**Long term outcomes of congenital lung malformations**

Nigel J Hall PhD1,2 , Michael P Stanton MD1,2

Affiliations:

1. University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, UK
2. Department of Paediatric Surgery and Urology, Southampton Children’s Hospital, Southampton, UK

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**Corresponding author**

Nigel J Hall

University Surgery Unit, Faculty of Medicine, University of Southampton, Mailpoint 816, Southampton General Hospital, Tremona Road, Southampton SO16 6YD UK

Tel: 023 8120 6146 / 6677; Email n.j.hall@soton.ac.uk

# Abstract

100-200 words

Congenital lung malformations comprise a group of anatomical abnormalities of the respiratory tree including congenital cystic malformations, bronchopulmonary sequestrations, bronchogenic cyst, bronchial atresia and congenital lobar emphysema. These anomalies are detected with increasing frequency by prenatal sonography, but may also present for the first time with symptoms in childhood or later life. When symptomatic, there is little controversy that resection is indicated, which is usually curative. When a lesion is asymptomatic there is greater debate regarding the benefit of resection versus continued observation. This article provides an overview of the spectrum of disorders, the management options available and the long-term outcomes associated with each treatment option.

Keywords (up to 6): congenital lung malformation; congenital pulmonary airway malformation, bronchopulmonary sequestration; long-term outcome

# Introduction

Congenital lung malformations (CLMs) encompass a varied group of disorders, the most common of which include congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), hybrid lesions that contain elements of both CCAM and BPS, bronchial atresia, congenital lobar emphysema (CLE) and bronchogenic cyst among other entities (1, 2). With widespread use of prenatal imaging and improving sonographic resolution, CLMs are increasingly detected in the prenatal period. As such their apparent incidence is increasing with recent data suggesting that a CLM may be identified prenatally in approximately 1 in 2400 live births (3). This most likely represents improved detection in the prenatal period rather than a genuine increase in incidence (4). CLMs may also present with respiratory symptoms later in childhood or even adult life, having remained undiagnosed up until that point.

For all symptomatic CLMs, whether diagnosed prenatally or not, there is little controversy that surgical resection is appropriate so long as other morbidities do not present excessive anaesthetic or operative risk. The surgical objectives are to remove the abnormal tissue in order to alleviate symptoms, prevent further complications, allow adequate intra-thoracic volume for inflation of the remaining lung and, particularly in the young child, allow space for compensatory lung growth. However, when a prenatally diagnosed CLM is asymptomatic at birth there is greater controversy. The risks of resection must be balanced against the risks of expectant management.

The emphasis of this article is not on the optimal management of CLM’s during the prenatal, postnatal or other period nor on the short-term outcomes related to this. We provide a brief overview of the range of conditions and options for management, but our focus is on the longer term outcomes of CLMs and of the range of management approaches as they are currently understood. Those seeking greater insight into the treatment options, short-term outcomes and controversies in this field are advised to seek out alternative texts (5-9).

# Conditions within the spectrum of CLM

**Congenital Lobar Emphysema**

CLE presents as overdistension of one or more of the pulmonary lobes and is thought to be a result of an abnormality of the bronchial tree resulting in focal bronchomalacia most likely due to cartilaginous deficiency. Airway collapse during expiration results in distal air trapping, focal overdistension and emphysematous change. CLE may be detected prenatally and may cause symptoms in the neonatal period ranging in severity from massive overdistension and respiratory collapse to mild respiratory distress with tachypnoea and an oxygen requirement. About one quarter of cases are symptomatic at birth and the majority within the first 6 months of life. Symptomatic lesions are typically resected which is usually curative provided there is adequate residual lung tissue. For asymptomatic lesions, or those with only very mild symptoms, resection may not be necessary and a conservative approach may be followed (10, 11).

**BC**

Bronchogenic cysts are mucus-filled lesions typically lined by respiratory epithelium, may have a cartilaginous component to their wall and arise from the bronchial tree usually in a mediastinal location. A solitary cystic lesion maybe seen on prenatal ultrasonography. Symptoms range from complete absence to acute respiratory distress due to compression of lung tissue by an extremely large cyst. Whilst expectant management of an asymptomatic lesion may be offered, the majority are excised due to the the risk of expansion, infection or haemorrhage (ashcraft ref 64). Few case reports of malignant transformation have been reported (12). Since most bronchogenic cysts are related to the proximal bronchial tree, resection without loss of significant lung tissue is usually possible. A variety of bronchogenic cyst that results in the formation of multiple cystic structures within the peripheral lung parenchyma (also known as bronchiolar cysts or cystic bronchiectasis) is associated with recurrent infectious complications and resection is recommended.

**BPS and CCAM**

A BPS is typically described as a mass of pulmonary tissue which may be solid or cystic in nature that lacks a connection to the tracheobronchial tree and which has a blood supply arising from the systemic (as opposed to pulmonary) arterial system. Intra- and extra-lobar varieties exist depending on whether the lesion is located within or without the lobar structure and surrounding visceral pleura. BPS are typically asymptomatic lesions at birth yet those with a particularly large systemic feeding vessel may give rise to high output cardiac failure.

CCAMs are lesions in which abnormal development of the distal bronchi-alveolar structures results in a multicystic lung mass. Cysts may be of varying sizes and the anatomical distribution of lesions varies from a small segment within a single lobe to lesions which cross lobar boundaries, may be multifocal and even bilateral. The classification of CCAMs is confusing and has changed over time. The original Stocker classification into 3 major subtypes has been expanded to 5 sub-types (0-IV).

BPS and CCAM are purposefully described together here, partly since there is often overlap between these lesions in what are called ‘hybrid’ lesions and partly since they are frequently diagnosed in the prenatal period and frequently remain asymptomatic after birth. It is these lesions around which there is the greatest controversy regarding the optimal management approach.

The main argument in favor of routine resection during infancy is the long-term risk of infection, although there is disagreement in the literature about the magnitude of that risk. Some authors also argue that the risk of complications is higher if the lesion has previously been infected (13-15), although not all studies have documented this difference [12]. Another argument in favor of routine resection is the assumption that early resection results in better compensatory lung growth than resection at a later age; however this remains a hypothetical advantage which is not universally supported in long-term follow-up studies (16-19).

A final argument for routine resection is the possibility that the lesion is not a benign CCAM, but is instead a Type I pleuropulmonary blastoma (PPB). PPB and CCAM may be difficult to differentiate one another clinically and radiologically (20-22) as well as on pathology (20). However, large series of asymptomatic cases have failed to demonstrate evidence of malignancy whether resected or not (21, 23-25).

# Outcomes

Antenatal outcome can be correlated primarily to lesion size (26). In a small proportion, intra-uterine death or termination will take place (3-4%). After birth a small proportion die from respiratory failure during the newborn period without surgery (1%) or following attempted emergency resection (7%) (27). For cases surviving the neonatal period, long-term outcome is determined a number of factors including development of symptoms, requirement or selection for surgical resection, extent of resection, pathology encountered and other comorbidities. In general terms, there is a paucity of truly long-term outcome studies (into adulthood) of cohorts of children known to have a CLM, so the following review is based on the available literature. Assessing outcomes of cases managed non-operatively is also difficult since the majority of lesions are resected, even if asymptomatic.

Lung development, lung function and compensatory lung growth following resection

Lung development and growth is believed to continue into childhood and even young adult life (28). Some growth is due to an increase in the number of alveolar units (a process that continues until 2 years of age (28, 29)) with the remainder being due to an expansion in size of existing alveoli (29). From this, it has been assumed that compensatory lung growth may be possible following pulmonary resection during childhood and in particular during infancy.

Whether compensatory lung growth actually does occur following resection is clearly difficult to determine due to lack of access to tissue. Most studies have therefore used respiratory function as a surrogate marker for lung growth and lung volume. Results span a wide time period and are somewhat conflicting. In 1961, Cook and Bucci (30) reported on 9 children undergoing curative lobectomy at median age 5.5 years (range 3 days – 11 years) who were assessed at median age 16 years (range 3.5-28 years). They reported reduced lung volumes compared to predicted, roughly in keeping with the volume of lung that had been resected. Total lung capacity (TLC) was mean 77% (range 61-92) of that predicted. Frenckner and Freyschuss found some evidence of compensatory lung growth based on lung volumes 90% of predicted despite lobectomy at follow-up 3-11 years post-procedure (31). McBride and colleagues reported near-complete normalization (mean 93% of predicted [range 80-103]) of TLC at 8-30 years of age after lobectomy for CLE in infancy despite resection of an estimated 8-45% of lung tissue (32). However, forced expiratory volume in 1 second (FEV1) was lower than predicted (mean 73% of predicted [range 46-92]). Interestingly, using a radiospiromtery technique, they demonstrated that TLC was equal between operated and non-operated sides of the chest but a higher residual volume (RV) was present in the operated side. In a comprehensive prospective study with healthy controls, Mandaliya and colleagues studied lung function in children aged mean 7.6 years who had undergone lobectomy for CLM in early life. Similar to previous reports, they identified normal TLC and lower FEV1 following lobectomy as well as evidence of uneven ventilation distribution (33). These results are largely supported by Werner and colleagues (34) who studied 14 children at mean age 11.6 years (range 3-20) who had undergone lung resection at mean 7 months (range 1 week – 30 months). Beres and colleagues reported normal lung function (>80% predicted values) in nearly all children who had undergone resection at age <12 months and were over 5 years of age at the time of testing (35).

Drawing conclusions from this mélange of data is challenging. It appears that following resection, TLC is generally preserved at long term follow-up, and may even be in excess of that expected from the extent of resection. However, this does not necessarily mean that adequate growth has occurred nor that any lung that has grown has normal function. The elevated residual volumes and functional residual capacity, combined with reduced FEV1 and uneven distribution of ventilation often found after lobectomy suggests that overexpansion of residual lung may be compensating for loss of tissue and contributing to TLC, rather than true lung growth (34, 36). How these detailed physiological tests translate into real life setting is also unclear. What is noteworthy, however, is that the majority of reports suggest that most children lead full and active lives with no day-to-day respiratory limitations following lobectomy.

Age at resection and subsequent lung function

One of the arguments for early resection of asymptomatic CLMs is that this may allow better compensatory lung growth (and function) than resection in later life. Only a handful of studies have attempted to address this issue. In 1998 Nakajima and colleagues (37) reported that resection at age less than 4 years was associated with improved lung function at follow-up. Similarly Komori and colleagues (16) have proposed that surgery before one year of age is preferable. This is based solely on their finding of increased air trapping (based on radionuclide imaging) on the operated, compared to the non-operated, side of the chest in children having surgery at less than one year, compared to children operated at an older age.

In contrast, Keijzer and colleagues failed to demonstrate a significant association between age at resection (before or after 2 years of age) and subsequent lung function at mean 10 years of age. Of note in their retrospective study, only FVC and FEV1 were determined. However, Naito and colleagues (19) performed a more thorough prospective analysis and also included exercise testing in their protocol. In similarity to previous studies they found a preserved TLC but reduced FEV1 following lobectomy when assessed between 8 and 23 years of age. Maximal power and maximal oxygen uptake (VO2 max) were both mean 84% of predicted value. Age at lobectomy (before or after 2 years of age) was not significantly associated with any abnormal (<80% predicted value) pulmonary function or exercise test parameter.

Effect of extent of resection

It stands as logical that lesions requiring massive lung resection will have a greater effect on respiratory function than those requiring removal of a lesser volume of lung tissue. The extreme of this is a lesion requiring complete pneumonectomy, fortunately a rare occurrence. In a recently reported series of 51 children who underwent pneumonectomy, approximately 20% were performed for some form of CLM (38). Long term morbidities included scoliosis in 20% of cases and post-pneumonectomy syndrome in 4%. Post-pneumonectomy syndrome results from mediastinal shift into an empty hemi-thorax (typically right) resulting in rotation of the heart and great vessels and bronchial compression. Treatment with implantation of prostheses into the empty hemi-thorax appears effective in children (39, 40). Interestingly, a previous study has demonstrated that respiratory function is generally reasonably well preserved following pneumonectomy so long as performed prior to 5 years of age (41).

More recently a number of authors have proposed parenchyma sparing surgery for CLMs in the form of segmentectomy, in place of lobectomy, when anatomically possible (42-44). To our knowledge no studies have investigated the potential long-term benefits of such a parenchymal sparing approach on pulmonary function. This should be balanced against the risk of recurrence, reported to be significantly higher after segmentectomy when compared with lobectomy (45).

Neurologic, musculoskeletal and cosmetic morbidity following surgery

Pulmonary resection via conventional open thoracotomy may be performed using a muscle cutting or sparing technique, with the latter preferred by some authors (46, 47). Complications include damage to the nerve to serratus anterior (resulting in winging of the scapula) adhesions between the scapula and the scar resulting in tethering, and an unsightly scar, and excessive re-approximation of the ribs (particularly in the infant) resulting in abnormal chest wall development and in some cases scoliosis. The precise prevalence of these is unclear due to a small number of reports. Chest wall deformity beyond 5 years after surgery was identified in 7% (30/409) of children undergoing surgery for CLM in a large Japanese series.

With increasing use of a thoracoscopic approach to pulmonary resection it is likely that these neurological, muscoluskeletal and cosmetic morbidities will be reduced (48, 49) although the long term follow-up required to state this with certainty remains lacking currently. A recent systematic review/meta-analysis of thoracoscopic and open resection in asymptomatic lesions reported a shorter length of stay with equivalent rate of surgical complications (50).

Resolution in unresected lesions

With increasing prenatal detection it is becoming evident that some CLMs appear to undergo spontaneous regression either pre- or postnatally (51, 52). One series describes prenatal resolution with an incidence as high as 14% (3). An example of post-natal regression is shown in Figure 1. To our knowledge there are no long term studies reporting on the incidence of regression in large numbers of patients, in part as ‘screening’ with cross-sectional imaging (CT scan) carries a small increased risk of malignancy.

Risk of developing symptoms in unresected asymptomatic lesions:

A large systematic review and meta-analysis (27) of 505 prenatally diagnosed cases of CCAM or BPS that remained asymptomatic beyond 1 month of age found that 16 (3.2%) became symptomatic, at a median age 7 months (range 2.5-10 months). The true long-term risk of developing symptoms is likely higher than this, since most asymptomatic infants included in the review underwent elective surgery during late infancy. Indeed, a recent Japanese national study reported that all cases that were asymptomatic beyond the newborn period became symptomatic by 10 years of age (53). However, minor clinical features including isolated cough were included in the definition of ‘symptomatic’. We have previously reported a series of 60 prenatally diagnosed asymptomatic cases followed up to median 5 years of age (range 1-10) in whom just 3 (5%) developed symptoms (pneumonia n=2, cyanosis due to shunting in BPS n=1) and were treated surgically (25). In a larger series of 154 prenatally diagnosed cases of CLM that remained asymptomatic following the newborn period (24), 20 (13%) developed symptoms requiring resection at median age 2 years (range 1-6) and no child became asymptomatic after 6 years of age. Hammond and colleagues (54) have reported a smaller series of 13 infants all of whom remained asymptomatic beyond the neonatal period and at follow-up (mean 2.6 years [range 6 months – 7 years]).

Risk of Malignancy

Histological features of congenital lung malformations have been reported in association with the known pulmonary tumours of childhood (rhabdomyosarcoma, pleuropulmonary blastoma and bronchioalveolar carcinomas). The potential risk of a prenatally-diagnosed CLM in fact being a lung tumour, or of possible ‘malignant transformation’ of a CLM, remains an important and controversial aspect of the long-term outcome of CLM. The role of surgery for asymptomatic cases hinges on further clarification of these risks, as well as the full elucidation of the protective effect of prophylactic resection.

*Rhabdomyosarcoma*

There is recognition and acceptance that lung rhabdomyosarcomas should now be classified as pleuropulmonary blastomas, and in 2 examples the published diagnosis has been amended (55, 56). There have been 15 publications describing 20 cases of lung RMS in children between 1984 and 2009, none of which had been diagnosed prenatally. In only half of these 20 cases was the histological description of RMS associated with a CLM (bronchogenic cyst in 2, CCAM in 8).

*Bronchioalveolar carcinoma*

Bronchioalveolar carcinomas (BAC) occur predominantly in adults (mean age 69 years) and account for 24% of lung adenocarcinomas and 5% of all non-small cell lung malignancies (57). BAC are extremely rare in childhood. There are approximately 20 cases (adults and children) reporting an association between CLM and BAC. Eight patients were under 16 years of age (7 CCAM and 1 bronchogenic cyst) (58-64). Again, none of these were diagnosed prenatally. Of particular interest, one adult (age 19 years) presented with respiratory symptoms/imaging which demonstrated a left lower lobar mass, subsequently shown to be BAC, and the patient died age 23 years. This patient had previously undergone segmentectomy for type I CCAM more than 20 years earlier (age 2 months).

*Pleuropulmonary Blastoma*

Pleuropulmonary blastomas (PPB) were first described in 1988 (65). Three types (I-III) are recognised and there is evidence that progression occurs from type I cystic lesions with a good prognosis (85-90%), through to type II and type III, the latter being a high-grade solid sarcoma with a worse outcome (45-60%) (66). Conversely, there are also descriptions of spontaneous resolution of type I PPBs (67). It appears that type I PPB, which are purely cystic, cannot be differentiated from type IV CCAM by imaging alone, and there is even debate amongst pathologists as whether they are indeed distinct entities. The majority are reported to the International Pleuropulmonary Blastoma Registry (IPPBR) which has reported on at least 450 such cases in patients <20 years of age (67, 68). Recent data, including a large series of PPB, suggests that risk-stratification of these cases, based on clinical, genetic (DICER-1 mutation) and radiological features, may be possible in the majority (21).

There are a small number of reports of prenatal detection of PPB as a congenital lung lesion diagnosed after surgery as containing foci of PPB within a CCAM. Three cases in the English literature (69, 70) and one in French (71) were asymptomatic at birth and underwent elective excision. Subsequent histology detected small foci of type 1 PPB within a CLM. The outcome was good without any further treatment. The significance of the increasing apparent incidence of CLM and the concomitant increase in histological detection of foci of PPB within a benign CLM will need further evaluation as more cases are described.

Adult Outcomes of Congenital Lung Malformations:

There are many case reports describing complications developing in CLMs in adults, ranging from infections through to spontaneous pneumothorax during air travel (72). The difficulty in interpreting these reports is the lack of knowledge of the underlying population denominator of patients with CLM who did not develop symptoms, as most adult cases thus described were born in the era before prenatal recognition was commonplace. The first prenatal confirmation of a CLM was described in 1975 (73), whereas current prenatal ultrasound is detecting CLM’s at a rate of up to 1 in 2400 pregnancies (3). As the majority of CLM diagnosed currently are resected, even if asymptomatic, there is a paucity of recent case series describing adults with CLM *in situ*. The largest series of adults with surgically-managed CLM was reported by Makhija *et al (74),* who described 102 patients with a median age of 47 years (82% were symptomatic). Of interest, the relative incidence of pathological findings was the reverse of that seen in the paediatric literature – with bronchogenic cyst occurring most frequently (45%), followed by sequestration (20%) and CCAM (8%). The majority of patients were treated with cyst enucleation, rather than lobectomy, and post-operative complications occurred in 10%. There were no cases of malignancy. There has been one recent report focusing on sequestration outcomes (75), which concluded that extra-lobar sequestrations rarely develop symptoms in adulthood, whereas previously undiagnosed intra-lobar sequestrations presented with infections.

# Conclusion

Whilst we have reviewed the available literature on long-term outcomes of CLM’s, we emphasise the limited number of studies reporting cohorts of cases beyond early childhood. We support calls for long-term outcome studies of infants and children identified as having a CLM either pre- or post-natally (76) into later childhood and adulthood. To this end we have established a prospective registry of cases of CLM (the International Congenital Lung Malformation Registry) with the aim of documenting, over time, the short and longer term outcomes of these lesions, however they are managed. We invite all institutions to collaborate in this initiative: [www.iclmr.org](http://www.iclmr.org) and hope that with time we can generate better quality evidence on which to base our treatment decisions.

Figure 1 (A) Newborn chest radiograph performed at 3 days of age in a child with a prenatally diagnosed CLM who was asymptomatic; (B) Chest radiograph at 4 years of age of the same child at which time the child remained asymptomatic and had not undergone surgery.

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