

## Original Article

# Underlying Causes of Persistent and Recurrent Pneumonia in Children at a Pulmonary Referral Hospital in Tehran, Iran

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## Abstract

**Background:** There is limited data on recurrent or persistent pneumonia in children, particularly in the developing world. This is a retrospective, cross-sectional study of children with recurrent or persistent pneumonia admitted to the Pediatric Department of Massih Daneshvari Hospital, Tehran, Iran.

**Methods:** Children under 18 years of age, who were admitted to the hospital with pneumonia between 2007 and 2013, were investigated to find out the prevalence of recurrent and persistent pneumonia and to recognize their underlying diseases. Descriptive statistics were calculated for all data.

**Results:** Out of 601 children admitted for pneumonia, 229 (38.1%) met the criteria for recurrent or persistent pneumonia. An underlying illness was identified in 194 patients (84.72%). The most common underlying causes of recurrent pneumonia included aspiration syndrome (51.75%), recurrent wheezing (20.17%), and congenital heart diseases (20.17%). The most common underlying illness of persistent pneumonia included pulmonary tuberculosis (38.75%), recurrent wheezing (28.75%), and aspiration syndrome (26.25%).

**Conclusions:** The result showed that the majority of patients with recurrent or persistent pneumonia had an underlying illness. New strategies and guidelines are required for early diagnosis of underlying causes of recurrent or persistent pneumonia in children.

**Keywords:** Aspiration, children, persistent pneumonia, recurrent, tuberculosis

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## Introduction

Pneumonia is a major problem in children; the World Health Organization (WHO) estimated that pneumonia occurred in approximately 156 million children (151 million in developing countries and 5 million in developed countries).<sup>1</sup> Pneumonia is the top infectious killer of children under five years worldwide, resulting in 935,000 deaths each year.<sup>2</sup> A subgroup of children with pneumonia develop recurrent or persistent pneumonia that is one of the most significant reasons for referral to pediatricians and is still a major challenging disease.<sup>3</sup> The causes of persistent or recurrent pneumonia overlap noticeably. The factors related to these infections might be recurrent aspirations, congenital malformations of the upper or lower respiratory tract and cardiovascular system, defects in clearance of airway secretions particularly cystic fibrosis, ciliary dyskinesia, or immune deficiency disorders.<sup>4</sup> There is limited data on the underlying diseases predisposing to recurrent or persistent pneumonia in children. In addition, few studies have addressed this problem in the developing world.<sup>5-7</sup> There is no data available

on the etiology of persistent or recurrent pneumonia in children in Iran. Identification of the etiologic factors of recurrent and persistent pneumonia can facilitate prevention, diagnosis, and management of these diseases in children.<sup>8</sup> The aim of this study was to determine the prevalence and underlying causes of recurrent or persistent pneumonia in children.

## Materials and Methods

We conducted a retrospective, cross-sectional study of children under 18 years of age admitted to the Pediatric Department of National Research Institute of Tuberculosis and Lung Disease (NRITLD), Massih Daneshvari Hospital between May 2007 and May 2013 with a hospital diagnosis of pneumonia to find out the prevalence of recurrent and persistent pneumonia and to determine their underlying diseases. The hospital is a pulmonary referral center that also serves as a pediatric hospital, located in Tehran, the capital of Iran. The diagnosis of pneumonia was established based on cough, chest wall in-drawing and/or difficult breathing, fever (rectal temperature > 38°C), tachypnea (respiration rate  $\geq$  50/minute in infants 3 to 12 months old;  $\geq$  40 /minute in children 12 to 60 months old;  $\geq$  30 /minute in children older than 60 months), and lobar or bronchopneumonic infiltration detected on chest X-ray.<sup>9</sup> Persistent pneumonia was defined as continuation of symptoms and radiologic abnormalities for more than 30 days in spite of receiving antibiotics for at least 10 days.<sup>7</sup> Recurrent pneumonia was defined as 2 episodes of pneumonia per year or three episodes of pneumonia at any time of life.<sup>3</sup> A standardized data extraction form was used to obtain information

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about demographic characteristics including gender, age of the child, age at diagnosis, duration of time between the onset of symptoms and diagnosis on first hospitalization, known contact with tuberculosis patients, history of foreign body aspiration, clinical and radiographic findings, laboratory results, and investigations for underlying diseases. The underlying diseases were recorded based on the diseases that were diagnosed with pneumonia, including immune deficiency disorders, recurrent wheezing, bronchial asthma, rhinosinusitis, aspiration syndromes, congenital anomalies, pulmonary tuberculosis (TB), primary ciliary dyskinesia, and gastroesophageal reflux.<sup>4,10</sup> Patients previously diagnosed with cystic fibrosis were excluded.

Underlying disorders were confirmed in each case according to the clinical features and diagnostic tests, including complete blood count, pulmonary function tests with methacholine challenge, sweat chloride testing, X-ray and/or computerized tomography of the chest and sinuses, bronchoscopy, echocardiography, barium swallow or esophageal pH manometry, quantitative serum immunoglobulins (IgA, IgG, and IgM) flow cytometry, human immunodeficiency virus (HIV) antibody assay, sputum microbiology, gastric lavage or broncho-alveolar lavage (BAL) samples, and tuberculin skin test. Descriptive statistics were used to analyze the data in our study.

## Results

From May 2007 to May 2013, 601 patients were admitted to the hospital with a diagnosis of pneumonia; 229 (34.64 %) of them fulfilled the definition for persistent and/or recurrent pneumonia with a mean age of 8 years (between 1 month and 17 years). There were 103 (44.98%) females and 126 (55%) males. Two children (1%) had onset of symptoms before 3 months of age, 13 (6%) between 3 and 12 months, 65 (28%) between 1 and 5 years and 149 (65%) after the age of 5 years. The most common presenting symptoms included cough in 212 (92.5%) cases, fever in 135 (58.9%), and respiratory distress in 61 (26.5%) cases. On examination, 136 (59.3%) cases had crackle, 62 (27%) cases had wheezing, 14 (6%) cases had decreased sound, 13 (5.6%) cases had clubbing, 1 (0.4%) case had hepatosplenomegaly, and 2 (0.8%) cases had rickets.

Imaging findings were available for 164 (71.6%) cases: 33 had chest X-rays, 102 had chest CT-scans and 29 had both. Chest X-ray

revealed infiltration in 14 (22%) cases, consolidation in 6 (9.6%), and lymphadenitis in 3 (4.8%). Chest CT showed infiltration in 38 (29%) cases, consolidation in 58 (44%), bronchiectasis in 32 (24.4%), air trapping in 19 (14.5%), atelectasis in 12 (9%), plural effusion in 8 (6%), interstitial lung disease in 2 (1.5%), and congenital lobar emphysema in 2 (1.5%).

Bronchoscopy was performed for 30 patients: foreign body was identified in 1 patient. In two patients, lavage led to identification of pulmonary alveolar proteinosis (PAP). Gastroesophageal reflux disease (GERD) was diagnosed in 63 of 81 (77.7%) patients using barium swallow, esophageal pH manometry and abdominal ultrasonography. Echocardiography was performed for 73 patients; an abnormality was identified in 5 of 17 (29%) cases of persistent pneumonia, and 23 of 56 (41%) cases of recurrent pneumonia.

### Underlying illnesses of persistent pneumonia

Persistent pneumonia was diagnosed in 101 (44.10%) patients. Predisposing factors could be recognized in 80 (78.20%) patients. The underlying illnesses found in children with persistent pneumonia are shown in Table 1.

Twenty-one (26.25%) patients had aspiration syndrome; GERD was identified in 17 (six patients had concurrent diseases), respiratory foreign body (FB) in 1, and other aspiration syndrome due to cerebral palsy in 1, seizure in 1 and Werdnig-Hoffman in 1.

One (1.25%) patient had immunodeficiency disorder; i.e. agammaglobulinemia. The causes of congenital heart disease included ventricular septal defect (VSD) in 1, tetralogy of Fallot (TOF) in 1, mitral regurgitation (MR) in 1, and complex anomalies in 2 (6.25%). Recurrent wheezing and asthma were identified in 23 (28.75%) and 2 (2.5%) patients, respectively. Rhinosinusitis was identified in 9 of 11 patients with sinus imaging (only two patients had rhinosinusitis alone). One (1.25%) patient had thalassemia major.

Pulmonary TB was diagnosed in 31 (38.75%) patients. Positive microbiological tests for TB were found in 29 patients; the other patients had clinical features, radiological findings and close contact with known adult cases of TB.

### Underlying illnesses of recurrent pneumonia

Recurrent pneumonia was diagnosed in 128 of 229 (55.89%) patients. Predisposing factors could be identified in 114 (89.06%)

**Table 1.** Underlying illnesses of persistent pneumonia in this study, compared with results from previous studies.

	Current Study	Egypt	India, 2003 <sup>5</sup>	India, 2009 <sup>7</sup>
<b>Cases with persistent pneumonia causes</b>	101 (44.10)	27 (2.20)	19 (0.86)	41*
<b>Aspiration syndrome (%)</b>	21 (20.79)**	7 (25.92)	3 (15.79)	13 (31.71)
<b>Congenital heart disease (%)</b>	5 (4.95)	4 (14.82)	0	2 (4.88)
<b>Immune deficiency disorder (%)</b>	1 (0.99)	4 (14.82)	1 (5.26)	3 (7.32)
<b>Asthma (%)</b>	2 (1.98)	0	5 (26.32)	0
<b>Recurrent wheezing (%)</b>	23 (22.77)	0	0	0
<b>Anomalies of respiratory tract (%)</b>	0	1 (3.70)	0	2 (4.88)
<b>Pulmonary TB (%)</b>	31 (30.69)	6 (22.22)	6 (31.58)	8 (19.5)
<b>Other (%)</b>	1 (0.99)	2 (7.41)	1 (5.26)	12 (29.27)
<b>Unknown (%)</b>	21 (20.79)	3 (11.11)	3 (15.79)	1 (2.44)

\*Number of all patients with pneumonia was unknown; \*\*six patients with GERD had concurrent diseases

**Table 2.** Underlying illnesses of recurrent pneumonia in this study, compared with results from previous studies.

	Current Study	Netherland	Canada	India	Turkey	Egypt
<b>Patients with recurrent pneumonia causes (%)</b>	128 (21.3)	62 (48.82)	238 (8.06)	70 (3.09)	62 (10.42)	86 (7)
<b>Aspiration syndrome (%)</b>	59 (51.75)*	16 (25.81)	127 (53.36)	21 (30)	11 (17.74)	13 (15.12)
<b>Congenital heart disease (%)</b>	23 (20.17)*	3 (4.84)	22 (9.24)	0	7 (11.29)	9 (10.46)
<b>Immune deficiency disorder (%)</b>	9 (7.89)	10 (16.13)	24 (10.08)	11 (15.71)	11 (17.74)	6 (6.98)
<b>Asthma (%)</b>	14 (12.28)	0	19 (7.98)	10 (14.28)	19 (30.65)	11 (12.79)
<b>Recurrent wheezing (%)</b>	23 (20.17)	0	0	0	0	0
<b>Anomalies of respiratory tract (%)</b>	8 (7.02)	10 (16.13)	18 (7.56)	6 (8.57)	3 (4.84)	4 (4.65)
<b>Pulmonary TB (%)</b>	2 (1.57)	0	0	5 (7.14)	0	10 (11.63)
<b>Other (%)</b>	10 (8.76)	1 (1.61)	23 (9.66)	10 (14.28)	5 (8.06)	11 (12.79)
<b>Unknown (%)</b>	14 (10.94)	19 (30.65)	18 (7.56)	11 (15.71)	6 (10)	14 (16.28)

\*In the current study, concurrent diseases were identified in 30 and 8 patients with Aspiration syndrome and Congenital heart disease, respectively.

patients. The underlying illnesses found in children with recurrent pneumonia are presented in Table 2.

Fifty-nine (51.75%) patients had aspiration syndrome; GERD was identified in 46 (30 patients had other concurrent diseases), respiratory FB in 2, and other aspiration syndrome due to esophageal atresia in 2, cerebral palsy in 4, seizure in 3, myasthenia gravis in 1 and paraplegia in 1.

Nine (7.89%) had immunodeficiency disorder; common variable immune deficiency (CVID) was found in 5, interleukin deficiency in 2, and ataxia telangiectasia in 2 patients.

The causes of congenital heart disease included atrial septal defect (ASD) in 1, mitral regurgitation (MR) in 4, patent foramen ovale (PFO) in 1, transposition of the great arteries (TGA) in 1, ventricular synchrony in 1, dextrocardia in 2, complex anomalies in 13 (8 patients had other concurrent diseases).

Recurrent wheezing and asthma were identified in 23 (20.17%) and 14 (12.28%) patients, respectively. Rhinosinusitis was identified in 34 of 38 patients with sinus imaging (only 4 patients had rhinosinusitis alone). Pulmonary TB was diagnosed in 2 (1.57%) patients, all of whom had positive microbiological tests for TB.

Eight patients (7.02%) had congenital anomaly of the respiratory tract; 2 patients had PAP, 4 had Swyer-James syndrome (SJS) and 2 had congenital lobar emphysema. Other illnesses were identified in 10 patients; these included cystic fibrosis in 5 (4.38%) patients and primary ciliary dyskinesia (PCD) in 5 (4.38%).

## Discussion

The present study demonstrated that an underlying cause was identified in most patients with persistent or recurrent pneumonia. In persistent or recurrent pneumonia, the most frequent underlying cause was aspiration syndrome, followed by hyperreactive airway disease or asthma, pulmonary TB, congenital heart disease, and immunodeficiency disorders.

The incidence and mortality rate of pneumonia in children are 10 times higher in developing countries than developed countries.<sup>9</sup> Additionally, it is important to note that lack of epidemiological reports from developing countries makes it difficult to design global strategies for prevention, diagnosis, and treatment.<sup>8</sup>

Persistent and recurrent pneumonia have been reported as < 1% – 2% and 1% – 49% in previous studies, respectively.<sup>5-8,11-14</sup> In the present study, a diagnosis of persistent and recurrent pneumonia was established in 17% and 21% of the children, respectively. This difference in the rate of persistent pneumonia may be due to the fact that our study was performed in a referral pediatric hospital. However, Hoving, et al. noted that 48% of the patients had recurrent pneumonia in a general hospital; the rate was higher than previous studies performed in tertiary care referral hospitals.<sup>11</sup> Effective treatment of persistent or recurrent pneumonia in children is based on a definitive diagnosis of the etiologic factors.<sup>3,14</sup> Thus, the risk of irreversible or progressive lung damage is diminished.<sup>15</sup> The results of studies on the underlying causes of persistent and recurrent pneumonia are summarized in Tables 1 and 2 in which more notable differences are presented. This may be due to patient selection bias related to the study settings and design.<sup>11</sup> Case control studies such as a recent study in Italy might provide a better approach to these patients.<sup>10</sup>

Many studies have shown that aspiration syndrome is the most common cause of persistent or recurrent pneumonia in children.<sup>5,8,11,12,16-18</sup> Aspiration syndromes include all situations in which oropharyngeal contents are inhaled into the lungs. They are most frequently related to GERD, swallowing dysfunction, structural abnormalities, and neurological disorders. Neurological disorders, such as cerebral palsy, muscular dystrophy, isolated superior laryngeal nerve damage, and vocal cord paralysis may be related to the risk of aspiration. Anatomic disorders associated with an increased risk of aspiration include esophageal atresia, tracheoesophageal fistula, cleft palate, laryngeal cleft, duodenal obstruction, or malrotation.<sup>19</sup> In our study, aspiration pneumonia was identified in 35% of the patients; 59 patients had recurrent pneumonia and 21 had persistent pneumonia. We noted that aspiration syndrome was the most common underlying disorder in patients with recurrent pneumonia. FB aspiration was detected in 3 patients; one patient was diagnosed by bronchoscopy. Identification of likely foreign body aspiration (FBA) is essential since it is a major cause of morbidity in children. More problematic patients are those in whom aspiration is not observed. Consequently, the child may present late with wheezing,

persistent or recurrent cough, lung abscess, persistent or recurrent pneumonia, hemoptysis, or focal bronchiectasis.<sup>20</sup> A CXR is the initial diagnostic investigation. However, if FBA is suspected but has not been detected on physical examination or radiological tests, flexible bronchoscopy should be performed.<sup>21</sup>

Tuberculosis is one of the 10 main causes of mortality in children with a worldwide estimation of 130,000 deaths per year.<sup>22</sup> In 2014, the incidence rate of TB from Iran was estimated at 13 cases per 100,000. Iran was classified in country groupings with 25% of notified cases globally.<sup>1</sup> Two situations influence the clinician to suspect that a child has TB. The first occurs when an ill child has a history of chronic illness of usually more than 3 weeks of duration that includes cough and fever, weight loss, or failure to thrive, and the symptoms are not responsive to antibiotics. This is a common situation in the developing countries. The second situation is when a child has a history of contact with an adult case of pulmonary TB.<sup>23,24</sup> In previous reports on recurrent pneumonia, pulmonary TB was detected as a cause in 5% – 12% of the patients.<sup>8,17,19</sup> Studies have identified pulmonary TB as a cause of persistent pneumonia in 19% – 32% of the patients.<sup>5,7,8</sup>

In our study, pulmonary TB was the most common underlying disorder in patients with persistent pneumonia. The high rate of pulmonary TB requires more attention to prevention, diagnosis, and control of this disease in our region.

In pre-school children, recurrent wheezing is defined as at least three episodes of respiratory tract infections in a time period of six months, parental reports of breathing difficulty and physician diagnosed dyspnea.<sup>5</sup> We found that recurrent wheezing was a cause of recurrent and persistent pneumonia. Asthma has been reported as an important underlying cause of recurrent and persistent pneumonia in children.<sup>6,7,25,26</sup> In our study, asthma was identified in more patients with recurrent pneumonia than persistent pneumonia. Nevertheless, asthma with recurrent wheezing was found in most patients with persistent pneumonia. In contrast to our study and previous reports, a study from the Netherlands discussed the diagnostic confusion between recurrent pneumonia and asthma. The study reported that asthma was not a common underlying cause of recurrent pneumonia in children, and a diagnosis of either recurrent pneumonia or asthma was questionable after critical review.<sup>11</sup> However, one recent Italian case-control study found that wheezing, atopy/allergy, asthma, and chronic rhinosinusitis were the main factors associated with recurrent pneumonia.<sup>10</sup> In agreement with this study, we found rhinosinusitis in most patients with recurrent pneumonia.

The limitations of this study include its retrospective nature, lack of facilities for immunological work-up, and an irregular set of investigations for all patients. If the investigations could have been followed up, there would have been fewer patients with undiagnosed causes.

In conclusion, our findings showed that most children with persistent and recurrent pneumonia had an underlying disease that could be revealed by investigations. In the present study, the most common underlying causes of persistent pneumonia were pulmonary TB, recurrent wheezing and asthma, and aspiration syndrome. The frequent underlying causes of recurrent pneumonia in our study were aspiration syndrome, recurrent wheezing and asthma, followed by congenital heart disease. The results of the present study would help pediatricians in our region to prevent and control the frequent underlying causes of persistent or recurrent pneumonia in children.

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