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Evaluation of Recurrent Pneumonia

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The incidence of community-acquired pneumonia in children ranges from 15 to 40/1000 children in developed countries.[1,2] Recurrent pneumonia is defined as ≥2 episodes in a single year or ≥3 episodes ever, with radiographic clearing of densities between occurrences.[3] By this definition, recurrent pneumonia occurs in 7.7–9% of all children with pneumonia.[2,4–6]

There is no single common cause for recurrent pneumonia. In one series, 40% of 81 children had asthma, 10% had aspiration and 5% had immunodeficiency syndromes.[7] Similarly in 60 of 71 hospitalized children with a known underlying condition, 32% had asthma, 15% had gastroesophageal reflux, 10% had immunodeficiency and 3% had aspiration syndromes.[5] In contrast, series from Canada[4] and India[6] found aspiration to be the leading cause.

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Evaluation and treatment depends on whether disease recurs in the same or different regions. Densities recurring in the same region imply a localized area of intraluminal obstruction, extraluminal compression or structural abnormalities of the airway or lung parenchyma. The most common cause for intraluminal obstruction in children is a retained foreign body. Extraluminal compression results from enlarged lymph nodes, enlarged or aberrant vessels, or parenchymal tumors. Structural airway abnormalities include localized bronchial stenosis or bronchomalacia, tracheobronchus or isolated areas of bronchiectasis. Parenchymal lesions include pulmonary sequestration, cystic adenomatoid malformation and bronchogenic cysts.

Right middle lobe syndrome is a unique entity of recurrent right middle lobe pneumonia and atelectasis. That lobe is prone to infection and collapse because the bronchus arises from the bronchus intermedius at an acute angle and is relatively long before it subdivides into segments. Adjacent lymph nodes can compress it when they enlarge. Finally there is no collateral ventilation between the right middle lobe and other lobes. The most common noninfectious cause of right middle lobe syndrome is asthma; tuberculosis remains the most common infectious etiology.

Evaluation of recurrent pneumonia in a single region begins with airway endoscopy. Direct visualization detects dynamic airway collapse and identifies lesions as distal as subsegmental bronchi. Samples from airways or alveolar spaces can be obtained for culture and cytologic examination.

For distal lesions or those outside of the airway lumen, chest computerized tomography, magnetic resonance imaging and angiography are useful. These modalities have largely supplanted angiography and bronchography. When lymphadenopathy is present, tuberculin skin testing should be performed. If there is a suggestive history, acute and convalescent titers for histoplasmosis, blastomycosis or coccidioidomycosis should be obtained.

Children who develop recurrent pneumonia in varying lobes may have impairment in cough or mucociliary clearance mechanisms, diffuse airway narrowing that hampers airway clearance or local or systemic immune dysfunction. Aspiration "from above" is associated with impaired cough and diffuse airway narrowing. It results from swallowing dysfunction, due to central nervous system abnormality, neuromuscular disease or anatomic lesion of the oropharynx. A history of coughing during feedings should provoke evaluation

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of the swallowing mechanism by direct observation, videofluoroscopy or endoscopy. Patients who aspirate chronically may lose their cough reflex. Radionuclide salivagram with ^{99m}Tc-sulfur colloid is a sensitive and noninvasive method to detect chronic aspiration of oral contents.[8]

Material from the esophagus can be aspirated into the lungs in cases of esophageal stricture, foreign body, dysmotility, achalasia or gastroesophageal reflux. The association of gastroesophageal reflux with aspiration is difficult to prove. The utility of a lipid-laden macrophage index of cells obtained by bronchoalveolar lavage remains controversial, in that macrophages filled with exogenous lipid secondary to aspiration cannot be distinguished from those containing endogenous lipid associated with inflammation and cell death. Children who develop recurrent pneumonia from aspiration in association with gastroesophageal reflux tend to be younger than 2 years of age.[4–6]

Children with recurrent pneumonia from asthma are older.[4,5,7] Radiographic densities represent areas of infection, atelectasis or both. Recent polymerase chain reaction and culture evidence proves that the majority of asthma exacerbations are associated with viral infections.[9] Children who have a history of nocturnal cough, cough or wheeze with exercise or protracted coughing after upper respiratory illnesses should undergo spirometry and assessment of bronchodilator responsiveness, or they should receive an empiric trial of inhaled corticosteroids and bronchodilators.

Cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are disorders of mucociliary transport. CF should be considered in any child with recurrent pneumonia, especially when symptoms of intestinal malabsorption are present. Recovery of *Pseudomonas aeruginosa* from the respiratory tract, especially the mucoid form, is highly suggestive of CF. Patients with PCD typically have chronic purulent rhinitis as well as recurrent middle ear disease. Approximately one-half have situs inversus. The triad of sinusitis, situs inversus and bronchiectasis, called Kartagener syndrome, is a subset of patients with PCD.

Systemic immunodeficiencies cause recurrent sinopulmonary infections as well as infections outside the respiratory system. Abnormalities in phagocytosis, the most common of which is chronic granulomatous disease (CGD), result in defective killing of bacteria and fungi.[10] In a national registry of CGD patients, 80% had at least 1 episode of pneumonia, most commonly with *Aspergillus* spp. (41%), *Staphylococcus* spp. (12%) and *Burkholderia cepacia* (8%).[11] Pulsed field gel electrophoresis patterns of isolates from serial episodes of illness revealed that these are new, rather than persistent infections.[12]

Absence of immunoglobulins (Ig) which help opsonize and clear encapsulated bacteria results in recurrent infections. Complete absence of IgG (Bruton, or X-linked agammaglobulinemia) is an isolated B cell defect, while patients with common variable immunodeficiency (CVID) manufacture some Ig and have abnormalities of T cell function. In 19 patients with CVID, 68% had a reduced number of B cells and 79% had a decreased ratio of $CD4^+$ to $CD8^+$ cells.[13] Recurrent pneumonia occurred in 74% most commonly with *Streptococcus pneumoniae* (37%) and *Haemophilus influenzae* (26%). Replacement therapy with intravenous gammaglobulin (IVIG) significantly reduces mortality and morbidity. In 23 patients with agammaglobulinemia treated with IVIG, the incidence of pneumonia fell from 0.82 to 0.12 episode per patient per year.[14]

Some children with recurrent pneumonia have normal levels of IgG but low levels of IgG subclasses. IgG2 subclass deficiency is associated with poor antibody responses to polysaccharides. IgA deficiency is one of the most common antibody deficiencies, but most patients are asymptomatic unless there is a coexistent IgG subclass deficiency.[15]

T cell abnormalities are associated with both pulmonary and extrapulmonary infections. *Pneumocystis carinii* (*Pneumocystis jiroveci*), fungi and viruses are important pathogens.

In summary, the majority of children with recurrent pneumonia have an identifiable underlying cause. Careful history, physical examination and serial radiographs will direct the evaluation and provide a diagnosis with a minimum of confirmatory tests.

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