Surfactant Protein Deficiency Syndrome in Childhood Interstitial Lung Disease

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September 17, 2020

Abstract

Surfactant, which was first identified in the 1920s is pivotal to lower the surface tension in alveoli of the lungs and helps to lower the work of breathing and prevents atelectasis. Surfactant proteins, such as surfactant protein B and surfactant protein C contribute to normal functioning of surfactant. Additionally, Adenosine Triphosphate Binding Cassette 3 and Thyroid Transcription Factor-1 are also integral for the normal structure and functioning of pulmonary surfactant. Through the study and improved understanding of surfactant over the decades, there is increasing interest into the study of childhood interstitial lung diseases (chILD) in the context of surfactant protein deficiencies. Surfactant protein deficiency syndrome (SPDS) is a group of rare diseases within the chILD group that is caused by genetic mutations of SFTPB, SPTPC, ABCA3 and TTF1 genes. This review article seeks to provide an overview of surfactant protein deficiencies in the context of chILD.

Introduction

An early history of pulmonary surfactant

The concept of surfactant was first mooted by Kurt von Neergaard in 1929, a German physiologist working in a laboratory in Switzerland. He was the first person to demonstrate that reduced surface tension in the lungs plays an important role in respiratory physiology and should be investigated further[1, 2]. Almost 2 decades later, Peter Gruenwald demonstrated the use of a surface active substance that could be used to reduce the resistance required for aeration of the lungs in his experiments with stillborn infants[3].

In 1959, Mary Avery and Jere Mead published their seminal paper describing how children dying of hyaline membrane disease had increased alveolar surface tension. Avery and Mead further concluded that hyaline membrane disease was associated with the absence or late appearance of a substance, which in normal subjects render the internal surface capable of attaining a low surface tension when lung volume is decreased[4]. It was only 5 years later, following the demise of President John Fitzgerald Kennedy and Jackie Kennedy's third child, Patrick Bouvier Kennedy who was born at 35 weeks gestation and died 2 days later, that the further study into surfactants, and the development of synthetic surfactants accelerated[5].

During the study of nerve warfare agents in the $1950s$, Richard Pattle conducted a study on lung fluid and identified that it mainly constituted of lecithin, protein and gelatin. He also demonstrated that this property of lowering surface tension disappeared when exposed to pancreatin and trypsin[6]. The components of this lung fluid was further delineated by Clements *et al* into 3 distinct categories; unsaturated phospholipids, non-phosphorylated lipids and proteins[2]. Following this, Weibel and Gil were the first to be able to preserve

the layer of surfactant and examine it under electron microscopy which further paved the way into the study of surfactant and surfactant proteins[7, 8].

Surfactant is important to lower the surface tension in alveoli of the lungs, it reduces the surface tension on the air/liquid interface down to a pressure of 1mN/m at low lung volumes[8], therefore surfactant is pivotal in not only lowering the work of breathing, but it also prevents end expiratory alveolar collapse which otherwise would lead to atelectasis[9].Besides lowering surface tension, surfactant also plays a role in the host defence mechanism within the lungs particularly in its' ability to regulate neutrophils, macrophage, T cells and dendritic cells[10, 11]. Through the study and improved understanding of surfactant over the decades, there is increasing interest into the study of childhood interstitial lung diseases (chILD)[12]. Several mutations of surfactant related gene have been identified as a cause of chILD and the body of research continues to grow in this field.

This review article seeks to provide an overview of surfactant protein deficiency in the context of chILD.

Production and components of surfactant

Surfactant is a product of the alveolar type 2 cells. This complex mixture of lipids and proteins starts being secreted into the alveoli form 24 weeks gestational age[13]. Following synthesis in the endoplasmic reticulum and Golgi apparatus, [14]surfactant is packaged in lamellar bodies[15] before exocytosis. The Adenosine Triphosphate Binding Cassette 3 (ABCA3) protein that is located on the limiting membrane of the lamellar body facilitates transport of phospholipids into the lamellar bodies[16]. After exocytosis into the alveolar surface, hydrophobic proteins become essential in the formation of the lipid monolayer at the air-liquid interface. This mixture forms a film that is made up of a lipid bilayer and a monolayer enriched with dipalmitoylphosphatidylcholine that is mostly responsible to lower surface tension in the air fluid interface of the alveoli[17].

Surfactant is made up of 90% phospholipids and 10% protein. The major component of phospholipid is phospatidylcholine which in about 80% exists in the dipalmitoylphosphatidylcholine form[18]. The next component of phospholipids is phospatidylglycerol that may play a secondary role in reducing surface tension. It has been demonstrated*in vitro* that mixtures with dipalmitoylphosphatidylcholine: phospatidylglycerol has better lipid adsorption when compared to mixtures with dipalmitoylphosphatidylcholine alone[19, 20]. Additionally, studies have demonstrated that phospatidylglycerol plays a part in the innate immune pathway and regulates both viral and bacterial infections[21-23]. The remainder of phospholipid components are made up of phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, sphingomyelin and neutral lipids (cholesterol and diacylglycerol), the exact function of these components remains unclear[24].

The protein component of surfactant is comprised of 4 protein types namely surfactant protein A (SP-A), Surfactant protein B (SP-B), Surfactant protein C (SP-C) and surfactant protein D (SP-D)[25]. These proteins can be divided into two groups based on their chemical properties, SP-B and SP-C are two small hydrophobic proteins, while SP-A and SP-D are hydrophilic. In addition to*ABCA3* , Thyroid transcription factor-1 (TTF-1) is also an important protein required for the normal structure and functioning of pulmonary surfactant [26].

SP-A was the first protein to be discovered as a component of surfactant[27]. SP-A and SP-D function as part of the innate immune system[11, 28] as opsonins that act against pathogens by increasing membrane permeability or facilitating the attachment of phagocytes[29]. SP-A deficient animal models are more susceptible to infections but at the same time able to maintain normal oxygenation, suggesting that SP-A does not influence the normal functioning of surfactant[23].

SP-B and SP-C are of particular interest in congenital surfactant protein deficiencies. SP-B and SP-C molecules are first synthesised as larger precursor molecules that are further cleaved into their mature forms. This process occurs in the lamellar body and it is here that ABCA3 enables phospholipid translocation and organelle development. ABCA3 (ATP-binding cassette, subfamily A, member 3) is an intracellular lipid transporter that is localized within the outer membrane of lamellar bodies in which transports phospholipids

and cholesterol into the lamellar body lumen[30]. Lamellar bodies function as a production and storage organelle for surfactant before secretion into the alveolar space[31].

The production of these molecules is under the control of TTF1 or NKX2.1 which is a nuclear transcription factor that also is expressed in the basal ganglia and thyroid gland[32, 33].

Pathophysiology of inherited protein surfactant deficiency

Surfactant protein deficiency syndrome (SPDS) is a group of diseases caused by genetic mutations of*SFTPB, SPTPC, ABCA3* and *TTF1* genes. Surfactant protein deficiencies are rare; the frequency of SFTPB deficiency was first described in 1993, as 1 in 1,000,000, while the frequency of *SFTPC, ABCA3* and*TTF1* deficiencies remain unknown[34].

The *SFTPB* gene is located on chromosome 2 with over 30 known pathogenic mutations that occurs as nonsense, missense, frameshift and splice site mutations causing autosomal recessive inherited SP-B deficiency[35]. This leads to abnormal surfactant composition and impaired function that results in increased alveolar surface tension. Infants with SP-B deficiency also lack mature SP-C due to incomplete and aberrant formation of pro SP-C protein[36] that further reduces the effectiveness of their surfactant[37]. The most common mutation associated with SP-B deficiency is the c.397delCinsGAA (previously known as 121ins2) mutation which occurs in 70% of patients with surfactant protein B deficiency -primarily in infants of northern European descend[38, 39]. This mutation occurs as a GAA substitution for C at the genomic position g.1549 in codon 121 which then results in an unstable transcript and an absence on pro SP-B protein[40].

The *SFTPC* gene is located on chromosome 8 with over 50 dominant mutations that may arise *de novo* in 55% of cases or have variable penetration[41]. These mutations can occur as missense, frameshift, insertion, deletion, and splice site mutations with the most common mutation p.Ile73Thr (or c.218 T>C), occurring in 25% of patients with SP-C mutations[42]. The *SFTPC* gene mutations can be divided into 3 groups: 1) Mutations in the*BRICHOS* domain which has been implicated with various other illnesses such as dementia, malignancies and SP-C deficiency[43]. These type of mutations (examples include SP-$C^{L188Q}$and SP-$C^{\Delta\varepsilon\xi o\nu 4}$) [42, 44]causes misfolding of SP-C pro-proteins and formation of cytosolic aggregates which then leads to endoplasmic reticulum stress, cell death, apoptosis and lung injury. 2) non- *BRICHOS* mutations (example include SP-C^{I73T}) that allows trafficking to the endosomal system without misfolded protein aggregation or endoplasmic reticulum stress but causes the formation of large autophagic vacuoles and the accumulation of defective mitochondria[45]. 3) N- terminal mutation that causes unfolding of SP-C and retention of amyloid fibrils on the endoplasmic reticulum[46-48]. .

The *ABCA3* gene is located on chromosome 16. ABCA3 deficiency is inherited in an autosomal recessive fashion with over 150 mutations identified. The most common mutation, p.Glu292Val (or p.E292V, c.875 A>T) accounts for under 10% of patients[49]. The frequency of ABCA3 deficiency has been estimated in individuals from European descent to be 1 in 3100 and 1 in 18000 in individuals from African descent[50]. Mutations of the *ABCA3 gene* can lead to production of abnormal lamellar bodies and to abnormal SP-B and SP-C proteins, although the exact reason for the effect on SP-B and SP-C remains unclear[50]. Kröner *et al* reviewed 40 patients with two disease causing *ABCA3* mutations and identified 2 major phenotypes namely those that died within the first 6 months or those that survive longer [51]. Patients with frameshift or nonsense ABCA3 mutations resulting in null/null genotypes are more likely to have a neonatal presentation and poor prognosis, while the presentation and prognosis is less predictable for other types of mutations resulting in null/other or other/other [52].

Mutations of the *NKX2.1* gene causing inactivation of at least 1 allele results in reduced DNA binding and transcription which leads to reduced TTF1 and reduced production of SP-B, SP-C and ABCA3. These autosomal dominant mutations usually occur *de novo* and sporadically and may result in low alveolar count and may adversely affect airway development[53]. TTF-1 is also expressed in the thyroid and forebrain and plays a role in cellular function and thus mutations of *NKX2.1* may result in a multisystemic presentation[54].

Clinical Features

The timing of presentation of interstitial lung disease can provide some indication towards the type of mutation causing surfactant protein deficiency. SP-B deficiency typically presents in full-term infants with diffuse lung disease which clinically and radiologically mimics the features of a pre-term infant with hyaline membrane disease. The disease rapidly progresses and results in respiratory failure and death within the first 3-6 months of life despite optimal medical treatment, although rarely some infants with partial deficiency of SP-B have survived longer. Longer survival could be attributed to a mild phenotype of the disease that allows for partial production of SP-B[35].

SP-C deficiency can present at various age groups particularly in later childhood, although there has been presentation as pulmonary fibrosis at the 5th or 6th decade of life [55]. This deficiency has a wide spectrum of clinical manifestation even in patients with the same genotype[56].SP-C deficiency is thought to be much rarer than SP-B deficiency or ABCA3 deficiency. In a case series of 22 patients with a median age of 3 months, patients presented with tachypnoea and hypoxemia with other symptoms that included failure to thrive and persistent cough[57]. Some children with SP-C deficiency can also present with recurrent non-resolving RSV bronchiolitis. Animal models that explored this relationship have shown that there is a demonstrable increase in severity in RSV- induced pulmonary inflammation[58]. It has also been suggested that RSV infection trigger severe lung injury or respiratory failure in SP-C carriers that have been previously asymptomatic[59]. In adults with idiopathic pulmonary fibrosis, a small case series showed only mild respiratory symptoms and almost normal lung function and survival after 27 years of follow up[60, 61].

The most common cause of surfactant protein deficiency is ABCA3 deficiency. Although it varies in presentation and severity, ABCA3 deficiency can either be identical to SF-B deficiency in terms of severity and high mortality or may manifest as subacute progressive lung disease in childhood. Genotype-phenotype correlations have been demonstrated in *ABCA3* mutations. Patients with two frameshift and/or nonsense mutations have ˜100% mortality or lung transplant by the age of one year while infants with only one frameshift and nonsense mutation with another mutation either a missense splice site or insertion/deletion have a milder phenotype and better outcomes[52]. In some instances, patients with ABCA3 deficiency may stabilise or even improve. In later childhood or early adulthood, the presentation can be cough, dyspnoea, reduced effort tolerance and chest wall deformities[62].

Patients with *NKX2.1* related disease classically present with a triad of neurological dysfunction, hypothyroidism and lung disease. Chorea is the most common form of neurological involvement, followed by ataxia, developmental delay or hypotonia. Lung involvement typically causes respiratory distress in the neonatal period or early infancy [63]. Similar to the ABCA3 deficiency and SP-C deficiency, there has also been description of chronic phenotypes with patients surviving into adulthood characterized with recurrent pulmonary infections[64].

Investigations

Inherited surfactant dysfunction has recently been classified under the diffuse lung disease (DLD) group of disorders by the American Thoracic Society.(Figure 1) In the clinical setting, chILD should be considered in any child under the age of two that presents with respiratory symptoms and signs, diffuse parenchymal changes on computerized tomography (CT) or X-ray, and hypoxemia[61]. Prior to genetic testing or lung biopsy, it is important to rule out other causes of DLD like illness including infection, recurrent aspiration and congenital heart disease or pulmonary hypertension. The latter should warrant an echocardiogram prior to the initialisation of investigations for surfactant protein deficiencies.

Chest x-ray is usually the first and most accessible imaging that is performed, although it will not specifically lead to the diagnosis of chILD, it may help to identify causes of DLD. Similarly, a chest high resolution computerized tomography (HRCT) may further characterise the radiological abnormality in chILD but again may not point towards a specific diagnosis. The usual features seen on CT in SPDS include ground glass opacification and thickening of the inter and intra-lobular septae. Over time, there may be resolution of the ground-glass opacification, but progress to develop parenchymal cysts. In the evaluation of chILD, it is essential to obtain high quality images which is often difficult in younger children due to motion and

respiratory artefacts[65, 66]. These images generally should be acquired following deep inspiration when lung volumes as closest to total lung capacity. In cooperative school age children, a HRCT with breath-hold manoeuvres provides the best quality images while in younger children and infants where volitional breath-hold manoeuvres are not practicable, controlled ventilation under general anaesthesia with the help of the anaesthetist may be employed to provide good inspiratory images. These techniques that provide greater lung inflation will enhance the contrasts between lung tissue and air. Children undergoing anaesthetic induction for the HRCT are prone to atelectasis and may also require images in both supine and prone positions if there are regions that shows dependent atelectasis.[66] (Figure 2)

Bronchoscopy and broncho-alveolar lavage can help with the diagnosis of SPDS although there is no clear biomarker to assist in the diagnosis. There is qualitative difference in the expression of SP-B and SP-C in the broncho-alveolar lavage fluid[67]; in patients with SP-B deficiency, the levels of SP-B may be low in the BALF while patients with low SP-C may have mutations in *TTF1, SFTPC, ABCA3* and other genes associated with surfactant metabolism. Studies have also shown raised SP-A and SP-D levels in SPDS although the precise correlation to SPDS is not yet known[68]. The main utility of broncho-alveolar lavage in the context of diagnosing SPDS is in identifying other causes of DLD like infection, pulmonary haemorrhage syndrome and alveolar proteinosis. Lipid laden macrophages are also important to be looked for as recurrent aspiration may also mimic DLD.

Lung biopsy may facilitate a histopathological diagnosis fairly quickly in cases where disease progression is rapid or there is insufficient time for genetic testing. Lung biopsy tissue can be obtained through video-assisted thoracoscopy, open thoracotomy, or transbronchial biopsy depending on the expertise available in the institution and the stability of the patient. Video-assisted thoracoscopy and open thoracotomy provide the largest yield of diagnosis (about 50% of cases) but is generally more invasive and have longer recovery periods, while it has been well known that transbronchial and endobronchial biopsy produce samples that are often inadequate to facilitate a diagnosis[69].The choice of biopsy technique is largely expertise dependent, although video-assisted thoracoscopy is a more preferred technique[70, 71].

Histological examination of lung tissue from patients with SPDS may show various differing patterns. The common characteristics include hyperplasia of the type 2 alveolar epithelial cells, interstitial widening, foamy macrophages and proteinaceous material in the distal airspaces.

Although there is significant overlapping in terms of the histological features, there can be certain features that show predilection to the different types of SPDS. In ABCA3 deficiency the most common histopathological finding is pulmonary alveolar proteinosis (PAP), desquamative interstitial pneumonitis (DIP) and non-specific interstitial pneumonia (NSIP). PAP appears to be more common in symptomatic, younger children with ABCA3 deficiency while NSIP is seen in older children presenting with the same deficiency[61].

SP-B deficiency may have congenital alveolar proteinosis or infantile desquamative interstitial pneumonitis changes on histology[72] while SP-C deficiency may show changes of chronic pneumonitis of infancy, particularly in children under 2 years of age[71]. SP-C deficiency and ABCA3 deficiency can also present with non-specific interstitial pneumonia on histology.

The study of the biopsy sample via electron microscopy may also help discern the genetic causes of surfactant dysfunction. In ABCA3 deficiency the lamellar body may appear small and dense or fusion of two or more lamellar bodies with some normal lamellar bodies[73] may be seen while *SFTPB* deficiency may show more disorganized and poorly lamellated lamellar bodies[74].

Genetic testing, when available in a timely fashion, may obviate the need to perform invasive lung biopsies and may assist in the prognostication of the disease. Genetics testing should be considered in children with a positive family history of SPDS, unexplained respiratory symptoms in either infancy or childhood [34, 75]. The choice of genetic tests can be guided by the age of presentation. In term newborns over the 36 weeks gestation period with unexplained DLD testing for mutations of *SFTPB* and *ABCA3* should be considered, while an older child DLD should be screened for *SPTPC* or *ABCA3*mutations[75]. Children with thyroid, neurological symptoms such as chorea, hypotonia or developmental delay associated with DLD features

should be tested for *NKX2.1* mutation as well. Genetic testing should also be considered in cases of diffuse lung disease on CT scan, histopathological findings of alveolar proteinosis or absence in lamellar bodies in lung biopsy. Nevertheless, despite advances in detecting a large array of mutations, there has been reports of patients with no identifiable genetic mutations despite the presence of clinical, familial and histological evidence of SPDS[76, 77].

Genetic counselling and testing of family members is also required once the genetic diagnosis is made and is particularly important in the context of SP-C deficiency which may developed into adult ILD.

Serum examination is not particularly helpful in the diagnosis of SPDS given the lack of any biomarkers at present, however there has been a small study that showed elevated levels of glycoprotein KL-6 in children with *SFTPC* and *ABCA3* mutations[78].

Treatment

Treatment strategies in SPDS are varied and not standardized given its heterogeneity and rarity. Two major clinical practice guidelines exist based on the consensus of clinicians. The first is the European treatment guideline that was developed though a Delphi consensus process and provides a consensus between clinicians from Europe and Australasia for children up to the age of 16[70, 79]. The second guideline was developed by the American Thoracic society for children under the age of two years[71]. Treatment of SPDS is often through immunosuppression as an attempt to reduce pulmonary fibrosis[12] and the need for lung transplant in severe cases[80].

Through the Delphi consensus process, the use of corticosteroids whether enterally or parenterally with subsequent consideration of other adjunct add-on therapies for example hydroxychloroquine and azithromycin was recommended. [79]The rationale of using pulse methylprednisolone stems from the postulate that glucocorticoids increase the expression of ABCA3 *in vitro* . Nevertheless, there is limited evidence of any benefits in the use of glucocorticoid in clinical practice. The decision to trial glucocorticoids should then be made on an individual basis and more importantly these patients should be monitored for the notorious side effects of steroids. Surveillance with long term steroid use should include serial ophthalmological review for cataracts, bone mineral density scanning and growth monitoring. The next option is hydroxychloroquine which also requires close monitoring in terms of retinal toxicity, bone marrow suppression and cataract formation[81, 82]. Retinal toxicity is a serious side effect that is relates to the total accumulated dose. The risk of developing retinal toxicity is ˜40% following use for 20 years[83, 84]. At present, there is an international, prospective, randomized controlled phase 2a trial ongoing to evaluate the efficacy, risks and benefits of hydroxychloroquine in children with chILD[85]. Azithromycin has also been used in to provide immunomodulation in SFTPC and ABCA3 deficiencies[86].

Studies into amino acid sequence of surfactant protein has enabled studies into the production of recombinant surfactant. Synthetic surfactants have been modelled from the structures of SP-B and SP-C for example KL4, an amphipathic peptide which is modelled after SP-B was approved for the use of respiratory distress syndrome in the USA by Food and Drug Administration[87]. Similarly, SP-B and SP-C like peptides has managed to improve lung function in animal models[88]. The clinical application in surfactant protein deficiency is yet to be clearly explored.

Supportive therapy is essential towards the management of SPDS. The use of supplemental oxygen should be evaluated in these children and in more severe cases of SPDS non-invasive ventilation may also have a role. Therefore, continuous saturation monitoring or performing overnight oximetry and capnography is important to elucidate requirement.

Nutrition also likely plays an important role in the prognosis of SPDS and is taken in the assumption that nutritional rehabilitation helps in children with cystic fibrosis and bronchiectasis. Increased work of breathing leading to increased calorie expenditure is fairly common in these chronic conditions and long-term nutritional support may be necessary[89].

Vaccination plays an important role in the supportive care of these children with suggestions of annual

flu vaccination. In view of the severe RSV bronchiolitis that occurs in patients with SPDS, in infants with severe SPDS it has been recommended for the use of palivizumab. Additionally, prophylaxis for *Pneumocystis jeroveci* should be given to children on immunosuppressants.

Although the psychological aspects of the management of SPDS in both patients and families is limited and often underappreciated in view of its rarity[90], evidence from families affected by other chronic lung diseases e.g. cystic fibrosis and bronchiectasis may benefits from psychological support both before and after diagnosis is made. In cases of more severe SPDS, the involvement of the palliative care service where available and socially accepted is also an important aspect in managing the psychosocial aspects of this disease.

Timing of lung transplant in SPDS is dependent on the age of the child, for infants they are most commonly transplanted for SP-B or ABCA3 deficiency while children were more commonly transplanted for SP-C or ABCA3 deficiency[91]. For infants, they were more likely to be mechanically ventilated at time of transplant and were less likely to develop bronchiolitis obliterans post- transplant, which is a feared complication particularly in children beyond 1 year from transplant[91]. Regardless of this however, studies have shown that there is no significant difference in the mortality rate of transplant either occurring in infancy or during childhood[92]. The 5 year survival rates are approximately 50% in patients undergoing lung transplant[93]. Although transplant permits for short term survival in an otherwise lethal disease, there is significant burden of care of these children post lung transplant which includes regular clinic reviews, admission, repeated blood test, bronchoscopies and CT scan in addition to medications that has significant side effect profiles[91]. The significant challenges and impact on families in this aspect must be properly evaluated. Discussion with families and allowing them to have a say in this decision is imperative and a review on decisions to transplant these children has shown that up to 50% of families have actually refused lung transplant[94].

Given the rarity of SPDS and the heterogeneity of this condition, it is important that the management is approached in a multidisciplinary perspective. This multidisciplinary team should include paediatric pulmonologists, cardiologist, geneticist, pathologists, genetics counsellor and other members of the allied health team[86]. Multiple such platforms exists worldwide; for example chILD-EU[79], chILD research network (chILDRN)[95] and chILD Research Australia and New Zealand (chILDRANZ)[96] and chILD network[97] to facilitate discussions, provide support for diagnosis and management of these conditions.

Conclusion

Increased awareness amongst physicians, of these rare but potentially lethal conditions can facilitate timely diagnosis and intervention. Furthermore, by identifying these children with features of surfactant protein deficiencies, we may be able to provide appropriate advice and support to the parents. It is imperative that a supportive clinical infrastructure is retained and continue to be strengthened particularly through collaborations amongst more established networks worldwide. This will eventually allow the adoption of a more standardized approach in the management of these conditions.

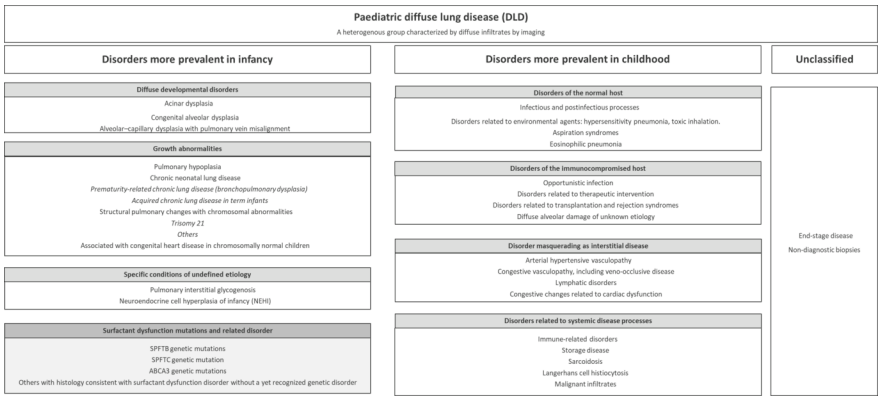

Figure 1: Definition of diffuse lung disease [91] and its classification. Adapted from [69, 92]. ABCA3, ATP-binding cassette sub-family A member protein 3; SFTPB, Surfactant Protein B; SFTPC, surfactant protein-C;

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Figure 2 : Suggested investigation strategy to diagnose chILD. Adapted from [71, 79]. chILD, childhood interstitial lung disease; CT, computerized tomography; ABCA3, ATP-binding cassette sub-family A member protein 3; SFTPB, Surfactant Protein B; SFTPC, surfactant protein-C; NKx2-1, NK2 homeobox 1; TTF1, thyroid transcription factor 1; CSF2RA, colony stimulating factor 2 receptor subunit alpha; CSF2RB, colony stimulating factor 2 receptor subunit beta; DNA, deoxyribonucleic acid; ACE, angiotensin converting enzyme; CD1a, cluster of differentiation 1a; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; VATS, video assisted thoracoscopic surgery.

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