and adenovirus were the most common pathogens detected in respiratory secretions by RT-PCR in patients hospitalized with recurrent pneumonia. Rhedin *et al.* [15] reported RSV (32%), rhinovirus (23%) and metapneumovirus (23%) as the most common causative agents, while Bénet *et al.* [16] found that *S. pneumoniae*, metapneumovirus, RSV and influenza A virus were the most frequently seen pathogens in children with pneumonia. Feikin *et al.* [17] found a similar frequency of *S. pneumoniae*, RSV and influenza A virus in pneumonia. These findings differed from our results because the studies included children who had not previously received a pneumococcal vaccine.

Coinfections are often seen in pneumonia. In our study, 40 coinfections were found in 151 episodes. Rhinovirus was the most prevalent coinfection virus, followed by adenovirus, RSV, coronavirus and influenza A virus. This result supports the theory that some respiratory viruses facilitate coinfections by predisposing a patient to the opportunistic colonization of other bacteria and viruses. Similarly, Radin *et al.* [18] found coronavirus, rhinovirus and adenovirus in coexistence with pneumonia infections.

There were some limitations to this study. Patients were identified using our hospital records. Accordingly, not all recurrent pneumonia patients who had been admitted to our clinic could be included in the study, as some patients might have been admitted to a different center during their recurrent pneumonia attacks. In addition, we have only been able to detect causative pathogens by RT-PCR in respiratory tract secretions since 2012, so our data only contained information about the patients' causative microorganisms for the past 4 years. Underlying

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diseases and the causative microorganisms could not be determined for all patients in the study group. Additionally, as our study was retrospective, we were not able to provide a control group to aid in the interpretation of the RT-PCR data. Another study limitation was that while we detected viruses (other than RSV) in nasopharynx samples, their presence does not necessarily imply a causal role in pneumonia, as these viruses can be detected at high frequencies in asymptomatic children. Similarly, detection of bacteria in the non-sterile nasopharynx environment does not imply causation of pneumonia, as *S. pneumoniae* and *H. influenzae* are frequent colonizers of the upper airway in asymptomatic children.

Our results demonstrate that underlying diseases should be considered in children with recurrent pneumonia. In addition, we found that rhinovirus, adenovirus and RSV were important microorganisms leading to recurrent pneumonia. Therefore, treatment should be based on an analysis of both the underlying diseases and causative microorganisms.

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