Underlying Causes of Recurrent Pneumonia in Children

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Objectives: To determine the relative frequency of underlying factors for recurrent pneumonia and the proportion of patients in whom the underlying illness diagnosis was known prior to pneumonia recurrence.

Methods: Retrospective medical record review for a 10-year period from January 1987 through December 1997 at The Hospital for Sick Children in Toronto, Ontario, a tertiary care pediatric hospital. Recurrent pneumonia was defined as at least 2 pneumonia episodes in a 1-year period or at least 3 during a lifetime.

Results: Of 2952 children hospitalized with pneumonia, 238 (8%) met criteria for recurrent pneumonia. An underlying illness diagnosis was identified in 220 (92%). Of these, the underlying illness was diagnosed prior to pneumonia in 178 (81%), with the first episode in 25 (11%), and during recurrence in 17 (8%). Underlying illnesses included oropharyngeal incoordination with aspiration syndrome (114 cases [48%]), immune disorder (24 [10%]), congenital cardiac defects (22 [9%]), asthma (19 [8%]), pulmonary anomalies (18 [8%]), gastroesophageal reflux (13 [5%]), and sickle cell anemia (10 [4%]). Clinical clues to diagnosis were recurrent infections at other locations and failure to thrive in the cases of an immune disorder, recurrences involving the same location in those with underlying pulmonary pathology, the association of respiratory symptoms with feeding in those with gastroesophageal reflux, or recurrent wheezing in asthmatic children.

Conclusions: Recurrent pneumonia occurs in fewer than one tenth of all children hospitalized with pneumonia. Most of them have a known predisposing factor. The most common cause was oropharyngeal incoordination.

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Editor's Note: This neat, simple study provides valuable information that should allow us to breathe easier regarding unwanted surprises in the case of children with recurrent pneumonia.

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PNEUMONIA IS a major problem in children, especially those younger than 5 years, accounting for up to 5 million deaths each year in developing countries.[1-4] In North America, the annual incidence of pneumonia ranges from 30 to 45 cases per 1000 children in those younger than 5 years to 16 to 22 cases per 1000 children in those aged 5 years and older.[5,6] A subgroup of these children suffer from recurrent pneumonia, raising the question of whether there is an underlying illness predisposing them to such pneumonia recurrences.

Recurrent pneumonia has been defined as at least 2 pneumonia episodes in 1 year or more than 3 at any time, with radiographic clearing between episodes.[7]

Although several review articles[7-11] describe possible approaches to investigations for recurrent pneumonia, there are surprisingly few primary studies of such children. These previous series may not be generalizable to most recurrent pneumonia patients cared for in our setting because they have consisted of immunocompromised populations,[12-14] were limited to cases of bacterial pneumonia,[15-17] or were not performed in an industrialized country.[18] The purpose of this study is to describe the underlying illnesses of children with recurrent pneumonia hospitalized in a tertiary care pediatric hospital. From these data, a series of investigations for the child with recurrent pneumonia is proposed.

RESULTS

Two thousand nine hundred fifty-two patients were admitted to the hospital with pneumonia during a 10-year span; 238 (8%) met the definition for recurrent pneumonia. Of these, 139 (58.4%) were male. The mean age when recurrent pneumo-

PATIENTS AND METHODS

A medical record review was performed on all children with recurrent pneumonia. All children admitted to The Hospital for Sick Children, Toronto, Ontario, from January 1987 through December 1997 with a hospital discharge diagnosis of pneumonia were identified. The hospital is a tertiary care referral center but also serves as the pediatric hospital for children in downtown Toronto. Children younger than 18 years are admitted to the hospital. The records of all children with diagnostic codes corresponding to a diagnosis of pneumonia were identified according to the *International Classification of Diseases, Ninth Revision, Clinical Modification*[19] (codes 480-487, 507). Patients were included in this analysis if they had 2 or more episodes of pneumonia per year or 3 or more episodes in a lifetime and if there was radiographic confirmation of pneumonia during hospital admission. Only patients with pneumonia who were hospitalized or whose diagnosis was recorded on admission to our hospital would be identified.

Patients were classified according to underlying illnesses that have previously been associated with childhood pneumonia.[7-11] These include oromotor incoordination and swallowing dysfunction predisposing to aspiration syndrome[20-22]; immune disorders, including primary and acquired immunodeficiency syndrome[13,14]; underlying congenital heart defects[23,24]; underlying lung and airway problems, such as bronchial asthma[25,26]; and gastroesophageal reflux.[27,28] Using a standardized data extraction form, information was obtained on patient demographic characteristics, including date of birth, sex, age at diagnosis, percentile weight on first hospitalization, dates of hospital admissions and discharges, and time between onset of respiratory symptoms and age at which the underlying illness diagnosis was determined. The duration of time between the underlying illness diagnosis and the initial pneumonia recurrence was calculated.

Confirmation of underlying pulmonary pathologic characteristics consisted of results from laboratory testing, including sweat chloride testing, pulmonary function tests with methacholine challenge, a computed tomographic scan of the chest, and/or laryngoscopy and bronchoscopy. Confirmation of cardiac anomalies was based on findings from an echocardiogram. Most cases of aspiration syndrome were diagnosed clinically. In some patients, however, fluoroscopic feeding studies were performed by occupational therapists to confirm oropharyngeal incoordination resulting in aspiration. Gastroesophageal reflux was documented either with a barium swallow or esophageal pH manometry.

Quantitative serum immunoglobulins (IgG, IgA, and IgM) were quantified using a nephelometer analyzer (Behring Nephelometer Analyzer; Behring Diagnostics Inc, Newark, NJ). The T and B lymphocytes were assayed using lymphoproliferation studies to assay cell function, and flow cytometry was used to assess the number of lymphocytes. Human immunodeficiency virus (HIV) antibody was assayed from serum samples using various enzyme-linked immunosorbent assay systems (IAF Biochem Detect HIV; Biochem Pharma, Montreal, Quebec, and MEIA; Abbott Laboratories Inc, Abbott Park, Ill). Microbiological studies, such as sputum samples and nasopharyngeal swabs, were obtained in only a subgroup of patients.

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nia was diagnosed was 3.7 years (age range, 2.5 months-15.6 years).

An underlying illness was identified in 220 (92.4%) of the patients (**Table 1**). One hundred fourteen patients (47.9%) had an underlying aspiration syndrome secondary to oropharyngeal muscular incoordination leading to an inability to handle respiratory tract secretions. Twenty-four patients (10.1%) had immune disorders; 22 (9.2%) had congenital heart disease; 19 (7.9%) had bronchial asthma; 18 (7.6%) had congenital or acquired anomalies of the airways or lungs; 13 (5.4%) had gastroesophageal reflux; 10 (4.2%) had sickle cell anemia; and no predisposing factors could be identified in the remaining 18 (7.6%).

All patients with aspiration disorders had involvement on radiography of more than one lung lobe. Of these, cerebral palsy accounted for nearly half the causes. The mean age at diagnosis of recurrent pneumonia in children with aspiration disorders was 6.3 years. Of the 24 patients who had immune disorders, 13 had malignant neoplasms; 5, dysgammaglobulinemia (3, hypogammaglobulinemia; 1, hyperimmunoglobulin E syndrome; 1, agammaglobulinemia); 5, HIV infection; and 1, autoimmune pancytopenia. The mean age at diagnosis of recurrent pneumonia in children with immune disorders was 3.8 years.

The patients with congenital heart disease included 16 (72.7%) with isolated left to right shunts, including atrial and ventricular septal defects, as well as patent ductus arteriosus. Six other patients had more complex cardiac disorders. The mean age at diagnosis of recurrent pneumonia in children with congenital heart disease was 1.8 years. The mean age at diagnosis of recurrent pneumonia in the 19 children with asthma was 4.5 years.

Airway and pulmonary anomalies were diagnosed early in life and were found in 18 patients. The mean age of diagnosis was 4 months (age range, 0 days to 6 months). Children with tracheoesophageal fistulas formed the largest group in this category with 7 patients. Two patients each had congenital cystic adenomatoid malformation, vocal cord paralysis, subglottic stenosis, and tracheomalacia. The 3 remaining patients had an esophageal bronchus, a tracheoesophageal cleft, and tracheal stenosis, respectively. The mean age at diagnosis of recurrent pneumonia in children with airway and pulmonary anomalies was 3.5 years.

Associated gastroesophageal reflux was found in 13 patients with recurrent pneumonia. In all patients there was a notable association between feeding and subsequent respiratory symptoms. All of these children were neurologically normal on physical examination. The mean age at diagnosis of recurrent pneumonia in children with gastroesophageal reflux was 1.4 years.

Children for whom no underlying etiologic diagnosis was identified had growth, development, and

Table 1. Patients With Underlying Causes of Recurrent Pneumonia	
Underlying Illness	**No. (%)**
Aspiration syndrome	114 (47.9)
Immune disorder	34 (14.3)
Congenital heart disease	22 (9.2)
Bronchial asthma	19 (8.0)
Anomalies of the respiratory system	18 (7.6)
Gastroesophageal reflux	13 (5.4)
Unknown	18 (7.6)

Table 2. Timing of Underlying Illness Diagnosis Relative to the Number of Pneumonia Episodes				
Underlying Illness	**Diagnosed Prior to Pneumonia**	**Diagnosed After First Pneumonia Episode**	**Diagnosed After Pneumonia Recurrence**	**Total**
Aspiration syndrome	109	1	4	**114**
Immune disorder	26	7	1	**34**
Congenital heart disease	22	0	0	**22**
Bronchial asthma	12	0	7	**19**
Anomalies of the respiratory system	9	7	2	**18**
Gastroesophageal reflux	0	10	3	**13**
Total	**178**	**25**	**17**	**220**

physical examination findings within reference limits. The mean age at diagnosis of recurrent pneumonia in these children was 4.8 years. All were asymptomatic prior to and after the illness leading to hospitalizations. Findings from all hospital investigations were within reference limits.

One hundred seventy-eight patients (80.9%) were diagnosed with an underlying illness prior to the first episode of pneumonia. Twenty-five patients (11.4%) were diagnosed during the first episode of pneumonia, and 17 (7.7%) were diagnosed only after recurrence (**Table 2**). Aspiration disorders, immune disorders, and congenital heart disease were underlying illnesses that tended to be known prior to the first pneumonia. Asthma, respiratory tract anomalies, and gastroesophageal reflux tended to be diagnosed after the first or recurrent pneumonia (χ^2 = 127, P = .001).

Of the 17 underlying illness diagnoses discovered after pneumonia recurrence, asthma was the most common, occurring in 7 patients, followed by oropharyngeal incoordination leading to aspiration in 4. The remaining causes included gastroesophageal reflux disease in 3 patients, underlying airway anomalies in 2, and immune disorders in 1.

Prior to their asthma diagnosis, children with asthma presented with episodes of pneumonia but were otherwise healthy. They underwent extensive laboratory evaluation, including sweat chloride and quantitative serum immunoglobulin measurements. Growth, development, and physical examination findings were all within reference limits. These children were clinically diagnosed as having asthma (multiple episodes of partially reversible airway obstruction) or diagnosed by pulmonary function tests.

Recurrent pneumonia prior to a diagnosis of an underlying aspiration disorder was seen in 4 cases. One patient who presented following recurrent pneumonia was found to have oropharyngeal incoordination with hypotonia. This patient was diagnosed as having nemaline rod myopathy after abnormal findings from electromyographic studies. The second patient had a brainstem tumor and presented with recurrent bilateral pneumonia from silent aspiration; neurological signs and symptoms, including headache, loss of appetite, and weight loss, did not develop until after the second episode of pneumonia. The remaining 2 patients had familial dysautonomia (Riley-Day syndrome) but were initially diagnosed as having bronchial asthma. One child had a family history of the disease prior to hospitalization with pneumonia.

In the group of patients with gastroesophageal reflux disease, all were diagnosed as a result of having a pneumonia episode. Ten patients were diagnosed before age 1 year during the first episode of pneumonia. Three patients were diagnosed at age 12 to 18 months after recurrent pneumonia.

Two patients with an underlying respiratory tract anomaly (1 with congenital cystic adenomatoid malformation and 1 with esophageal bronchus) were diagnosed after pneumonia recurrence. Both patients had recurrent pneumonia involving the same lung lobes. Seven patients (2 with tracheoesophageal fistulas; 1, congenital cystic adenomatoid malformation; 2, subglottic stenoses; 1, tracheomalacia; and 1, bronchomalacia) were diagnosed during the first episode of pneumonia.

One patient with hypogammaglobulinemia was diagnosed following pneumonia recurrence. This patient also presented with other features of immune disorders, including recurrent otitis media, oral candidiasis, and failure to thrive. Two patients were diagnosed with sickle cell anemia during their first episode of pneumonia. This was suspected secondary to anemia, race, and/or family history. The remaining 8 patients had known sickle cell anemia prior to pneumonia presentation. Five patients with an underlying immune disorder presented with pneumonia (3 with acquired immunodeficiency syndrome, 1 with acute lymphoblastic leukemia, and 1 with a neuroblastoma). Of the 3 patients with HIV infection, the diagnosis was suspected during the initial episode of pneumonia because of the presence of the classic interstitial pattern on chest radiograph films and multiple etiologic agents on bronchoalveolar lavage specimens, including *Pneumocystis carinii*, respiratory syncytial virus, influenza, parainfluenza, and cytomegalovirus. The patient with acute lymphoblastic leukemia presented with pneumonia and an elevated white blood cell count.

COMMENT

Our study demonstrates that most patients with recurrent pneumonia are known to have an underlying illness at the time of pneumonia recurrence. The most fre-

quent underlying illness is aspiration pneumonia secondary to oropharyngeal incoordination, followed by immune disorders, congenital heart disease, asthma, respiratory system anomalies, gastroesophageal reflux, and sickle cell anemia.

The remaining patients, however, who presented with recurrent pneumonia without a known underlying illness diagnosis present an interesting diagnostic challenge. In more than half, a final diagnosis was determined. Asthma was the most common illness diagnosed in this population, followed by disorders causing aspiration, gastroesophageal reflux, and respiratory tract anomalies. Interestingly, congenital immune disorders was rarely a diagnosis following investigations for pneumonia recurrence. In approximately one tenth of our population, a predisposing factor was not found despite comprehensive evaluation. In these patients, however, follow-up information was incomplete.

A considerable number of children with recurrent pneumonia in our study had concomitant sickle cell anemia. It has long been recognized that children with homozygous sickle cell anemia are at increased risk for pneumonia relative to other children, even with penicillin prophylaxis treatment.[29-31]

In children with recurrent pneumonia, age and location of pneumonia recurrence may be important clues in discovering underlying illnesses. In the first few months of life, structural or functional anomalies of the airway may present as multiple pneumonias of the same lung lobe. Before age 18 months, gastroesophageal reflux may contribute to recurrent pneumonia. These illnesses should be confirmed with barium esophagography and/or continuous pH monitoring in children in this age group presenting with recurrent pneumonia.[32] Bilateral interstitial pneumonias on chest radiograph films and/or the presence of opportunistic infections were paramount in diagnosing HIV infection as an underlying factor in recurrent pneumonia. Older children with recurrent pneumonia were often found to have asthma following extensive investigation.

Our study design had several limitations. Our study includes only hospitalized patients. However, one would suspect that most children with recurrent pneumonia would ultimately be hospitalized. By using the *International Classification of Diseases, Ninth Revision, Clinical Modification*[19] codes for hospital discharge diagnoses of pneumonia to identify children with recurrent pneumonia, we may be underestimating the true number of patients with this condition. Other children who would have met clinical criteria for pneumonia would not have been included once other diagnoses, such as cystic fibrosis, were made. Perhaps identifying children by hospital admission diagnoses or secondary diagnoses would have allowed a more representative sample.

The radiographic diagnosis of pneumonia in our patients is susceptible to bias.[33] Reports describing chest radiograph films could not always differentiate atelectasis or consolidation. The occurrence of true pneumonia may have been overestimated.

The retrospective nature of our study restricted diagnoses and the types of investigations performed at the time the patients were diagnosed with pneumonia. Since children had not undergone a uniform set of investigations, diagnoses may have been inaccurate or incomplete. Furthermore, our study ascribes a single underlying illness as the cause of recurrent pneumonias, potentially excluding additional factors or multiple diagnoses in children. The assumption that an underlying patient illness contributed directly to the recurrence of pneumonia in our study population is also a weakness in our study. The severity of underlying illnesses was not assessed, and the "underlying diagnosis" may have been coincidental, rather than causal.

To our knowledge, this study represents the largest pediatric series of recurrent pneumonia. Most instances of recurrent pneumonia have a known underlying cause, namely oropharyngeal incoordination predisposing to aspiration. This underlying cause has tended to be ignored in previous studies of pediatric recurrent pneumonia.

In most children with recurrent pneumonia, underlying illnesses are known prior to the first episode. In undiagnosed recurrent pneumonia, however, asthma and gastroesophageal reflux, in particular, should be eliminated in the differential diagnosis.

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