Respiratory sequelae of viral diseases: from diagnosis to treatment

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Abstract

Objective: the objective of the present article is to present a review of the main clinical issues faced by pediatricians while defining the diagnosis, management and prognosis of postinfectious bronchiolitis obliterans.

Sources: data from national and international scientific journals selected from the Lilacs and Medline databases.

Summary of the findings: with the purpose of establishing the diagnosis, a radiological investigation shows high levels of pulmonary insufflation, thickened bronchovascular bundles and, less often, bronchiectasis, atelectasis and pulmonary hyperlucency. The CT exam allows the visualization of structural and functional findings, such as air trapping, bronchiectasis and mosaic pattern. Lung function tests in children and infants always reveal significant reduction of expiratory flows. Pulmonary biopsy is not mandatory in order to confirm bronchiolitis obliterans. Diagnosis can be established through the combination of history of bronchiolitis, chronic obstructive pulmonary disease and typical tomographic findings. The treatment used by most services includes oral and inhaled corticosteroids and bronchodilators for long periods. The management of exacerbated conditions often requires antibiotics and physical therapy.

Conclusions: most patients present a favorable outcome with slow improvement of the pulmonary function and reduced necessity for supplementary oxygen. Some patients present progressive worsening of hypoxemia and CO2 retention, which leads to pulmonary hypertension and cor pulmonale. Postinfectious bronchiolitis obliterans is mild and moderate in most patients, with consequent good prognosis and low mortality.


Introduction

The advances in intensive therapy that have occurred over the last few years have allowed the survival of many children who, after being affected by serious respiratory infections, develop persistent and severe ventilatory sequelae. This clinical syndrome is called postinfectious bronchiolitis obliterans (BO).1,2 Its main characteristics are the severity of respiratory obstruction, the absence of response to the treatments employed as opposed to the most benign and self-limited conditions that follow acute viral bronchiolitis. The patient typically has wheezing, tachypnea, dyspnea, and persistent cough for weeks or months after the
initial infection. The disease may persist for years after its onset and may worsen due to exacerbations caused by viral infections, causing supuration, atelectasis, and pneumonias. There are no epidemiological data available, but apparently BO has a high prevalence in the southern region of Brazil, in Uruguay, Argentina and Chile, and it is one of the main causes of chronic obstructive pulmonary diseases in children in these regions, generating a demand for hospital and clinic services similar to that observed in patients with cystic fibrosis. The knowledge about the risk factors, physiopathology, inflammatory and pulmonary function disorders caused by this disease, which is not so rare in our patient population, is still scarce.

Phisiopatology

Etiology

Bronchiolitis obliterans is a disease characterized by an inflammatory process and fibrosis of the airways. Among the several etiologies described in children, such as inhalation of toxic substances, aspiration syndromes, and immunological diseases, postinfectious BO is the most frequent cause in our patient population. The major infectious agents that trigger fibrosis are the influenza, parainfluenza, and measles viruses, adenovirus, and respiratory syncytial virus. Mycoplasma pneumoniae may also be associated with the development of BO. More recently, with the improvement and diffusion of diagnostic methods for respiratory viruses, it is possible to know the prevalence and behavior of each of these agents. Nowadays, the investigation of viral etiology by immunofluorescence is carried out in many centers, which allows the identification of the viruses in cases of acute viral bronchiolitis, especially in the most severe cases. Nevertheless, many patients are referred for investigation weeks or months after the initial infection, whose etiological agent could not be identified.

Adenovirus is associated with the most severe cases. Factors such as viral genotype, immune response, viral load, genetic predisposition, and environmental influences can be associated with the severity of the disease in its acute phase and with its sequelae as well. In South America, the determination of adenovirus strains made during several years has shown that type 7, a new adenovirus variant, was the infectious agent in most severe and fatal cases.

Histology

The typical histological pattern of postinfectious BO is that of constrictive bronchiolitis, characterized by variable obstruction of the airways by fibrous tissue. In general, it is a lesion of the small airways with slight involvement of the pulmonary parenchyma. The bronchial mucous membrane is affected and its lumen is occupied by fibrous tissue, producing partial or total obstruction of terminal bronchioi. Collagen deposition occurs on the submucosa, leading to the progressive concentric narrowing and distortion of the bronchial lumen, mucus stasis and chronic infection. Two recent Brazilian studies of children with postinfectious BO have confirmed that, in most patients, lesions correspond to the pattern of constrictive bronchiolitis, which characteristically has a poor response to corticoid therapy.

Pulmonary Function

Functional studies involving children and infants have revealed, almost invariably, an enhanced reduction of expiratory flows. Bronchiolitis obliterans with a constrictive pattern is usually characterized by fixed obstruction and minimum response to the administration of corticoids. Table 1 presents the main pulmonary functional studies in children with BO. The obstructive pattern is predominant, especially when the test is applied in the first months or years after the initial event, as shown by Teper and Jones. Forced expiratory maneuvers show remarkable concavity and reduction of expiratory flows, especially of tele-expiratory flows, Figure 1 presents a forced expiratory maneuver performed in a 19-month-old infant with BO. The presence of reduced vital capacity suggesting a restrictive pattern occurs in few patients and is probably secondary to air entrapment. In the studies in which pulmonary volume was measured, the vast majority of patients presented a normal total pulmonary capacity. The functional studies performed several years after the onset of the disease showed an improvement in the ventilatory obstruction and normal spirometry in some patients.

Diagnosis

The diagnosis of BO is based on the past history of a lower airway infection, usually an acute viral bronchiolitis followed by a persistent chronic obstructive pulmonary disease. Clinically, the disease is characterized by cough, wheezing, crepitations and hypoxemia, which persist beyond the normal period observed in a bronchiolitis. Older children present intolerance of physical exercise and, quite often, tapering fingers. Initially, what draws our attention to this disease is the persistence of obstructive symptoms and the absence of response to the employed treatments, even with the use of systemic corticoid in high doses and the continuous use of oral and/or inhaled bronchodilators.

A plain chest x-ray typically reveals pulmonary hyperinflation, thickening of the bronchovascular bundles, hyperlucent, bronchiectasis, and atelectasis. The use of pulmonary scintigraphy with intravenous infusion of radioactive macroaggregates has good sensitivity to detect perfusion disorders. Perfusion and pulmonary ventilation disorders are almost always present in this disease. Hypoperfused areas correspond to regions with hypoxic vasoconstriction detected in a plain chest x-ray with hyperlucent and hyperinflated areas.
Bronchography, used until recently as a method for the detection of bronchiectasis, is no longer used since it is too invasive and due to the availability of higher quality methods such as computed tomography (CT). Nowadays, the exam that best describes pulmonary disorders is high-resolution CT. In Zhang series, the following disorders were observed, in order of frequency: bronchial thickening, bronchiectasis, and a mosaic pattern, which corresponds to areas of higher and lower attenuation (Figure 2). A CT is more sensitive than a conventional radiogram for the detection of segmental and subsegmental atelectasis and bronchiectasis. In addition, the comparison of inspiratory and expiratory images offers the possibility of combining structural and functional information, thus enabling the assessment of the presence of air entrapment and hypoxic vasoconstriction. The method is limited by the need for intubation and anesthesia in young children and the exposure to radiation exceeding over 100 times the radiation of a plain chest x-ray. Recently, some authors have proposed the use of a laryngeal mask or simply positive airway pressure instead of anesthesia and tracheal intubation to perform a CT examination, which may potentially increase the safety of the exam. However, the indication of high-resolution CT for the investigation of BO should be limited to patients in whom the disease is highly suspected.

The final diagnosis is obtained by means of an open lung biopsy. However, according to several authors, diagnosis can be done with a large margin of safety, based upon the presence of persistent symptoms of obstructive pulmonary disease and specific alterations on chest computed tomography. Recent studies, which combine high-resolution CT and lung biopsy have confirmed this. It is important to emphasize that lung biopsy not always confirms the diagnosis. According to the heterogeneous distribution of pulmonary lesions, the material obtained from a lung biopsy may contain slight histopathological alterations, which might easily go unnoticed.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Age</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teper17 Buenos Aires, Argentina</td>
<td>13</td>
<td>3 to 14 months</td>
<td>Forced expiratory maneuvers in infants</td>
<td>Severe obstruction in all patients</td>
</tr>
<tr>
<td>Jones18 Porto Alegre, Brazil</td>
<td>14</td>
<td>3 months to 3 years</td>
<td>Forced expiratory maneuvers in infants</td>
<td>13 patients with moderate and severe obstructive pattern, 1 patient with mixed pattern</td>
</tr>
<tr>
<td>Zhang3 Porto Alegre, Brazil</td>
<td>8</td>
<td>5 to 7 years</td>
<td>Spirometry</td>
<td>4 patients with obstructive pattern, 3 with mixed pattern, 1 normal</td>
</tr>
<tr>
<td>Colom19 Buenos Aires, Argentina</td>
<td>7</td>
<td>7 years</td>
<td>Spirometry and Lung volumes</td>
<td>Moderate obstruction, without response to BD, No restrictive pattern was observed</td>
</tr>
<tr>
<td>Hardy2 Philadelphia, USA</td>
<td>7</td>
<td>4 to 15 years</td>
<td>Spirometry and Lung volumes</td>
<td>Obstructive patterns in 6 patients, Restrictive pattern in one patient</td>
</tr>
<tr>
<td>Kim33 South Korea and USA</td>
<td>14</td>
<td>&gt; 7 years</td>
<td>Spirometry and Lung volumes</td>
<td>Severe obstructive pattern, No restrictive pattern was observed, Response to BD over 10% in 3 patients</td>
</tr>
<tr>
<td>Chang21 South Brisbane, Australia</td>
<td>9</td>
<td>&gt; 7 years</td>
<td>Spirometry</td>
<td>7 patients with obstructive pattern, 2 normal, No response to the bronchodilator</td>
</tr>
</tbody>
</table>
The proposed diagnosis of postinfectious BO is based on the following criteria:

1) initial infectious event;

2) persistence of obstructive symptoms, such as wheezing, crepitations, dyspnea for over 6 weeks after the initial event;

3) high-resolution computed tomography showing bronchiectasis and a mosaic pattern;

4) exclusion of pulmonary disorders, such as cystic fibrosis, foreign body aspiration, congenital malformation, tuberculosis, AIDS, and other immunodeficiencies.

Treatment

The treatment of bronchiolitis obliterans has not been universally established yet. Most pediatric pneumology services use a combination of corticoids and bronchodilators continuously, in addition to other supportive measures.
**Corticosteroids**

Apparently, the disease, once established, has characteristics of fixed obstruction. However, a variable obstructive component may also be present. This component is characterized by periods of recovery and worsening, possibly due to the sporadic response to the bronchodilator; which might also be an expression of bronchial hyperreactivity. As the characteristics of the pulmonary inflammatory process (especially its duration) are unknown, the use of corticoids is maintained for long periods of time, not with the intention of reversing the fixed and severe obstruction, but with the aim of reducing bronchial hyperreactivity and bronchoconstriction secondary to viral infections and allergy.

Some animal studies have suggested that corticosteroids may modify the course of the disease.\(^{25}\) The use of corticoids in the first 60 to 90 days after the disease has been established aims at reversing the inflammatory activity, especially fibroblast deposition.

Similar studies have not yet been performed in humans. There have not been enough studies in order to affirm that corticosteroids might play a decisive role in the control of the original inflammatory process or in the prevention of the progression of postinfectious BO in children. Their use is based on successful reports on adult BO patients\(^{26}\) and on the empirical observation of recovery after their introduction and worsening after their suspension.

The form of dispensing corticoids is controversial. Zhang\(^{3}\) used oral systemic corticoids in most patients, based on the fact that severe respiratory obstruction would keep the aerosol from reaching the lung periphery. Other groups prefer to use high doses of inhaled corticoids, i.e., beclomethasone in doses greater than 1,500 µg, with the intention of reducing systemic effects\(^{5}\) to a minimum. The use of inhaled corticosteroids allows reducing bronchial hyperreactivity at least partially; however, they cannot be safely indicated. Since these patients are often unstable in the first two years of life, the use of inhaled corticoids can contribute to a better clinical stability.

Pulse therapy (IV methylprednisolone, 30mg/kg/day for three days) every 30 days has been proposed to reduce the side effects of prolonged systemic administration of corticoids, and has been an alternative for patients with severe BO. Limited and non-controlled reports on pulse therapy have proved successful\(^{20}\).

**Bronchodilators**

Just like oral or inhaled corticosteroids, bronchodilators (BD) are also empirically indicated. Their use can partially reduce the obstructive symptoms, especially in the first two years of life. Inhaled short-acting ß2-adrenergics, dispensed in metered dose aerosols with age-appropriate spacers, are preferable. The functional evaluation before and after the use of BD in infants and children with BO shows a variable response to the use of bronchodilators, but in most patients an immediate response is not observed.\(^{17,20,21}\) Their use should be guided by clinical criteria.

As far as long-acting ß2-adrenergics are concerned, the therapeutic principles for severe persistent asthma should be applied. In other words, these drugs should be used with the intention of reducing the dose of inhaled or systemic corticoids and never as a monotherapy. Nevertheless, there have been no studies so far that precisely define the systematic use of these drugs.

**Antibiotics**

Since many patients present frequent respiratory infections and bronchiectasis, the use of antibiotics is often necessary. Usually the bacteria isolated in these patients are the ones most commonly found in the respiratory tract, such as Streptococcus pneumoniae, Haemophilus influenzae, Brahmanella catarrhals. Therefore, antibiotic therapy should be focused on these causative agents. Bacterioscopy and sputum culture may guide antibiotic therapy in older children. In younger children, information on the etiology of infection may be obtained by tracheal aspiration or by bronchoalveolar lavage. Such findings, however, should be carefully assessed because it is often impossible to differ between colonization and infection. In patients with diffuse bronchiectasis, the need for antibiotic therapy is more frequent. The literature does not include any studies that support the continuous use of antibiotics for this kind of patient. A strategy is to use them in case of fever or when secretion worsens (increased volume or thicker sputum). The length of use may vary from 14 to 21 days in each course of antibiotics.

**Physical therapy**

For children with BO, the main indications for physical therapy are related to the treatment of bronchiectasis and atelectasis. Just like in other therapeutic strategies for such patients, the use of physical therapy is empirical, although its results can be observed, with improvement of secretion retention, quality and quantity of secretions, as well as re-expansion of atelectasis. Techniques for the rehabilitation of ventilatory muscles may also be used in patients with chronic and acute ventilatory obstruction. Its use in children has not been widely studied, but inferences can be made based on studies involving adults with chronic obstructive pulmonary disease.

**Oxygen therapy**

Many patients need supplementary oxygen for long periods (months or years) and some of them need it on a permanent basis. Generally, the O\(_2\) concentrations necessary to maintain a saturation above 94% are low (FiO\(_2\) from 0.25 to 0.4) and can be obtained through portable oxygen concentrators.\(^{27}\) Hemoglobin saturation should be measured on each clinical follow-up visit. Ideally, saturation should
also be measured during sleep. Many patients may present saturation within normal levels while they are awake and an important decrease in saturation during sleep, as occurs in many other respiratory diseases. In the experiment conducted in Porto Alegre, home oxygen therapy was informally implemented by means of donations and support from the local community and from the medical staff. Later on, a specific program for children who depended on oxygen was established and maintained by the Unified Health System.

**Nutrition**

Similarly to other chronic lung diseases in which energy consumption is elevated, the patient should receive an adequate calorie and energy supply. Even though such needs should be analyzed on a case-by-case basis, the goal is to maintain the child’s weight and height adequate for his or her age. In cases in which it is not possible to supply proteins and calories orally, the use of a nasogastric or nasoenteral tube might be necessary for supplementary feeding. Also, in cases of patients who cannot have an adequate supply of proteins and calories, a gastrostomy should be performed.

**Surgery**

In patients with localized bronchiectasis or chronic lobar collapse, the resection of the affected lobe may avoid a higher frequency of infectious exacerbations and reduce the need for physical therapy. A surgical procedure to reduce pulmonary volume in cases of extreme pulmonary hyperinflation has been proposed and the results have been encouraging.

**Gastroesophageal reflux**

A high frequency of gastroesophageal reflux (GER) has been observed in children with BO. The reflux is probably caused by the increase of abdominal pressure due to pulmonary hyperinflation, which is characteristic in such patients. The diagnosis should be preferably made by 24-hour pHmetry. If this is not possible, and whenever there is clinical suspicion, therapeutic measures should be implemented, such as thickened foods, adequate positioning (the supine position should be avoided), use of acid secretion inhibitors and medication to accelerate gastric emptying.

**Prophylaxis**

As in other chronic pulmonary diseases, environmental preventive measures may have a considerable impact. Exposure to tobacco must be avoided, as well as the contact with viral respiratory diseases, especially in the first months after the initial viral infection. Great attention should be paid to the possibility of nosocomial viral infection, because these children have a higher risk of clinical deterioration if exposed to new involvement of the respiratory tract. For the same reason, the contact of these patients with other potentially infected children in daycare centers and schools should be restricted, especially during winter until the disease has stabilized.

Immunizations should be applied according to the vaccine calendar. Vaccines for the prevention of respiratory diseases such as those caused by Haemophilus influenzae type b, pneumococci and the influenza virus may play an important role in reducing infectious exacerbations.

**Lung transplant**

Transplantation should be considered for patients who show a persistent and severe obstructive condition with decrease in pulmonary function and growing needs for supplementary oxygen. In the USA, three patients have been followed up for one to six years after lung transplant. The possibility of lung transplant from a living donor from the patient’s family may be a good alternative for patients with end-stage disease. In Porto Alegre, three patients with BO have undergone this kind of lung transplant.

**Prognosis**

Bronchiolitis obliterans has a variable course depending on the level of the initial infection. Some patients have an unfavorable outcome, with accelerated loss of pulmonary function, hypoxemia, and CO2 retention, which leads to pulmonary hypertension and cor pulmonale. Most patients with postinfectious BO present mild to moderate scenarios, which results in a usually good prognosis, with low mortality. With supportive treatment and adequate medical follow-up the patient’s quality of life and pulmonary function are gradually improved and the need for supplementary oxygen is reduced.

**Perspectives**

Postinfectious BO is not a very well known clinical entity, especially with regard to its prevention and prognosis. Since it is a disease that has affected a significant number of infants in Latin America, it is necessary to carry out cooperative studies in order to identify the risk factors of this disease and other aspects that may result in a better treatment. A group of Latin American pediatricians and pediatric pneumologists have been carrying out research about BO, which may help to understand the physiopathology and treatment of this disease.

**Pediatrician’s attitude towards a patient with a possible diagnosis of BO**

Every child who has a chronic obstructive disease needs an appropriate investigation, which should be made in reference centers that have the necessary resources for a specific and differential diagnosis of this condition. These patients should proceed with continuous pediatric follow-
up since the pediatrician is the one who should be in charge of the supportive measures. As soon as the diagnosis has been established, the pediatrician has to focus on the individual needs of patients with chronic diseases as to their nutrition, immunizations, evaluations and treatment of infectious exacerbations, emotional support, identification of learning difficulties, among several others.

References


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