Intensivmed 45:12–18 (2008)
DOI 10.1007/s00390-007-0810-x

REVIEW

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Congenital lung malformations

Diagnostic and therapeutic approaches

Received: 12 March 2007
Accepted: 8 April 2007
Published online: 13 August 2007

Serie:
Respiratorisches Versagen im Früh- und Neugeborenenalter
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Angeborene Lungenerkrankungen: diagnostische und therapeutische Möglichkeiten

▶ **Zusammenfassung** Angeborene Lungenerkrankungen sind selten, stellen jedoch eine Gruppe von Erkrankungen dar, die bereits in der Perinatalperiode zu deutlichen Symptomen führen können und somit in die differentialdiagnostischen Überlegungen bei Neugeborenen mit einer respiratorischen Insuffizienz miteinbezogen werden müssen. Das Spektrum sowie die Symptome der angeborenen Lungenerkrankungen ist breit und wird im Wesentlichen durch die Schwere der angeborenen Abweichung determiniert. Aufgrund des antenatalen Ultraschallscreenings werden angeborene Lungenfehlbildungen bereits vorgeburtlich diagnostiziert. Im Folgenden sollen die angeborenen Lungenabweichungen mit Hinblick auf deren diagnostischen und therapeutischen Aspekte besprochen werden.

▶ **Schlüsselwörter** angeborene Lungenabweichungen – angeborene Zwerchfellhernie – CCAML – Lungensequester – kongenitales lobäres Emphysem – alveolo-kapilläre Dysplasie

▶ **Abstract** The developing lung is a highly intricate organ with endless possibilities for maldevelopment. Individually, congenital abnormalities of the lung are rare but collectively they form an important group of conditions that are not infrequently encountered by physicians. The range of malformations is broad and the clinical impact is very variable, depending on the degree of malformation. Congenital lung anomalies are increasingly discovered on routine prenatal ultrasound or incidentally during postnatal imaging for respiratory insufficiency of unknown origin. This article groups these conditions under their traditional headings and considers their management.

▶ **Key words** congenital lung malformations – congenital diaphragmatic hernia – CCAML – bronchopulmonary sequestration – congenital lobar emphysema – alveolar capillary dysplasia

Congenital diaphragmatic hernia in the neonate

Congenital diaphragmatic hernia (CDH) refers to a defect in the diaphragma that allows abdominal organs to be present in the chest cavity (Fig. 1). Because the herniation coincides with a critical period of lung development when bronchial and pulmonary artery branching occurs, the herniated "abdominal" contents interfere with the space of the developing lung, resulting in pulmonary hypoplasia. Pulmonary hypoplasia is most severe on the ipsilateral side but may also be present to some extent on the contralateral side. With increased severity of abnormal lung

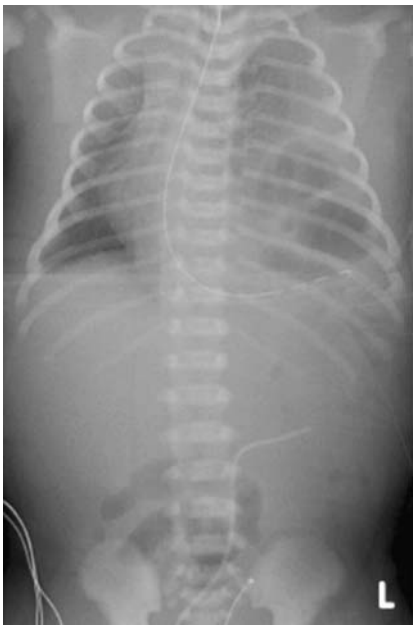

Fig. 1 Anteriorposterior x-ray image of a newborn with a left-sided congenital diaphragmatic hernia. Bowel loops can be seen in the left hemithorax

growth, there is a corresponding decrease in the bronchial branching resulting in a reduction of generations of bronchi and lung tissue [9]. In most cases of CDH, herniation occurs on the left. Right-sided diaphragmatic hernias occur in 11% of cases and bilateral herniation in 2%. Right-sided CDH have a similar morbidity and mortality profile to left-sided CDH [11, 13].

With the increased use of antenatal ultrasound, many cases are nowadays diagnosed prenatally. Infants with CDH most often develop respiratory distress in the first few hours or days of life. The spectrum of presentation can vary from acute, severe respiratory distress at birth to minimal or no symptoms, which is observed in a much smaller number of patients. A limited number of cases is detected beyond the newborn period into childhood. Associated anomalies are seen in approximately 50% of CDH cases and include chromosomal abnormalities, congenital heart disease, and neural tube defects [10]. Among the infants in whom CDH is not diagnosed in utero, the diagnosis should be suspected in any full term infants with respiratory distress especially in the absence of breath sounds. The diagnosis is made by chest radiography showing herniation of abdominal contents into the hemithorax. There is little or no visible aerated lung on the side of the herniation. Other findings include the contralateral displacement of the heart and other mediastinal structures, compression of the contralateral lung, and reduced size of the abdomen with decreased or absent air-containing intra-abdominal bowel. Placement of a feeding tube into the stomach may facilitate the diagnosis if the chest radiograph demonstrates the feeding tube within the thoracic cavity or deviation from its expected anatomic course [7, 24].

In many neonates with respiratory insufficiency the clinical presentation is complicated by persistent pulmonary hypertension (PPHN) due to changes in vascular anatomy. PPHN is defined as failure of the pulmonary circulation to adapt normally to extrauterine life resulting in unoxygenated blood shunting to the systemic circulation. Postdelivery, hypoxemia, acidosis, and hypotension cause reactive vasocontriction. Combined with the preexisting arterial medial smooth muscle cell hyperplasia, this increases the incidence of PPHN. Mechanical ventilation is the initial therapy for infants with respiratory failure from CDH. In the delivery room, infants with CDH should immediately be intubated to prevent hypoxia-induced pulmonary vasoconstriction. Because of gastric and abdominal distension and the resulting compression of the lung, supply of oxygen by bagmasking must be avoided. A delay in obtaining an airway can intensify acidosis and hypoxia which triggers pulmonary hypertension. For decompression of the abdominal contents in the thorax and to help the available lung tissue to expand, early placement of a nasogastric tube and continuous suctioning of the stomach is warranted. For optimal mechanical ventilation, blood pressure support by isotonic fluid and inotropic drugs such as dopamine and/or dobutamine should be given to maintain arterial mean blood pressure levels $\geq$50 mmHg, and thus to minimize any right to left shunting. The aim of mechanical ventilation is to maintain preductal oxygen saturations above 80% or preductal partial oxygen pressure (paO_2) above 60 mmHg. Barotrauma to the hypoplastic lungs may be largely responsible for the instability of the infant and contributes to 25% of CDH deaths [8, 15, 31]. Initiation of conventional ventilator management includes pressure limited ventilation at rates of 30 to 100 breaths/min at peak pressure of 20 to 25 cm H_2O [14]. Peak inspiratory pressures that exceed 28 cm H_2O are used only for a short period as a bridge to other therapeutics modalities such as HFO with or without inhaled NO or extracorporeal membrane oxygenation (ECMO) [3]. The early institution of high frequency oscillation (HFO), especially in case of CO_2 retention, should be considered [2]. PEEP should be maintained at physiological levels (3–5 cm H_2O) whenever possible [23]. At present no RCT's are available that show a benefit of HFO as an initial ventilation modality in CDH. Hyperventilation, hypocarbia and alkalosis may decrease ductal shunting and control pulmonary hypertension in CDH, but at the expense of increased volu-/barotraumas [26]. Permissive

hypercapnia, the so-called "gentle ventilation" approach, is now commonly used in neonates with CDH and shows increased survival rates compared to hyperventilation and alkalization and less pulmonary sequelae. The optimal mode of ventilation in CDH remains controversial, but clinical data suggest that management strategies designed to limit lung distension and barotraumas result in improved survival. Preemptive analgesia, paralysis and sedation reduce air swallowing and may enhance compliance and reduce sympathic vasoconstriction, potentially leading to lower ventilator settings [33]. Nevertheless, the loss of the infant's spontaneous contribution to ventilation and increased third-space edema negate the benefits of paralysis. Therefore, paralysis should only be applied after thoughtful consideration.

The administration of surfactant therapy has been suggested in treating infants with CDH [1]. There is a body of data showing that the lungs of infants with CDH are not surfactant deficient [20, 34]. Whether a primary surfactant deficiency really exists or whether secondary inactivation of surfactant is the underlying problem is the subject of ongoing debate. Up to now there is no evidence that surfactant therapy improves outcome of infants with CDH. Using surfactant in neonates with a gestational age ≥34 weeks can be considered in case clinical radiological findings of alveolar atelectasis suggesting respiratory distress syndrome exists. Cogo et al. studied the surfactant phosphoditylcholine kinetics in CDH patients who did not require ECMO by using stabile isotopes [4]. Although the amounts of surfactant disaturated surfactant and surfactant associated protein A (SP-A) in the tracheal aspirates of CDH patients were reduced, these patients had rates of endogenous surfactant synthesis comparable to control patients. In CDH patients who did require ECMO a decreased surfactant phosphatidylcholine synthesis was found which could serve as a rationale for the need for ECMO and might be a result of lung damage by ventilator induced lung injury. Nevertheless, because of several side effects (bronchial obstruction, hypoxia etc.) surfactant should be used with caution in infants with CDH.

Surgical repair consists of reduction of the abdominal viscera and closure of the diaphragmatic defect. The diaphragmatic defect may be repaired with sutures alone, but increased tension, which compromises total thoracic compliance, often requires a gore-tex patch to be used in repair of the defect. However, a patch is associated with a higher rate of recurrence of hernia and infection. The use of a patch may also cause chest wall deformities by tethering of the ribs. If the abdominal wall is difficult to close following reduction of the hernia, the use of a temporary abdominal wall silo or patch may be helpful. The timing of the surgery is dependent on the severity of the respiratory distress [12]. In patients with mild symptoms only and no signs of pulmonary hypertension, repair can be undertaken after 48 to 72 h. In patients with mild pulmonary hypertension or reversible pulmonary hypertension, the timing of repair is delayed until maximum benefit is achieved from short-term treatment of pulmonary hypertension and improvements in pulmonary compliance. In patients with severe pulmonary hypoplasia and pulmonary hypertension, there will be no response to therapy including ECMO. In this group support is often withdrawn. In summary, the optimal clinical condition and timing of surgical repair remains unclear and is dependent on the severity of the respiratory distress [18].

Congenital cystic adenomatoid malformation

Traditionally cystic lung lesions can be subdivided into three groups: simple single lung cysts, multiple cysts and congenital cystic adenomatoid malformations (CCAM) [29, 30] (Fig. 2). Cystic adenomatoid malformations (CCAM) are rare congenital lung anomalies with an estimated incidence of 1:10 000 to 35 000 births. CCAM results from an abnormality of branching morphogenesis of the lung [32]. The different types of CCAMs are thought to originate at different levels of the tracheobronchial tree and at different stages of lung development. CCAMs are hamartomatous lesions that are comprised of cystic and adenomatous overgrowth of terminal bronchioles and occasionally airspaces. Large lesions can compromise alveolar growth and development by compressing adjacent normal tissue. CCAMs are equally distributed between the right and left lungs. Many cases are nowadays detected by routine prenatal ultrasound examinations. Large CCAMs and shift of the mediastinum may lead to obstruction of the inferior cava vein and cardiac compression, resulting in development of hydrops from increased central venous pressure with a negative effect on outcome [5]. Affected patients may present with respiratory distress in the newborn period or may remain asymptomatic until later in life. The diagnosis of CCAM is made by radiographic imaging.

The approach to treat congenital cystic lung lesions depends upon whether the patient has respiratory distress or is asymptomatic [27]. Complications eventually develop in virtually all patients. The most common complication is pneumonia, which may respond poorly to medical treatment. Other complications include the development of malignancies (carcinomas and pleuropulmonary blastoma), pneumothorax and

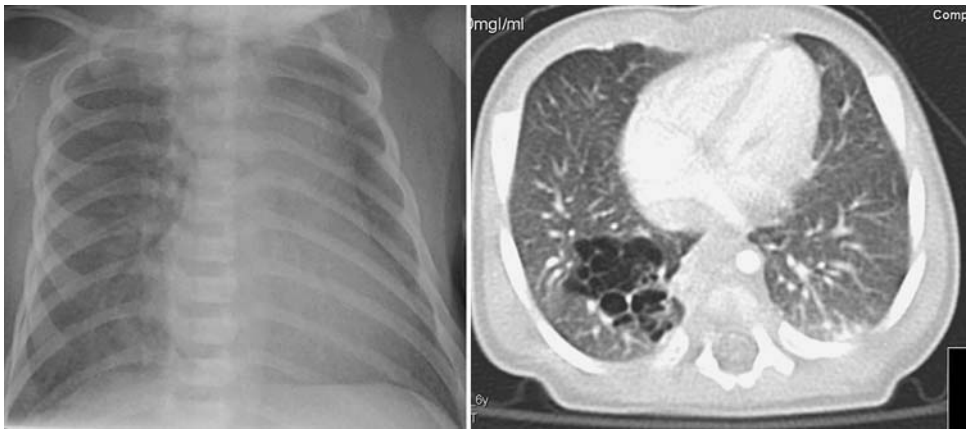

Fig. 2 Left: X-ray image of an asymptomatic newborn with an antenatally diagnosed CCAML in the right lower lobe. Right: CT scan confirming the presence of multiple normal cysts in the right lower lobe

hemoptysis or hemathorax. For patients diagnosed prenatally, we recommend surgery at 3 to 6 months of life at the latest, so that compensatory lung growth can occur. Mediastinal bronchogenic cysts also tend to become symptomatic and elective resection is recommended. In the management of infants with congenital cystic lung lesions, the same therapeutic approach as in patient with hypoplastic lungs with persistent pulmonary hypertension and poor compliance with increased pulmonary vascular resistance has to be considered. Postnatally some patients with CCAM may need even ECMO, either due to respiratory insufficiency or post-surgical following pneumectomy due to increased blood flow to the remaining lung and reactive pulmonary vascular resistance

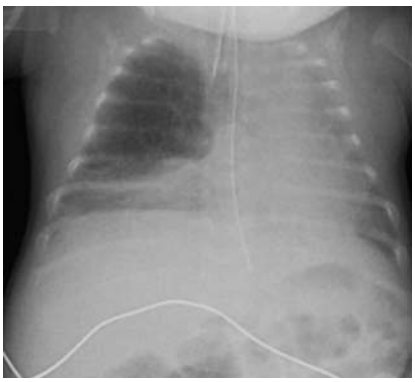

Fig. 3 X-ray image of a newborn ventilated because of respiratory insufficiency, showing hyperinflation of the right upper lobe

Congenital lobar emphysema

Congenital lobar emphysema (CLE) is a potentially reversible though possibly life-threatening cause of respiratory distress in the neonate [27]. CLE is a developmental anomaly of the lower respiratory tract that is characterized by overexpansion of a pulmonary lobe with resultant compression of the remaining ipsilateral lung [16] (Fig. 3). Mediastinal shift can also compress the contralateral lung. The cause of CLE is unclear in some patients, but in many, the absence or hypoplasia of bronchial cartilage rings with a resultant bronchial collapse during expiration, creates lobar air trapping, resulting in CLE. Other possible causes of CLE are intrinsic parenchymal elastin defects and fibrosis of the interstitium. Extrinsic compression, such as by a large pulmonary artery, may also cause bronchial narrowing. In this case cartilage rings are malformed, soft, and collapsible. CLE almost always involves one lobe. The diagnosis can be made prenatally or shortly after birth from its characteristic appearance on a chest radiograph. The x-ray typically demonstrates distension of the affected lobe and mediastinal shift, with compression and atelectasis of the contralateral lung. The diaphragm often appears flattened because of hyperinflation. If the chest radiograph is obtained immediately after birth, the affected lobe appears opacified due to retained fetal lung fluid. Computed tomography of the chest or magnetic resonance imaging may help establish the diagnosis CLE in atypical cases and may demonstrate an intrinsic or extrinsic source of airway obstruction [21, 28]. In neonates, CLE presents with respiratory distress and a fluid filled overdistended lobe. Approximately 10% of patients have associated anomalies, primarily congenital heart disease.

Emergency surgical lobectomy was once considered to be the only treatment for CLE, but nonsurgical treatment may be appropriate in some infants with only moderate respiratory distress. If possible, endotracheal intubation should be prevented to diminish the risk of progressive hyperinflation. If mechanical

ventilation is unavoidable ventilatory pressures and volume as low as possible avoids producing ventilator-related hyperexpansion of the affected lobe. Management by a conservative, gentle ventilation technique is often successful. After diagnosis and initial treatment, the affected lobe only occasionally continues to expand and the clinical cause may direct management. Infants with CLE who are not clinically in respiratory distress and who are able to feed and grow do not necessarily need surgery [17, 27].

Congenital alveolar capillary dysplasia

Congenital alveolar capillary dysplasia (ACD), with or without misalignment of the pulmonary veins, is a rare cause of persistent pulmonary hypertension of the neonate (PPHN) and respiratory distress in the newborn [22]. This malformation represents a failure of capillaries to extend into alveolar tissue of the lung [25]. Histology shows increased septal connective tissue and pulmonary veins accompanying small arteries in the centers of the acini rather than occupying their normal position in the interlobular septa (Fig. 4). The number of pulmonary arteries is decreased and they show increased muscularization. Pulmonary lobules are small, and radial alveolar counts may be decreased. Alveoli are also decreased in complexity, their walls contain few capillaries, and there is poor contact of capillaries with alveolar epithelium. The primary defect is poorly understood. ACD causes severe and irreversible PPHN with a uniformly fatal outcome. Although most cases are sporadic, a familial predisposition has been reported, and a number of studies have suggested that ACD should be considered in any infant with severe respiratory acidosis and PPHN who fails to improve after the application of routine treatment modalities. As Michalsky et al. reported, the usual presentation is that of a term neonate, appropriate for gestational age, who appears to be normal at the time of delivery [22]. Most infants develop progressive respiratory distress and cyanosis with hypoxia, respiratory acidosis, and hypotension within 48 h of birth. The rapidly progressive nature of this process results in the need for full ventilatory support soon after the onset of symptoms. Associated anomalies have been noted in approximately half of the infants with ACD.

Initial chest X-rays are often reported to be unremarkable or to show a mild haziness. Radiographic changes associated with barotrauma may develop later in the course of treatment.

Clinicians should have a high suspicion for ACD in a term infant with good Apgar scores who goes on to experience respiratory deterioration within a few hours of age. The patient may have a transient

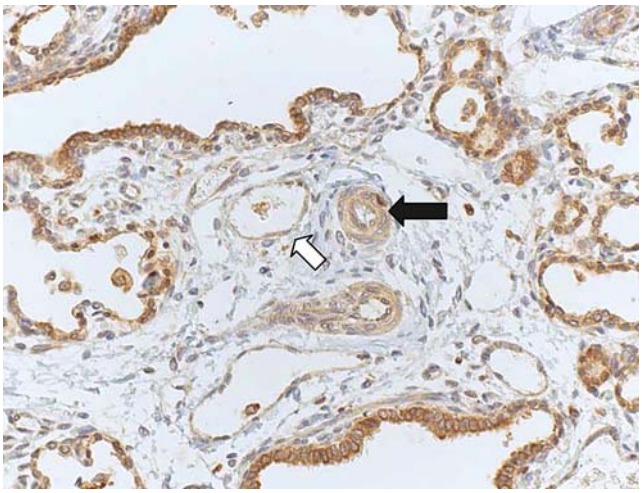

Fig. 4 Typical picture of congenital alveolary capillary dysplasia showing increased septal connective tissue on pulmonary veins (white arrow) accompanying small arteries (black arrow) in the centers of the acini

response to NO, minimal response to HFO, and variable response to prostacyclin. Although ECMO is typically used as rescue therapy, resulting in rapid hemodynamic stabilization, open lung biopsy should be considered before initiation of ECMO to prevent the institution of futile and expensive treatment modalities [26].

Pulmonary alveolar proteinosis and interstitial lung diseases

There are a number of genetic and environmental factors that have been clearly identified as affecting the severity of neonatal respiratory distress syndromes. Congenital alveolar proteinosis syndromes are characterized by the accumulation of surfactant material in the alveolar space. Surfactant-protein B (SP-B) deficiency is known to lead to alveolar proteinosis but there are probably many other causes which may lead to similar pathology [6].

Interstitial lung diseases (ILDs) in childhood are a diverse group of conditions primarily involving the alveoli and perialveolar tissues, leading to derangement of gas exchange, restrictive lung physiology, and diffuse infiltrates on radiographs [6]. However, most ILDs share a common pathophysiologic feature, namely structural remodeling of the distal air spaces, leading to impaired gas exchange. In general, this remodeling has been believed to be the consequence of persistent inflammation; however, more recently, the paradigm has shifted away from inflammation to one of tissue injury with aberrant wound healing resulting in collagenous fibrosis. The

multiple possible diagnostic entities and lack of randomized clinical trials make specific recommendations regarding treatment of childhood ILD impossible. If the process is secondary to an underlying condition, patients should be treated for the underlying disease. The appropriate management depends on the patient's age at presentation, the severity of symptoms, and the anticipated course of the disease. Mechanical ventilation is necessary in children with congenital alvelveolar proteonosis and in some case of interstitial lung diseases. There are no reports that show any benefit from the use of high-frequency oscillatory ventilation (HFO) or other unconventional forms of mechanical ventilation.

Bronchopulmonary sequestration

Bronchopulmonary sequestration (BPS) is a rare congenital malformation of the lower respiratory tract [19]. It consists of a non-functioning mass of lung tissue that lacks normal communication with the tracheobronchial tree and receives its arterial blood supply from the systemic circulation (Fig. 5). Sequestrations are divided into two types based on the nature of their pleural covering. An extralobar sequestration is a mass of pulmonary parenchyma with a distinct pleura covering separating it from the adjacent normal tissue of the lung. In contrast, an intralobar sequestration is located within a normal lobe and lacks its own visceral pleura. Both types are composed of normal lung tissue, including airway and alveolar elements.

The most frequently supported theory to explain how a sequestration arises is that an accessory lung bud develops from the ventral aspect of the primitive foregut [29]. The pluripotential tissue from this additional lung bud migrates in a caudal direction with the normally developing lung. It receives its blood supply from vessels that connect to the aorta and that cover the primitive foregut. These attachments to the aorta remain to form the systemic arterial supply of the sequestration. Both types of sequestration usually have arterial supply from the thoracic or abdominal aorta. Usually, no communication occurs with the tracheobronchial tree. The most common location is in the posterior basal segment, and nearly two thirds appear in the left lung. Venous drainage is usually by the pulmonary veins. Prenatal diagnosis of BPS is made by ultrasonography. The presentation of BPS on prenatal ultrasound is typically an the incidental finding of an echogenic thoracic mass that may be small or occupy most of the hemithorax. Mediastinal shift is often noted. In the majority of cases, the lesion regresses during the course of gestation, while hydrops occasionally develops, likely because of vascular compression.

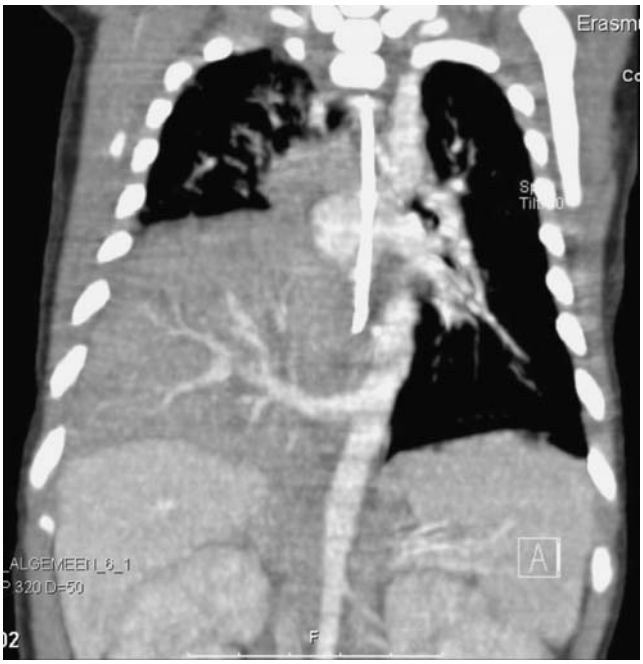

Fig. 5

Postnatally, extralobar sequestrations generally present earlier than intralobar sequestrations, although the age at presentation is variable. Infants with extralobar sequestrations who become symtomatic typically present with respiratory distress and less commonly with recurrent pneumonia. Patients with intralobar sequestration usually present in late childhood or adolescence with recurrent pulmonary infections. Treatment of patients with bronchopulmonary sequestration depends upon the symptoms. In symptomatic patients, BPS is treated by surgical excision, which is curative and is associated with minimal morbidity. Surgical excision is performed immediately after birth in newborns with severe respiratory distress. It may be done electively in older children who present with recurrent infections. In asymptomatic patients, elective resection is recommended for intralobar sequestration to prevent recurrent pulmonary infections. For extralobolar sequestration, serial monitoring is appropriate unless symptoms develop. Heart failure may rarely occur, when excessive flow through the abberant artery exists. In the absence of other significant congenital anomalies, the prognosis for children with pulmonary sequestration is generally very good.

▶ **Acknowledgments** We thank Janine Felix for help in preparing the manuscript.

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