CONGENITAL LUNG MALFORMATIONS

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ABSTRACT

Congenital lung malformations (CLMs) are rare developmental anomalies of the lung, including congenital pulmonary airway malformations (CPAM), bronchopulmonary sequestration (BPS), congenital lobar overinflation, bronchogenic cyst (BC), and isolated congenital bronchial atresia (CBA). CLMs occur in 4 per 10,000 live births. Postnatal presentation ranges from an asymptomatic infant to respiratory failure. CLMs are typically diagnosed with antenatal ultrasonography and confirmed by chest computed tomography angiography in the first few months of life. Although surgical treatment is the gold standard for symptomatic CLMs, a consensus on asymptomatic cases has not been reached. Resection, either thoracoscopically or through thoracotomy, minimizes risk of local morbidity, including recurrent infections and pneumothorax, and avoids the risk of malignancy that has been associated with CPAM, BPS, and BC. However, some surgeons suggest expectant management, as the incidence of adverse outcomes, including malignancy, remains unknown. In either case, a planned follow up and a proper transition to adult care are needed. The biological mechanisms through which some CLMs may trigger malignant transformation, are under investigation. KRAS has already been confirmed to be somatically mutated in CPAM, and other genetic susceptibilities linked to tumor development have been explored. By summarizing current progress in CLM diagnosis, management, and molecular understanding we hope to highlight open questions that require urgent attention.

[H1] INTRODUCTION

Congenital lung malformations (CLMs) refer to a continuum of developmental disorders that involve the lung parenchyma, the tracheobronchial tree and the pulmonary vessels, or a combination of the above. At one end of the spectrum, congenital lobar overinflation (CLO; previously known as congenital lobar emphysema) represents abnormal lung supplied by normal vessels. At the other end of the spectrum, pulmonary arteriovenous malformations are characterized by abnormal vessels within normal lung parenchyma [1].

This Primer focuses on the most common congenital lung anomalies: congenital pulmonary airway malformation (CPAM; previously known as congenital cystic adenomatoid malformation, CCAM); bronchopulmonary sequestration (BPS); CLO, and bronchogenic cyst (BC). We also discuss congenital bronchial atresia (CBA), which has been recognized as a separate CLM entity. BPS can be intralobar (ILS) or extralobar (ELS). CPAM is further classified into five histological subtypes, defined by the suspected anatomical level of the airway they originate from [2,3] (**Figure 1**). Of note, some clinicians and researchers consider all the CLMs under the umbrella of CPAM, but CPAM is only one of the CLM types, and adherence to the precise definition of each CLM is required when reporting new cases. CLMs arise during embryonic lung development (**Box 1**) as a result of an abnormal organogenesis or a dysregulation of cellular signaling within the epithelial-mesenchymal interaction **[G]** [4]. The timing of this dysregulation is likely to determine the type or subtype of CLM.

Most newborns with CLMs are asymptomatic, and fewer than 10% have respiratory symptoms. Professionals agree to surgically treat symptomatic patients with CLMs, but there is an ongoing debate worldwide whether asymptomatic patients should be managed surgically or conservatively. Prophylactic elective surgery is recommended in asymptomatic cases to avoid the long-term risk of development of pulmonary infections and to prevent the possible malignant transformation. The best way to address this controversy is to invest resources into researching the natural history of

CLMs, the biological relationship between CPAM, BPS, BC and malignancy, and potential drivers of malignant transformation. In addition, clinical professionals, surgeons and researchers continue to envision prognostic tools, standardize care, especially in asymptomatic cases, standardize respiratory and imaging follow up, provide transition of care into adulthood, and build a global registry.

This Primer describes the epidemiology and pathophysiology of CLMs as well as progress in diagnosis and management, and the different viewpoints of pediatric and non-pediatric thoracic surgeons on CLM management .

[H1] EPIDEMIOLOGY

[H2] Demographics

CLMs have been estimated to comprise up to 18% of all congenital anomalies **[G]** [5]. Historically, the overall incidence of CLMs was estimated at ~0.5 to 1.5 per 10.000 live births but, in 2015, registry studies in the UK reported an incidence of around ~1 per 2,500 live births [6-9]**.** The apparent rising incidence of these malformations is probably a consequence of the widespread availability and the improved resolution of prenatal ultrasonographic screening, which have increased CLM detection, especially in high-income countries [8,10]. Due to a lack of global registries the exact number of patients with these rare malformations and possible regional differences remains unknown.

CPAM type 1 is the most common type of CPAMs, representing 50-70% of CPAM cases[11]. CPAM type 2 underlies 15-30% of all CPAM cases [12], whereas CPAM type 3 represents 5-10% of CPAM [12]. The individual incidence of other CLMs remains unknown.

Around 11.7% of patients with a CLM have an associated anomaly in other organs, but only 5-10% of them have an additional major malformation[13]. Associated developmental defects in other organ systems may, therefore, stem from the same dysregulation in epithelial–mesenchymal

interactions during embryonic development that causes CLMs, but this link has not been demonstrated yet. The most common associated malformations are congenital heart defects (32%) and gastrointestinal defects (18%) [14]. BC was found to have the highest proportion of associated anomalies (29%), particularly vascular malformations, followed by CPAM (12%), which was more frequently associated with congenital heart diseases and gastrointestinal malformations. A concurrent malformation existed in 10% of patients with BPS and in 9% of those with CLO, mainly gastrointestinal for BPS and cardiac for CLO [14]. Clinicians should be aware of these possible co-occurring anomalies and consider additional diagnostic imaging.

[H2] Risk factors

CLMs seem to occur sporadically and have not been associated with any karyotype anomalies[15]. Their formation has not been associated to maternal factors, such as race, age, or exposure to environmental factors[15]. No gender predilection has been demonstrated [15]. Risk factors for developing symptoms after birth are not yet known. Multicenter international collaborations, including long term follow-up registries, and prospective trials, such as the CONNECT trial by the Collaborative Neonatal Network together with the equally needed molecular biology studies [19] will help understand the natural history of CLMs and how some of them (CPAM, BPS and BC) may be associated with malignant transformation.

[H3] Association of CLMs with lung cancer

The incidence of malignant degeneration in CLMs remains unknown. In 1983 [20], it was estimated to be 4% considering all CLMs. In 2010 [21], the incidence of pleuropulmonary blastoma (PPB), specifically, was found to be 2% in CPAM. PPB has been historically associated with CPAM, but it remains unclear whether the initially identified lesion was a CPAM preceding PPB or an unrecognized PPB [22]. In earlier studies, CLOs in two children were associated with a PPB [23] and a rhabdomyosarcoma [24], respectively, and CLOs in ten adults, at that time diagnosed as

congenital cystic emphysema, were associated with bronchogenic carcinoma [25]; however, the histological definition of these CLOs might have been inaccurate. On the other hand, it has been suggested that a CPAM type 4 evolves into PPB through the acquisition of a somatic mutation in *DICER1* [26,27]. However, a specific relationship between *DICER1* mutations and CPAM or other CLMs has not been demonstrated yet. A pathognomonic molecular marker for PPB has not yet been discovered, but association with *DICER1* heterozygous germline mutation is found in up to 66% of PPBs. Mutations in *DICER1* are known to considerably increase the risk of several types of cancer, including PPB. DICER1 syndrome predisposes to the development of tumors in the lung, kidney, ovary, and thyroid [26]. To comprehensively elucidate the complex interplay between germline and somatic mutations in *DICER1* and PB, initiatives such as the International PPB/DICER1 Registry and the DICER1-Related Pleuropulmonary Blastoma (PPB) Syndrome Study conducted by the National Cancer Institute are essential. These projects are extremely useful for characterizing the risk associated with pathogenic variants, for studying the clinical course of patients with these variants, for better management and, ultimately, for definitively understanding whether an association between CLMs and *DICER1* mutation exists.

Except for CLO and CBA, all other CLMs (CPAM, ILS, ELS, and BC) may be associated with a malignant lung lesion both in pediatric and adult patients, making none of them 'safer' than others and eligible for conservative treatment [22]. In the pediatric population, the CLM more frequently associated with a lung tumor is CPAM [22]; in adult patients, tumors co-occur mainly with CPAM or, to a similar extent, with BC [22]. In children, more than half of the CLMs were associated with a PPB, followed by an adenocarcinoma in 27% of the patients; in adult patients, 43.5% of CLMs were associated with adenocarcinoma, 15.2% with squamous cell carcinoma, and 7.6% with bronchial carcinoid.

The onset of malignant transformation happens at any age starting from months of life up to elderly patients [22], and the interval of time between the first detection of a CLM and the discovery of an

associated tumor is very variable, making a lifelong follow up imperative in case of conservative treatment. Of note, only the pathologist can make a definitive diagnosis [22].

Mucinous cell clusters (MCCs) are pre-malignant or malignant cell clusters that occur in 75% of patients with CPAM type 1 (**Figure 2**) and are not as common in CPAM types 2 and 3 (45%). MUC5AC has been identified as a valuable marker of MCCs [28], and mucinous proliferation tissue in CPAM type 1 sections have similar MUC5AC expression patterns as mucinous lung adenocarcinoma. MCCs are thought to be a precursor reservoir for potential invasive mucinous adenocarcinomas. *KRAS*, one of the most mutated genes in lung cancer, has been found to be mutated in both mucinous [29] and non-mucinous cells [30] of CPAM type 1. Sequencing analyses revealed *KRAS* exon 2 mutations in MCCs from all 18 patients examined, irrespective of whether they were diagnosed with CPAM type 1, CPAM type 3, or CPAM with an intermediate morphology between 1 and 3 [29]. Furthermore, *KRAS* mutations were also found in 17 of the 25 CPAMs without MCC analyzed, and the p.G12D mutation was specifically correlated with type 1 morphology. In patients harboring both CPAM type 1 and adenocarcinomas [31], both lesions can have the same *KRAS* mutations, which is an indication that mutated *KRAS* in CPAM may confer susceptibility to cancer. In contrast to adult lung cancer, in which a KRAS mutation confirms malignancy, the clinical relevance of these mutations within pediatric lung specimens still needs to be investigated. If mucinous cell clusters (MCCs) are considered a malignant or pre-malignant finding, long-term follow-up of patients with *KRAS* mutations in CPAM tissue may be indicated, especially if resection margins contain KRAS-positive CPAM tissue.

How CLMs are related to lung cancers is still a matter of debate. Similar to cancer cells, CPAM epithelial cells have a double proliferation index compared with normal cells and a lower susceptibility to apoptosis [32]. As CPAM is not inheritable and usually involves only one lung lobe, the mutations potentially linking CPAM with cancer are probably somatic and not germline. Despite this, the possibility of predisposing germline mutations has also been explored. De novo mutations in genes that encode proteins implicated in cancer, such as SMAD7 or KDM6A, have been found

in 38.8% of patients with CPAM, providing some evidence to support prophylactic resection of CPAM[191]. Moreover, genes involved in embryonic development and cell proliferation have been found to be differentially methylated in ELS samples (*HOX3B1*, *HOXD4*, *CTNNA1*, *NR2F2*, *HSF4*, *MEIS1*), in ILS samples (*HOXA3*, *HOXB1*, *TGFB1I1*, *BRD2*, *CTNNA1*, *CTSZ*, *GPR37L1*, *S100A13*; *TSPAN3*, *FOXP2*), in CPAM type 1 lesions (*PLD6*, *S100A13*, *MXS2* and *TXNRD1*), and in CPAM type 2 (*ZFP57* and *MEIS1*)[190]. In CPAM type 3, differentially methylated regions were identified in *MSX2* and in an intergenic region involving a cis-regulatory element of *PITX2*, low methylation of which has been associated with an increased risk of lung cancer progression [33], and of *ENPEP*, which is downregulated in lung adenocarcinoma [34].

[H1] MECHANISMS/PATHOPHYSIOLOGY

[H2] CPAM

CPAM is in direct communication with adjacent lung parenchyma, and it is characterized by overgrowth of terminal bronchioles to the detriment of the alveoli. CPAM usually affect one lobe, most commonly the lower ones, and multi-lobar or bilateral disease is less common [35]. There are several hypotheses about the mechanism of CPAM pathophysiology. One theory assumes that focal lung morphogenesis is interrupted during CPAM pathogenesis as a result of genetic defects that cause continuous expression of lung growth markers, such as SOX2 and thyroid transcription factor-1 (TTF1), together with a decreased expression of retinoic acid enzyme RALDH-1 [36]. The obstructive hypothesis, which is based on histological studies, advocates that focal obstruction of the airway tree, such as a sort of bronchial stenosis or an abnormal airway peristalsis, might lead to a local increase of mediators that can trigger immune responses, such as fibroblast growth factor 10 (FGF10), interleukins and chemokines,, leading to CPAM formation[37]. However, the timing of these events is poorly understood [38]. Other hypotheses on CPAM pathogenesis, include the disruptive spatial patterning of epithelial cells in cysts that resemble proximal airway structures,

branching morphogenesis, and imbalance between cell cycle, cell proliferation and apoptosis (**Box 1**) [39,40].

Studies in transgenic murine models suggested that heterotopic overexpression of FGF7 [41] and FGF10 [42], and orthotopic expression of FGF7 [43] markedly perturb lung morphogenesis, and concur in the development of CPAM. The FGF family of potent mitogens regulates cellular proliferation, migration and differentiation, with FGF7 and FGF10 being expressed in lung mesenchyme [44]. Injection of FGF10 in fetal rat lung resulted in formation of cystic lesions, which varied depending on the developmental stage and injection location [45]. However, no alteration of FGF10 expression was found in fetal and postal-natal CPAM samples in humans, and this indicates that FGF10 overexpression may be a transient phenomenon during CPAM pathogenesis [46]. Cystic lung lesions are also found in mice overexpressing Krueppel-like factor 5 (KLF5) [48] or Notch1 receptor[49], and in mice lacking expression of peroxisome proliferator-activated receptor gamma (PPARγ) [50].

The most widely adopted classification scheme of CPAM is the Stocker classification [51], that combines gross and histologic features and proposes that each type arises at different level of the lung from trachea to alveoli (**Figure 1**). However, this classification has been critiqued because it brings together lesions of different etiologies under the heading of CPAM, such as type 0 and type 4 [52]. Acinar dysplasia **[G]**should be the preferred term for the diffuse malformation described as CPAM type 0, that is now a quite obsolete definition [53]. Acinar dysplasia is an interstitial lung disease due to bilateral impairment of bronchioles, alveolar ducts, and alveoli development. The affected lung is similar to 16-week lung in its pseudoglandular phase with no alveolar spaces for gas exchange. It is usually lethal and associated with mutations in genes that regulate embryonic development, cell proliferation and cell differentiation, including the genes encoding FGF10, FGFR2 and the transcription factor TBX4 [54,55].

CPAM type 1 arises from the proximal bronchioles or distal bronchi (**Figure 1**). CPAM type 2 lesions are believed to arise secondary to bronchial obstruction and may contain *KRAS* mutated cells [30,38,56-58]. CPAM type 3 is believed to originate from acinar-like tissue **[G]** and has been associated with activating *KRAS* mutations or mutations in other genes involved in cell cycle regulation and growth; 50% of CPAM type 3 have a *KRAS* mutation, most commonly p.G12V. Overall, the formation of CPAMs type 1 and type 3 seems to be driven by mosaic *KRAS* mutations arising in the lung epithelium early in development and places them within the growing cluster of mosaic RASopathies. Moreover, among the 351 genes that were identified as differentially expressed in pediatric CPAM, BPS, or hybrid lesions, compared with unaffected tissue of the resected lobe, genes in the Ras complex, PI3K-AKT-mTOR and mTOR signaling pathways, and Myc transcriptional targets were significantly enriched [59]. It has been argued that CPAM type 4 is identical to type 1 PPB [60], and should be considered a PPB, which is generally not diagnosed prenatally [26,53,61,62].

[H2] BPS

BPS is a hamartomatous mass of non-functioning lung tissue , and the mechanisms involved in BPS formation generally remain unknown. A role of *Hoxb5* has been demonstrated in the developing mouse lung. The expression of the homeobox protein Hoxb-5 is strong during the airway branching, and becomes negligible near term and later. High expression of Hoxb-5 protein has beem found in a newborn with BPS and this misregulation might be involved in BPS pathogenesis [63]. BPS lesions are not in continuity with the tracheobronchial tree and supported by an aberrant systemic artery [38]. Intralobar sequestrations (ILS), which appear within the visceral pleura, represent 75% of BPS lesions and are often localized in the lower lobes. Even though the abnormal lung parenchyma is non-aerated, some collateral ventilation is supported by the pores of Kohn **[G]** and channels of Lambert **[G]** of the adjacent lung tissue [38]. Consequently, ILS are at increased risk of bacterial seeding and pneumonia or other complications [35]. ILS are usually fed by a single artery most commonly coming from the descending thoracic aorta and branching to

the lower lobe after passing through the inferior pulmonary ligament. Multiple arterial supply has been described in 16% of the cases [64]. The venous drainage is most commonly to the left atrium through the pulmonary veins [64].

Extralobar sequestrations (ELS) correspond to a 25% of BPS lesions and are covered by a distinct pleura. ELS have one or, in 20% of the cases, more than one feeding artery, usually stemming from the thoracoabdominal aorta, and systemic venous drainage that is separated from normal lung parenchyma. In 80 % of cases, the systemic venous drainage occurs through the azygos or hemiazygos system, or through the vena cava to the right atrium [64]. Infections are less common in ELS, as ELS are not connected with the tracheobronchial tree, and presenting symptoms of ELS are mainly associated with the abnormal systemic vascularization, which sometimes leads to high-output congestive heart failure as a result of the right-to-left shunt, or to torsion of the vascular pedicle. ELS is usually found in the thoracic cavity, but it can also develop below the diaphragm in the abdomen, or within the diaphragm [38].

CPAM/ILS and CPAM/ELS 'hybrid/mixed' lesions found in the pediatric population share histopathological features of CPAM type 1 and type 3 and of CPAM type 2, respectively, and rely on systemic blood supply [65,66]. Such lesions are distinct from acquired lesions diagnosed in adults following lower lobe infections that cause the cystic degeneration of the parenchyma and the proliferation of systemic arteries entering the lung through the pulmonary ligament or across the pleura [64].

[H2] CLO

CLO is caused by a focal cartilaginous abnormality of the bronchial wall, which creates a valve effect and a consequent overinflation of a pulmonary lobe after birth [67]. The bronchial narrowing may be caused by intrinsic factors, such as absence of bronchial cartilage, bronchial stenosis or bronchomalacia, or by an extrinsic cause, as a vascular sling[68]. In ~50% of patients, however, CLO is idiopathic, and a clear etiology cannot be identified [68]. The left upper lobe and the right middle lobe are most commonly affected by CLO.

[H2] BC

BC is a unilocular malformation resulting from abnormal budding of the primitive ventral foregut. BCs contain cartilaginous tissue, smooth muscle, and bronchial glands, all lined by ciliated columnar epithelium. Most BCs are localized in the mediastinum adjacent to the trachea or the mainstem bronchi (subcarinal space), but sometimes they can be intrapulmonary, or appear outside the chest, in the areas of the neck, the abdomen or the skin [35,69]. The pathophysiology of BC is still unknown. BC can be asymptomatic. Mediastinal BCs do not communicate with the tracheobronchial tree, but they contain mucus and may enlarge or compress the bronchi, causing dyspnea[69]. Intrapulmonary BCs are connected with the tracheobronchial tree and can lead to respiratory symptoms in newborns or in infants, or infection in children, as a result of air trapping [69].

[H2] CBA

CBA stems from a focal interruption of a lobar, segmental, or subsegmental bronchus, and is associated with the presence of a mucocele and overinflation of the involved lung segment. The presence of the mucocele is pathognomonic and results from mucus accumulation following airway obstruction [70]. CBAs are hypothesized to occur after the 16th week of gestation, probably due to intrauterine ischemia. The apicoposterior segmental bronchus of the left upper lobe seems to be most commonly affected by CBA [70]. Proximal CBA is located at the level of the mainstem, or the proximal lobar bronchi and it is almost always fatal during pregnancy or immediately after birth [67]. Peripheral CBA involves the segmental or subsegmental bronchi and it has also been associated with other prenatal lung malformations, including CPAM, BPS, CLO [67], as part of the histopathological spectrum of these CLMs. In this Primer, we discuss peripheral CBA, when it presents as an isolated lesion[67].

[H1] DIAGNOSIS, SCREENING AND PREVENTION

[H2] Clinical presentation

Prenatally diagnosed CLMs have highly variable clinical presentation, ranging from lack of any symptoms to respiratory distress at birth [15,35]. The latter is a rare event that occurs in <10% of patients mostly as a result of a mediastinal shift caused by a CLO or a large CPAM [15,35], and requires emergency surgery. After birth, the progressive hyperinflation of the lobe affected by CLO may result in mediastinal shift **[G]** and consequent compression atelectasis of normal lung parenchyma [71]. Acute and rapidly worsening air trapping at birth, can lead to severe respiratory symptoms and need of surgery. In some instances, the hyperinflation of the lobe is slower and accounts for a delayed onset of respiratory symptoms within the first weeks of life [71]. However, some patients have minimal pulmonary symptoms or are completely asymptomatic, and are, therefore, managed with serial observation [35]. Most commonly, however, children with prenatally diagnosed CLMs remain asymptomatic postnatally [72], and admission to an intensive care unit is not justified in an asymptomatic newborn[35].

Nearly half of the patients that are asymptomatic at birth develop symptoms in their first year of life, with a peak at a median age of two years [17]. Long-term follow up has revealed that most infants with CLM develop symptoms [17,73]. The most common symptoms are respiratory infections, pneumonia, fever, chronic cough, pneumothorax, and respiratory distress. The incidence of respiratory infections in children with CLM is not clearly defined and varies across studies between 5 and 86% [16-18] High-output cardiac failure is a rare complication resulting from large systemic feeding vessels[38].

[H2] Prenatal screening and diagnosis

[H3] Fetal ultrasonography

Although CPAM, BPS, CLO, BC, and CBA are distinct pathologies, their embryology and imaging phenotyping overlap [1], and they also share some common clinical and histological features [66]. The prenatal diagnosis of CLMs relies on the cystic or solid appearance of space-occupying lesions within the fetal thorax, or the abnormal size of the lungs and consequent deviation of the heart

from its normal 45-degree position (**Figure 3**). According to the Adzick classification for fetal ultrasonography, CLMs are described as either macrocystic lesions that present as single or multiple cysts >5 mm, or microcystic lesions with solid appearance that feature cysts <5 mm[74].

CLMs are easily detected during routine prenatal ultrasonographic examination at 18-22 weeks of gestation. The differential diagnosis includes congenital diaphragmatic hernia **[G]** , esophageal duplication **[G]**, foregut duplication cysts **[G]** and other thoracic masses, such as pericardial teratoma. CLMs usually increase in size between 20 and 26 weeks of gestation before reaching a plateau by 29 weeks of gestation [75]. Later, the decrease in size of CLMs seems to be related not only to growth of the fetus but also to the transition from the canalicular to saccular stage of lung development (**Box 1**), with consequent changes in proliferation and apoptosis rates of epithelial and mesenchymal cells [76]. CLMs become isoechoic to normal lung tissue late in gestation, and this can be mistakenly considered as disappearance of the lesions. For this reason, it is imperative to perform a CT angiography scan after birth to confirm or exclude the presence of a CLM. Amniocentesis is not recommended in pregnancies with a diagnosis of CLM if a solitary lung lesion is identified. A vaginal delivery at a local birthing center without neonatal intensive care or pediatric surgical support is safe for fetuses with small lung lesions [15].

CPAM and BPS are the two CLMs most commonly diagnosed in utero, as intrathoracic, usually unilateral, cystic, or solid masses [77]. CPAM is usually recognized at mid gestation as a multilocular lesion with cysts from few millimeters to 10-12 mm in size (macrocystic type), or as well-defined homogeneously hyperechogenic mass (microcystic type) [77]. In both cases, the heart is usually pushed to the contralateral side [77]. BPS appears as a well-defined homogeneously hyperechogenic mass that is indistinguishable from the microcystic type of CPAM [77]. However, exploration with color Doppler ultrasonography can help identify any aberrant feeding artery arising from the aorta, and this is specific to BPS. 3D and 4D ultrasonography may provide greater information regarding the spatial relationship, volume, and vascular feeding of both CLMs [78]. A large CPAM can grow and cause mediastinal shift with consequent esophageal compression,

pulmonary hypoplasia, polyhydramnios [G] and obstruction to venous return leading to hydrops [G] [79] (**Figure 3**). Thus, it is recommended to monitor CLM growth by serial calculation of CPAM volume ratio (CVR) [80].

ILS hydrops may develop in the fetus because of abnormal systemic arterial blood supply with increase of venous drainage via the pulmonary veins, leading to "left-to-left" shunting which sometimes results in high-output cardiac failure. it is therefore recommended to assess cardiac function , for example based on Tricuspid annular plane systole excursion (TAPSE) [G], every 2 weeks since hydrop's diagnosis, usually around 22-24 weeks, to identify hemodynamic deterioration [81] (**Figure 3**).

CLO is identified only rarely via prenatal screening, mainly because of the isoechoic appearance and lack of mediastinal shift in utero [71]. CLO appears in fetal ultrasonography as uniformly enlarged lung, mildly hyperechoic, without cysts or systemic arterial supply [78]. The identification of a tubular cystic hilar structure consistent with a dilated bronchus and prominent oblique lung fissure at 2D and 3D ultrasonography may hint towards the correct diagnosis [78] (**Figure 3**).

Mass size, rather than CLM type, is the major predictor of perinatal outcomes[15,82]. CVR, the ratio of the 3D size of the lesion to the fetal head circumference, is the most commonly used metric for CLM mass (**Figure 3**) [83]. Risk of developing fetal hydrops is ~80% for fetuses with a CVR exceeding 1.6, and CVR increase during pregnancy has been associated with increased rates of prenatal intervention and adverse postnatal outcomes [84,85]. CVR has been associated with development of hydrops, neonatal respiratory distress (NRD), and increased rates of oxygen supplementation, mechanical ventilation, and resection at birth [15]. In addition, high CVR at diagnosis or high maximum CVR values were predictive of risk for NRD for both term and preterm infants [86], but consensus on a precise cut-off value is lacking [87]. One cohort study showed that a CVR ≤0.39 measured between 25-30 weeks predicts a low probability of need for respiratory support at birth but does not rule out respiratory problems later on [88]. The low probability of NRD (<10%) for a maximum CVR <0.40 supports this cut-off value [86]. A CVR >0.84 seems to be a

reliable predictor of respiratory morbidities, such as respiratory distress, recurrent infections, cough, and the need for surgical resection at birth [89,90] (**Figure 3**).

[H3] Fetal MRI

The merit of MRI for the prenatal diagnosis of CLMs remains controversial [35]. MRI can be used to accurately assess the location, size, and mass effect of CLMs [91,92], and one study has shown the superiority of MRI against ultrasonography in identifying vascular supply [91]. However, in fetuses with small lung lesions, the limited additional information provided by prenatal MRI is not sufficient to amend management plans. For this reason, MRI is only selectively recommended, for example, when a lung lesion in not clearly defined at prenatal ultrasonography or in the presence of a large CLM. MRI might help to characterize the malformation or to prepare a treatment plan if prenatal management or early neonatal resection are needed [87,91].. In such cases, the best timing for fetal MRI is between the 24th to 30th week of gestation [93].

[H2] Postnatal diagnosis

[H3] Computer Tomography Angiography

Postnatal chest CTA at 2 months of age is essential for confirming prenatal diagnosis of CLMs (**Figure 4**) and for outlining a management plan. Chest CTA is the current gold standard for the postnatal evaluation of CLMs due to its ability to provide the highest spatial resolution and sensitivity [94,95]. The scan range of chest CTA should cover the anatomical area from the thoracic inlet to the mid-abdomen to enable full capture of the extent of any aberrant vasculature, which may arise or extend below the diaphragm [96]. The CTA protocol should be tailored to the patient's weight in accordance with the ALARA principle and include thyroid function monitoring to promptly detect any temporary thyroid dysfunction [97].

Third-generation CT scanners use a lower amount of radiation and have a rapid acquisition speed that overcomes the need for sedation [94]. They deliver diagnostic-quality images in >95% of patients [94,95], regardless of age or compliance with breathing instructions. Structured assessment

of CTA results [98] can consistently provide precise information about the size, location, and other characteristics of CLMs [99] that are crucial for surgical planning.

[H3] Chest radiograph

CR is a first-line screening tool, being noninvasive and cost-effective. However, a prenatally diagnosed CLM should never be ruled out in a newborn based on CR only, as CR fails to detect CLM in 50% of patients [100-102], and the information it provides fails to predict the potential onset of symptoms or to inform the surgical plan [94] (**Figure 4**). In pediatric patients that present with recurrent pneumonia in the same lung lobe but lack a prenatal diagnosis of CLM, certain radiographic features, such as persistent opacities or radiolucency, can raise suspicion for an underlying undiagnosed CLM [103]. In case of strong clinical suspicion of CLM, after the complete healing of the pneumonia, further imaging evaluation using cross-sectional techniques, such as CTA or MRI, is necessary to obtain a comprehensive and accurate diagnosis (**Figure 4 and 5**).

CR can also be applied to assess potential complications of CLM surgery, such as pneumothorax, bleeding, and infections[94]. In previously asymptomatic children with CLM that newly develop symptoms CR is often the first imaging modality used to evaluate the cause of these symptoms [94] and assess them as potential complications of BPS or CPAM, in the case of infections, and CLO or BC, in the case of progressive hyperinflation.

[H3] Lung ultrasonography

Lung ultrasonography (LUS) has limited application in the detection of CLMs after birth, as ultrasound waves cannot penetrate normally aerated lungs and can only be used to image peripheral lung lesions [94,104]. LUS can still be a cost-effective method for the diagnosis of complications in pediatric patients with respiratory distress [105] or infection, as the consolidation of the lung parenchyma in these patients makes the visualization of the CLM easier.

[H3] MRI

Chest MRI has the potential to replace CTA for assessing CLMs in the future[92,106], especially in medical centers that have expertise in chest MRI techniques [92]. However, in current practice, surgical plans cannot be based entirely on MRI, as CTA provides superior quality images of lung parenchyma, especially in infants. In addition, sedation is required for infants and young children between 6 months and 5 years of age undergoing MRI[94,107].

Chest MRI protocols have the added advantage of not requiring use of contrast to visualize the vascular anomalies associated with CLMs [108]. In cases of CLMs with abnormal blood vessels, chest MRI can be combined with cardiac MRI to assess blood flow and shunting [94]. There are several clinical scenarios in which chest MRI may be used to assess CLMs, including follow-up of a previously identified CLM to avoid repeated exposure to radiation, evaluation of a mass in an atypical location, or complementary characterization when CTA is incomplete [92].

[H2] Histopathology

Histopathological assessment of lung tissue is necessary to confirm diagnosis of CLM and to identify the subtype of CLM.

[H3] CPAM

CPAM type 1 appears as a cystic lung lesion, with cyst size ranging from <0.5 cm to >7 cm in greatest dimension. CPAM type 1 cysts are lined by ciliated cuboidal to stratified columnar epithelium, occasionally featuring cartilage in the cyst wall, and are interspersed within a lung parenchyma with enlarged and simplified alveoli [56,109]. Multiple connections are observed between the thick cyst wall and adjacent alveolar wall, and epithelial complexity, including papillary projections, may occur [56,109]. Some CPAM type 1 lesions may have solid appearing areas with features of both type 1 and type 3 CPAM. In CPAM type 2, there are both identifiable cysts lined by ciliated columnar epithelium and mildly malformed alveolar type spaces [56,109]. Cysts can measure up to 2.5 cm in greatest dimension and are also interspersed within normal appearing

lung parenchyma. Striated skeletal muscle occasionally appears in the septa between cysts. CPAM type 3 lesions have a solid, often lobulated appearance, and are well-demarcated from uninvolved lung parenchyma characterized by small irregularly shaped airway spaces lined by ciliated cuboidal to columnar epithelium [56,109]. Surrounding septa often appear thickened, with prominent mesenchyme and cuboidal epithelium [56,109].

[H3] BPS

BPS is defined by an anomalous systemic vascular supply and sequestration from the tracheobronchial tree. The systemic feeding vessel is usually identified only radiologically, but it may still be identifiable in intact gross specimens. The BPS parenchyma has a variable macroscopic appearance, ranging from grossly normal to cystically altered[109]. Histologically, systemic artery branches may appear thickened with some features that are characteristic of pulmonary hypertension in older patients [110]. All patients have at least mild parenchymal maldevelopment with enlarged and simplified alveoli [65,66]. Pools of mucin and foamy intra-alveolar macrophages may suggest presence of mucostasis [52]. Foci of skeletal muscle may be seen in septa between larger cysts [109]. Prominent lymphangiectasia is seen in a subset of extralobar bronchopulmonary sequestrations [109].

[H3] CLO

In CLO, tissue architecture is maintained, unlike in acquired emphysema. However, lack of acinar maturation with age and overinflated alveoli are seen [109]. In many CLOs, there are normal numbers of radial alveoli at birth, but with acinar development arrested in the postpartum period [109]. In the hypo-alveolar and poly-laveolar subtypes fewer or more than the expected number of alveoli are present, respectively [111].

[H3] BC

BC presents as a unilocular cyst filled with serous or mucinous material, lined by respiratory type epithelium, reminiscent of bronchial wall with variable amounts of seromucinous glands, cartilage, and smooth muscle [109]. Secondary changes related to previous infection or procedures may include acute and chronic inflammation with epithelial denudation or squamous metaplasia, and evidence of hemorrhage with cholesterol clefts and/or hemosiderophages, as well as variable fibrosis [109].

[H3] CBA

Surgical specimens of CBA have an atretic bronchus with distal pink hyperaerated lung with occasional subpleural blebs [112]. There is no proximal or central tracheal communication of the atretic bronchus, whereas distal to the atresia there is cystic dilatation of the bronchus, sometimes amounting to a mucocele, that contains plugs of desquamated tissue and mucus as an unvarying component [112]. The blind end of the proximal or distal bronchus is lined with bronchial epithelium without scar formation or granuloma [70]. Microscopic examination of the distal pulmonary parenchyma is essentially normal except for dilatation of alveoli and hypoplasia as evidenced by a reduced number of alveoli per unit area [112].

[H1] MANAGEMENT

[H2] In utero management

[H3] Maternal steroids

The first-line therapy for giant microcystic lesions (CVR>1.6) and hydrops or impending hydrops is maternal administration of two doses of systemic steroids [113]. This treatment is most effective before the 26th week of gestation. [114,115].It has been suggested that steroids act by speeding the passage from canalicular to saccular stage of lung development [35] (**Figure 3**). However, steroids show no efficacy in fetuses with macrocystic lesions [116].

[H3] Thoracoamniotic shunts

When hydrops complicates a pregnancy with large fetal lung lesions containing a dominant macrocyst , the insertion of a thoracoamniotic shunt **[G]** (TAS) (**Figure 3**) has been demonstrated to decrease the mass effect of the malformation, improving hydrops, and increasing fetal survival [113]. This ultrasonography-guided minimally invasive procedure can rely on double pigtail catheters to minimize dislodgement. However, it carries risk of premature preterm rupture of membranes, preterm labor, chorioamnionitis, shunt occlusion or dislodgment, and chest wall deformities [113].

[H3] Fetal surgery

The introduction of steroid therapy has considerably limited the need to recur to fetal surgery in case of severe hydrops before the third trimester [117]. Similarly, the indications for EXIT-to-resection **[G]** management with the aim of creating space for the the lung to function postnatally are very rare and considered for large lesion with CVR >2 and persistent mediastinal shift [117].

[H3] Fetal management of BPS

Expectant management of fetuses with BPS and associated hydrops can lead to pulmonary hypoplasia and consequent poor prognosis [118,119]. However, the use of TAS has proved to help decreasing the hydrops, and neonatal death [35]. Laser coagulation of the feeding vessel contributes to decrease the malformation's volume [120] (**Figure 3**). A multicenter study [121] has demonstrated that laser ablation interrupting blood supply to the malformation helps to achieve better perinatal outcomes compared with TAS, including longer gestational age and less frequent postnatal surgery.

[H2] Postnatal management

[H3] Surgical treatment

The superiority of thoracoscopic approach over thoracotomy has been extensively proved [122-126], because it is a minimally invasive approach with improved visualization, it is feasible at any size and weight of the patients [123,127], has decreased the invasiveness of the surgical procedure, resulting in less pain, shorter hospital stay, and decreased long term morbidity, including a

decreased risk of chest wall deformity, shoulder girdle weakness, and scoliosis, in comparison with open thoracotomy [128,129]. Moreover, the magnification provided by thoracoscopy enables better visualization, especially of fissures and vessels [129].

The standardization of thoracoscopic technique, including an anterior approach to the patient and vessel sealing to manage the pulmonary vessels, has resulted in a reproducible and consistent method that can be taught worldwide. Most procedures are elective and, therefore, should be scheduled in centres experienced and trained to perform this minimally invasive procedure [124]. Moreover, lobectomy is considered safer than sublobar/segmental resections, as it is not possible to accurately determine the limit between CLM and normal parenchyma in the latter procedures and incomplete resections have been demonstrated to result in complications, such as pneumothorax [130]. Thus, thoracoscopic lobectomy in children for CLMs should be considered standard of care [122-126].

The timing of resection is debatable with some preferring earlier surgery, by 4 months of age (**Figure 5**), and some as late as 1 year of age, although delayed resection has not shown improved outcome [131]; in older infants, substantial adenopathy and inflammation in the fissures and around the pulmonary artery can lead to more difficult identification and safe division of these vessels (**Figure 4**). Data suggest earlier resection is associated with shorter operative times, hospital stays and reduced rates of inflammation in specimens [127,132-134]. Early resection may also reduce the likelihood of pre-operative respiratory infections, which can distort tissue planes, create thick adhesions and complicate surgery, causing more frequent conversion from a minimally invasive approach to open surgery because of impaired visualization and difficult lung mobilization [135,136]. Moreover, the same patients with pulmonary infections before surgical treatment had increased incidence of post-surgery infections [135]

In asymptomatic CLO or CBA, there is agreement that no surgical treatment is required [137] and serial observation is adequate [35]. However, if CLO or CBA become symptomatic due to progressive air trapping of the affected lobe or infection, respectively, surgery is performed.

A sublobar anatomical resection is only relevant if there is multi-lobar disease.

[H3] Management of asymptomatic CLMs

Prenatally diagnosed CLMs that are symptomatic at birth or become symptomatic during the neonatal period are managed with surgical resection. However, there is still an unresolved controversy among pediatric surgeons about management of prenatally diagnosed CPAM, BPS, or BC that are asymptomatic after birth. Most pediatric surgeons are still in favour of prophylactic surgical resection of asymptomatic CLMs (**Figure 5**). However, some specialists consider conservative (non-operative) management as an alternative to surgical resection, unless symptoms and complications emerge [16,138,139].

Three lines of argumentation are used by clinicians favoring a conservative management approach. First, it has been suggested that unnecessary invasive surgery and general anaesthesia may have negative effects on long-term neurodevelopment, and some potentially serious or even life-threatening complications in infants and children [8,140-143]. Second, it has been argued that most asymptomatic patients remain asymptomatic during childhood [16,18,144-146]. Third, professionals favoring the conservative non-operative management consider the risk of malignancy as being small [20].

However, the thoracoscopic approach has transformed the procedure into a mini-invasive one [128,129]. In addition, normal neurodevelopment outcomes have been demonstrated for children who undergo surgical removal of a CLM in comparison with their healthy peers [147], and early prophylactic elective surgery can facilitate compensatory lung growth [72]. Moreover, records of long term follow-up for emergence of symptoms later in life are lacking. Of the patients with CLMs that have been followed up until adulthood and patients who have been diagnosed with CLM in adulthood (**Box 2**), 80% have become symptomatic and often present with acute onset of symptoms at diagnosis [148-151]. In addition, pre-operative infections make surgery more challenging and increase the rate of conversion to thoracotomy [135]. Finally, even though the true incidence of

malignancy in patients with CLMs remains unknown, lung cancer may appear at any age and is accompanied by nonspecific symptoms of respiratory infections that may be missed[22], whereas radiological imaging fails to predict risk of malignancy or provide an early diagnosis of cancer[22]. The real conundrum in following a conservative approach is to design a clear follow up program for the patients in terms of frequency, duration, and methodology. Chest radiograph (CR) is inadequate to detect malignant transformation in CLMs[94]. Repeated exposure to chest CTA poses a risk of iatrogenic malignancy [152], precluding its adoption for radiological surveillance during childhood. Also CTA fails to detect malignant transformation at an ealy stage and it raises suspects of malignancy only when a cancerous mass has already formed. In addition, long-term surveillance is challenging in terms of high cost, patient compliance, and transition of care with the involvement of adult thoracic surgeons and pulmonologists[79].

[H1] QUALITY OF LIFE

So far, literature reviews on CLM outcomes have mainly focused on how the timing of lobectomy can enhance compensatory lung growth [153-155]. Modalities in diagnostics and surgical techniques have changed over time. The introduction of structural fetal ultrasonography that has led to an increased antenatal detection rate [9] and intensive care treatment, has helped improve survival rates of neonates with severe respiratory problems, and minimal access surgery has gained popularity [123]. Thus, the data on long-term outcomes of children born in the past century can probably not be extrapolated to the cohort of neonates born with CLM during the past 10 years. To optimize postnatal management and parental counselling, an international multicenter registry is important and initiatives for such a registry are underway [155].

Uniform data on pulmonary morbidities are still lacking, especially data on general health, quality of life, and societal participation. The focus of the currently available data is on general outcomes, such as physical growth, disease-specific outcomes, such as respiratory tract infections, lung

function and exercise tolerance, and treatment-related outcomes, such as musculoskeletal deformities.

Physical growth in infancy was found to be similar between infants who underwent surgical CLM resection and patients with non-resected asymptomatic CLM [156]. In a prospectively followed cohort of patients with resected CLM, weight-for-height was slightly below average at 2 years of age but within the normal range at 8 years of age [157,158].

Susceptibility to respiratory tract infections was studied in a population-based cohort including 31 individuals with resected CLM that were born between 1991 and 2007[159]. Pneumonia and infections, including influenza, were more common in CLM-resected individuals than in the control cohort of 310 individuals of a population-based administrative data repository .

Small studies assessing lung function during infancy showed mild abnormalities in heterogeneous groups of patients with CLM, including reduced tidal volumes **[G]** [160,161], reduced lung compliance **[G]** [160], and increased airflow obstruction [156]. Interestingly, reduced lung compliance and airflow obstruction had also been reported in infants with CLM who did not undergo lung resection [156,160]. At school age, airflow obstruction mainly occurred in children who had undergone resection [157,162], although normal spirometry was reported in 76-86% of patients[163]. Exercise tolerance has been studied in only one group of eight-year-old participants of a structured longitudinal follow-up program. Reduced exercise tolerance was observed in 40% of children who underwent resection and in 28% of the non-surgery group [157]. Lobectomy had been performed in most of the operated patients, although segmentectomy was done in few patients. The current results do not enable drawing any conclusion on the optimal surgical strategy for preservation of lung volumes, and functional MRI may be useful for further evaluation in the future [164]. Minimally invasive surgical techniques have more favorable outcomes than thoracotomies in terms of lung function [165] and development of musculoskeletal deformities [166,167].

International collaboration and registries for CLMs and the various treatment modalities, complications, and outcomes are important to determine the long-term quality of life of patients with CLM.

[H1] OUTLOOK

There are ongoing advancements in the surgical treatment of CLMs. The thoracoscopic approach is already widely used [123]; however, future advences may focus on refining and expanding its application to further improve outcomes and reduce invasiveness. Moreover, personalized surgical plans can optimize outcomes and minimize potential risks related to surgery. Integration of advanced imaging technologies, such as 3D imaging and printing, can provide detailed anatomical information for surgical planning. 3D-printed models of the affected lung segments can assist surgeons in preoperative planning and intraoperative guidance, potentially improving surgical precision and outcomes.

A combination of virtual reality (VR) and augmented reality (AR) with emerging artificial intelligence (AI) algorithms has been explored for the preoperative planning of pulmonary segmentectomy in adult patients [168]. In addition, a combination of VR and AI has also been used to preoperatively try to identify the exact vascular and bronchial anatomy and segmental borders in children with CLM[169]. However, although this approach could be used to remove gross disease, microscopic lesions might be left untreated, maintaining the risk of malignant transformation [22,170,171]. Unfortunately, current imaging modalities do not adequately distinguish between healthy and abnormal lung parenchyma, at least not at a microscopic level. Moreover, segmentectomy is burdened by a higher incidence of complications [130]. Thus, VR-led and AI-led anatomical segmentectomy could be considered as an approach only if gross disease seems to be limited to a single segment or in case of bilateral CLM.

Robotic surgery has been widely applied in adult patients, especially for urological and gynecological surgeries, but also in thoracic oncology [172]. The technical advantages over thoracoscopy include intuitive movements, more manipulative freedom, and high-definition stereoscopic vision. Moreover, similarly to thoracoscopy, robotic surgery has been associated with shorter hospital stay, quick restart of daily activities, and better cosmesis [172]. Although robotic surgery has been expanded to pediatric patients [173,174] , its uptake in younger infants, especially for procedures in the thorax, has been slow due to technical challenges . The reduced chest space of infants would call for a miniaturization of the devices and for a smaller distance between ports to decrease external cluttering [173,174]. So far, only a few series of pediatric robotic-assisted thoracic surgery have been reported[174,175], and even fewer infants with CLMs have undergone robotic-assisted lobectomy [176]. Until a dramatic miniaturization of the devices is reached, robotic-assisted thoracic surgery won't be an option for small infants.

Future efforts will likely focus on optimizing long-term outcomes for individuals with congenital lung malformations through standardized follow-up protocols, monitoring, and research to understand the long-term effects of surgical interventions. Continued research, collaboration, and integration of innovative technologies will shape the future of surgical treatment for congenital lung malformations, ultimately aiming to improve patient outcomes and quality of life. Moreover, genetic and biological studies should focus on addressing the potential trigger of CLM malignant transformation and identify specific genetic mutations or alterations associated with the malignant transformation of CLMs. Understanding the underlying genetic mechanisms can guide targeted therapies or early detection strategies.

Author contributions

Introduction (F.P.) Epidemiology (F.P. and J.M.S.); Mechanism/pathophysiology (K.K.Y.W., A.P.D. and F.P.); Diagnosis, screening and prevention (R.A., P.C.; F.P. and J.v.d.T.); Management (N.H., J.M.S., S.S.R, and F.P.); Quality of life (H.I.); Outlook (F.P.). All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Competing interests

The authors declare no competing interests.

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Figure 1: Types of congenital lung malformations.

Abnormal organogenesis or dysregulation of cellular signaling within the epithelial-mesenchymal interaction during embryonic development might cause a congenital lung malformation (CLM). The timing of this dysregulation determines the type of CLM, which comprise five subtypes of congenital pulmonary airway malformations (CPAMs); bronchopulmonary sequestration (BPS), which can be intralobar (ILS) or extralobar (ELS); congenital lobar overinflation (CLO); bronchogenic cysts (BC); and congenital bronchial atresia (CBA). Stocker's classification identifies five types of CPAM; however, CPAM type 1 should now be called acinar dysplasia, and CPAM type 4 is doubted to be a peuropulmonary blastoma (PPB). CPAM type 1 arises from the proximal bronchioles or distal bronchi, CPAM type 2 from the bronchioles, and CPAM type 3 from acinar-like tissue. BPS (both ILS and ELS) is not in continuity with the tracheobronchial tree and fed by an aberrant systemic artery. CLO is caused by a focal cartilaginous abnormality of the bronchial wall. BC is a unilocular malformation resulting from abnormal budding of the primitive ventral foregut. CBA is due to a focal interruption of a bronchus with associated mucocele and overinflation of the involved lung segment.

Figure 2: Histology of congenital pulmonary airway malformation type 1 (CPAM 1) with mucinous cell clusters.

Hematoxylin and eosin stained low power (2.5x, **A**) and high power (10x, **B**) micrographs of CPAM type I lesion demonstrating large cystic spaces (*) lined by non-atypical respiratory and cuboidal epithelium, surrounded by alveolar tissue with collapsed but apparently normal morphology, with focal proliferation of columnar mucinous cells (arrows). These mucinous proliferations, as well as the adjacent cystic spaces were shown to contain a KRAS exon 2: c.35G>A; p.G12D mutation by next-generation sequencing.

Figure 3: Prenatal congenital lung malformation (CLM) diagnosis and management

a. Ultrasonographyc prenatal diagnosis of CLM relies on the size of the lungs and the identification of space-occupying lesions, either solid or cystic, within the fetal thorax. Congenital pulmonary airway malformation (CPAM) may present as either a multilocular lesion with cysts (macrocystic type), or as a well-defined homogeneously hyperechogenic mass (microcystic type). Bronchopulmonary sequestration (BPS) appears as a homogeneously hyperechogenic mass wiith an aberrant feeding artery arising from the aorta. Congenital lobar overinflation (CLO) appears as uniformly enlarged lung, mildly hyperechoic, without cysts or systemic arterial supply, like microcystic CPAM. CPAM and BPS can cause fetal hydrops, which would benefit from the insertion of a thoraco-amniotic shunt (macrocystic CPAM), administration of steroids (microcystic CPAM), and vascular laser ablation (BPS). b. Illustrative diagram of CPAM volume ratio (CVR) and its calculation on prenatal ultrasonography images. CVR is a 3D (width: red arrow; depth: blue arrow; length: yellow arrow) sonographic indicator of the mass volume normalized for gestational age to evaluate fetuses at risk of developing hydrops.

Figure 4: Asymptomatic patient with CPAM becoming symptomatic.

A: Anterior-posterior chest radiograph at birth shows some radiolucent round abnormalities in the perihilar region of the right lung (arrow). **B**: Coronal lung window of chest computer tomography angiography (CTA) at 6 months shows a multicystic lesion (arrow) with cysts <2 cm surrounded by low-density lung parenchyma, which is consistent with a congenital pulmonary airway malformation (CPAM) type 2. **C**: CTA at 5 years old of the same patient admitted with signs of pneumonia. The coronal CT reformat shows consolidation (arrow) of the lung parenchyma surrounding the cystic component of the CPAM.

Figure 5: Algorithm of postnatal diagnosis and surgical management in asymptomatic and symptomatic congenital lung malformations (CLM).

In asymptomatic prenatally detected CLM, the diagnosis must be confirmed with computer tomography angiography (CTA) at 2 months. Asymptomatic congenital lobar overinflation (CLO) and congenital bronchial atresia (CBA) can be managed conservatively. However, if CLO or CBA become symptomatic due to progressive air trapping of the affected lobe or infection, respectively, surgery is performed. By contrast, asymptomatic congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS), and bronchogenic cyst (BC) undergo elective surgery by 4 months of age. A symptomatic newborn needs emergency chest radiograph (CR) and CTA to confirm prenatal diagnosis and, in case of persistence of symptoms, undergoes emergency surgery. In case of incidental detection of a previously undiagnosed CLM, a CTA is needed to confirm the diagnosis and elective surgery is planned. When a CLM is suspected in a symptomatic patient, CR and CTA are needed to confirm the diagnosis and surgery is planned as soon as possible.

Box 1. Lung development

Lung development begins at 4 weeks of gestation and can be classified into five stages [177]:

Embryonic: Two lung buds appear as sacs of respiratory epithelial cells on the ventral part of the foregut [178]. Several genes are expressed at this stage: *Nkx2-1*, encoding TTF1, in the ventral wall, and *Sox2*, *Hox 5* and *Hoxb5* in the dorsal wall of the anterior foregut [39]. At 4-7 weeks, the lung buds extend and separate into branches creating the primitive bronchi [179], while the pulmonary arteries develop from the 6th aortic arches and form a vascular plexus by growing into the mesenchyme [179]. Simultaneously, BMP4 and its antagonists Noggin, FGF10, Wnt2 and Wnt2b are expressed on mesenchyme [180,181]. Dicer1, which encodes an endonuclease involved in the maturation process of siRNAs and miRNAs, generally influences embryonic development and normal cell physiology. [182]. Dicer1 inactivation in the lungs of mouse embryos shortly after the beginning of lung branching caused branching defects and prolonged ectopic cell death [183].

Pseudo-glandular: By the end of 7 weeks, repetitive sprouting forms pre-acinar airways. At 8-16 weeks, the primitive airway epithelium starts to grow and FGF10 regulates differentiation [179,184]. Sox2 and Sox9 are the main transcription factors in lung progenitor cells for branching morphogenesis and cell differentiation [185,186].

Canalicular stage: At weeks 16-25, the blood–air barrier and the terminal bronchial branches take shape. At ~20 weeks, pulmonary epithelium cells differentiate into type I and type II pneumocytes, which are crucial to lung development [187]. The pulmonary vessels also begin to proliferate and develop the mesenchymal capillary network.

Saccular stage: This stage, starting at 26 weeks of gestation is the earliest period of lung viability and the formation of saccules on terminal airways. Surfactant production begins at ~26 weeks and primitive alveoli start to develop at 30 weeks [188,189].

Alveolar stage: This stage begins after birth and continues for 4-5 years with secondary septation in saccules. Alveolar ducts are divided into terminal alveoli and 85% of alveoli are formed after

birth. The gas exchange surface area of the lung expands, and the thoracic growth carries on until adolescence.

Box 2. Adults with CLM

Most CLMs are diagnosed during pregnancy. However, some remain undetected in the prenatal period and in childhood and are discovered in adulthood. An insight into the management of adults with CLM might give the pediatric specialists a perspective of the possible future of children with CLMs managed conservatively.

Most adult patients with CLM (80%) complain about cough and respiratory infection as acute events or as recurrent symptoms throughout life; however, nearly 20% remain asymptomatic and the CLM is incidentally detected at screening imaging [148,150]. The presence of a CLM has been described in patients aged from 15 to 80 years. In all patients, a CR is performed as first line imaging and, in all cases, can reveal an infection, but fails to detect the CLM. A CTA is, therefore, always performed to define the diagnosis and plan the surgery [150]. Adult thoracic surgeons recommend surgical resection as treatment of choice in all adult patients with CLM, even in asymptomatic cases, as they are concerned about the susceptibility to infections and the risk of malignant transformation, which occurrs in almost 10% of prenatally undiagnosed CLMs [148,150] and over 20% of prenatally undiagnosed CPAM described in literature [148,150]. Conservative treatment is offered only when surgery is not feasible together with the recommendation of annual CTA to monitor the CLM.

Highlighted References

[Au: Please list here the references that are particularly worth reading (5-10 of the total), please provide a single bold sentence that indicates the significance of the work.]

Glossary

Epithelial-mesenchymal interaction: A series of programmed, sequential and reciprocal communications between the epithelium and the mesenchyme with its heterotypic cell population that result in the differentiation of one or both cell populations.

Congenital anomalies: structural or functional anomalies occurring during intrauterine life, and affecting an estimated 6% of global live births (WHO definition)**.**

Acinar-like tissue: A tissue composed of polarized epithelial cells rich in rough endoplasmic reticulum and characterized by an abundance of secretory zymogen granules.

Pores of Kohn: Small communications between adjacent pulmonary alveoli that provide a collateral pathway for aeration.

Channels of Lambert: Microscopic collateral airways between the distal bronchiolar tree and adjacent alveoli.

Mediastinal shift: The deviation of the mediastinal structures towards one side of the chest cavity.

Congenital diaphragmatic hernia: A defect in the diaphragm causing the herniation of abdominal contents into the thoracic cavity, resulting in lung hypoplasia and altered pulmonary vascular development.

Esophageal duplication: separate masses along or in continuity with the native esophagus

Foregut duplication cysts: benign developmental anomalies that contain foregut derivatives

Polyhydramnios: a condition that occurs when too much amniotic fluid builds up during pregnancy**.**

Tricuspid annular plane systole excursion (TAPSE): A scoring system used with non-invasive Doppler echocardiography to determine right ventricular function.

Thoracoamniotic shunt: A shunt that drains fluid from the lung into the amniotic sac to treat pleural effusion, for example in congenital pulmonary airway malformations.

EXIT-to-resection: In the EXIT-to-resection procedure a hysterotomy is performed to exteriorized the fetal head and torso enabling orotracheal intubation and placement of peripheral IV; the lung malformation can be resected while the fetus is still on placental support [35].

Tidal volumes: The amount of air that moves in or out of the lungs with each respiratory cycle

Lung compliance: A measure of the expansion of the lung,

Hydrops: Abnormal interstitial fluid collection in two or more compartments of the fetal body

Acinar dysplasia: A rare malformation characterized by growth arrest of the lower respiratory tract and complete absence of gas exchanging units, resulting in critical respiratory insufficiency at birth.

ToC blurb

Congenital lung malformations are rare developmental anomalies of the lung, that can lead to recurrent infections, pneumothorax and malignancy in some patinets. This Primer summarizes the epidemiology, pathophysiology and diagnosis of this disorder, and discusses current management and quality of life of patients.