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REVIEW

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Childhood interstitial lung disease

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KEY WORDS

Childhood interstitial lung disease; children's interstitial lung disease; rare disease.

ABSTRACT

Childhood interstitial lung disease (chILD) is a non-specific umbrella term encompassing a broad spectrum of over 200 rare respiratory pediatric disorders. These disorders mainly affect the lung parenchyma leading to impaired alveolar gas exchange. The clinical presentation is usually non-specific. Most commonly, patients present with tachy-/dyspnea, crackles, hypoxemia, and dry cough. Clinicians should be familiar with these disorders as they are associated with high morbidity, mortality and healthcare resource utilization as well as medical costs. Different diagnostic tools are available, while treatment options are limited. Growing data and knowledge of pathogenetic genetic variants as well as pathophysiological models increase therapeutic options for personalized treatments in chILD.

INTRODUCTION

Childhood interstitial lung disease (chILD) is a non-specific umbrella term encompassing a broad spectrum of over 200 separate respiratory disorders (1). The aim of this review is to give

an overview about chILD to help clinicians in their diagnostic approach and guide treatment decisions.

What is chILD?

The acronym chILD encompasses a broad group of rare respiratory diseases that are usually separated from other diseases including airway disorders, pleural disorders, neoplasm, and gross structural abnormalities (**Table 1**). In childhood, the term “interstitial lung disease” may be misleading as not only the interstitial space, but also the surfactant homeostasis, capillary network, lymphatic vessels, terminal bronchioles, neuroendocrine cells and alveoli may be affected (**Figure 1**).

Therefore, other generic terms including diffuse parenchymal lung disease (DPLD), childhood diffuse interstitial lung disease, children’s interstitial lung disease, interstitial lung disease in infancy, children’s interstitial and diffuse lung disease, or chronic interstitial lung disease in children have been introduced. In affected children, efficient gas exchange is impaired, but the clinical presentation is non-specific (**Figure 2**). The earliest clinical presentation is unexplained respiratory distress after birth. Further clinical features include tachy-/dyspnea, (dry) cough, hypoxemia, fine crackles (crepitations), wheezing, hemoptysis, exercise intolerance, digital clubbing, subcostal retractions, chest wall deformities (*i.e.*, *pectus excavatum*, *pectus carinatum*), pulmonary hypertension and failure to thrive/ weight loss (2, 3). None of these clinical symptoms are specific to chILD, and there is a broad overlap to the clinical presentation of children with other respiratory conditions. Before suspecting chILD, a variety of diagnoses need to be excluded (pulmonary infections with different pathogenic agents, cystic fibrosis, primary ciliary dyskinesia, congenital or acquired immunodeficiencies, recurrent aspirations, structural airway abnormalities, sleep disorder breathing or bronchopulmonary dysplasia). Importantly, also congenital heart defects may mimic chILD (4). The interest in chILD has increased in recent years (**Figure 3**), leading to the development of large national and international registries, including chILD-EU in Europe (www.childeu.net), RespiRare in France

(www.respifil.fr), The Children's Interstitial and Diffuse Lung Disease Research Network (ChILDRN) in the USA (www.child-foundation.org), and chILDRN in Australia and New Zealand (www.lungfoundation.com.au).

Why is chILD important?

For chILD, the overall mortality is suspected to be around 15%, with deaths within the first six months of life being most common (5, 6). A recent study analyzed health-care resource utilization and costs for chILD across different European countries. Patients at young age presented with extraordinarily high healthcare costs, which were mostly caused by high hospitalization rates (7). Also, health-related quality of life (HrQoL) is significantly impaired in chILD compared to healthy children (8, 9). Further studies are needed to assess how these factors can be influenced and HrQoL improved.

Why is it hard to diagnose chILD?

As chILD is rare, most pediatric pneumologists will only see a few cases in their working life. Prevalence rates of chILD have been reported to be between 3.6 and 46.5/1,000,000 in United Kingdom/Ireland (10) and Spain, respectively (11). The annual incidence rates have been calculated to be 1.3/1,000,000 in Germany (5), 3.1/1,000,000 in Denmark (12) and 8.2/1,000,000 in Spain (11). In contrast to that, interstitial lung diseases in adults are more common, less diverse, have been studied more intensively and are therefore better understood than chILD (**Figure 3**) (13, 14). Over ten different classifications for chILD have been proposed (1). Most classifications are based upon histopathology entities, which has limitations particularly in relation to histopathological findings are overlapping with entities caused by gene mutations (3). The ability of clinicians to categorize a working diagnosis in the most commonly used classification system (15, 16) needs structured training for correct disease allocation (17). The most recently proposed classification offers an easy memorable, etiologic based system (1). Disorders are divided into four different categories: (1) lung only (native parenchymal) disorders, (2) systemic disease related disorders, (3) exposure related

disorders and (4) vascular disorders. Specifiers and subcategories allow to describe the different disease characteristics (**Table 1**). The etiologic approach helps harmonizing the pediatric and adult classification, and lumps disorders with similar diagnostic and therapeutic principals.

What are the diagnostic tools for chILD?

For children with suspected chILD, it is recommended determining a specific chILD diagnosis to enhance clinical decision making regarding specific treatment options.

Imaging

For patients with suspected child, high-resolution computed tomography (HR-CT) scans of the chest are the first-line investigation (4, 18, 19). The most common findings associated with chILD are noduli, ground-glass opacities (GGO), consolidation, septal thickening hyperinflation, air trapping, (traction-) bronchiectasis, or mosaic perfusion. Of note, protocols for optimization of image quality are crucial as approximately 30% of external recordings from the Kids Lung Registry were of poor image quality (20). When describing HR-CT scanning results, it is recommended to use terms in accordance with the glossary of terms for thoracic imaging as suggested by the Fleischner Society (21, 22). In chILD, the presence and absence of specific HR-CT findings may lead to a specific pattern, *e.g.*, 'Neuroendocrine hyperplasia of infancy/NEHI-Pattern' (GGO located in the middle lobe, lingula, and the parahilar/ paramediastinal distribution without other major abnormalities (23, 24), 'crazy paving pattern' (GGO in concert with septal thickening), and 'Fibrosis' (reticular opacities, traction bronchiectasis, architectural distortion, honeycombing, cystic lucency) (25). In most cases, however, the picture remains non-specific. Thus, HR-CT scanning results are helpful to diagnose chILD, but mostly unsuitable for identifying a specific etiology (19). Data on magnetic resonance imaging (MRI) findings in chILD, however, are scarce. MRI has been reported to detect consolidation as well as interstitial thickening, while septal thickening, GGO, nodules and cystic lesions might be missed (26, 27). Until more studies on the interpretation of lung

MRI scanning results are available, the clinical utility of MRI remains limited. At initial evaluation, MRI studies may be performed as add-on to HR-CT scanning, whereas it is more commonly used for follow-up evaluation. Lung ultrasound may be a promising diagnostic tool as a recent controlled prospective study performed in children with the specific chILD diagnosis (persistent tachypnea of infancy (PTI)/neuroendocrine hyperplasia of infancy (NEHI)) demonstrated a close correlation between the presence and features of B-lines (28).

Bronchoscopy

Bronchoscopy including bronchoalveolar lavage (BAL) is mostly performed to exclude pulmonary infections or other diagnoses, like structural airway abnormalities or recurrent aspirations. Findings leading to a specific chILD diagnosis are rare but are known to be reported in pulmonary hemorrhage syndromes, pulmonary alveolar proteinosis, eosinophilic lung disease, and hypersensitivity pneumonitis (3).

Histopathology

The analysis of lung tissue is reported to be the gold standard to establish a specific chILD diagnosis (17, 29). Lung tissue can be obtained via open, video-assisted thoracic surgery or less invasive cryobiopsies, the latter being a rather new diagnostic tool available for children. Two recent studies investigating cryobiopsies in children reported that the intervention was safe while maintaining high diagnostic yield (30, 31). Of note, transbronchial biopsies are not recommended to perform because the samples are usually too small not containing a sufficient quantity of lung parenchyma to analyze. The current Standard Operating Procedure of the chILD EU register recommend the biopsy to be performed prior to commencing treatment, to be performed in centers with expertise in processing the biopsy. Also, the sample should yield at least 20 x 15 x 10 mm, while the tip of the lobes should be avoided. Electron microscopy is important for the diagnosis of some conditions and therefore to be collected (32). The lung tissue should be evaluated by a pathologist specialized in chILD.

Genetics

Due to recent developments in capability, processing time and fees, testing for pathogenic genetic variants has become increasingly important. Genetic analysis is recommended for all pediatric patients with chILD as specialized treatment is available for certain diseases. Although disease-causing mutations are considered common in chILD, currently pathogenic variants were identified in only 20% of patients with chILD (17). Most genetic centers offer gene panels or whole exome sequencing to scan for the most common pathogenic variants. For correct interpretation of testing results, the analysis should be carried out by specialized genetics centers.

Multi-disciplinary team

In contrast to children, when diagnosing adult interstitial lung diseases, multi-disciplinary teams (MDTs) are standard for some time (33). Comprehensive consideration of all available data concludes with the most precise diagnosis (34). Before coming up with a final working diagnosis, the goal is to ensure adherence to diagnostic standards and exclusion of differential diagnoses. The chILD EU register implemented an expert board for peer-review respiratory pediatricians, pediatric radiologists, geneticists and pathologists (17). Of note, even with intensive investigations and a thorough evaluation, in 10-30% of cases no specific diagnosis was found (35).

What are the treatment options for chILD?

There is no specific therapy that is approved for chILD, yet (36). The clinical care of patients with chILD is mainly based on supportive measures including supplemental oxygen/ invasive or non-invasive ventilation, specific nutritional support and respiratory physiotherapy (3, 4). Respiratory infections are the main driver of acute pulmonary exacerbation in chILD and lead to increased morbidity/mortality, persistent lung function decline and impaired HrQoL (37). However, there are no studies that systematically investigate what preventive measures in

chILD are beneficial. Pharmacological treatment for chILD is mainly based on anecdotal evidence and small case collections. Most commonly used are glucocorticosteroids, hydroxychloroquine, and azithromycin, of which only the clinical effect of hydroxychloroquine has been systematically evaluated (38). While including only a small study population, one double-blind, randomized, placebo-controlled trial showed no efficacy of the treatment besides being well tolerated (39). Another double-blind, randomized, placebo-controlled trial in patients with chILD and fibrosis on chest HR-CT reported an acceptable safety and tolerability for the antifibrotic drug nintedanib (40). There were no statistical differences between the placebo and nintedanib group on pulmonary function testing results or peripheral oxygen saturation at rest, although the study was not powered to assess efficacy.

Pulmonary alveolar proteinosis (PAP) is a specific chILD diagnosis that is associated with impaired removal of surfactant (41) due to a variety of different underlying mechanisms including genetic defects in the surfactant metabolism, impaired function as well as reduction of alveolar macrophages or autoantibodies that block GM-CSF signaling (42-44). Whole lung lavage (WLL) is the standard treatment for PAP feasible for stabilizing the clinical condition until a specific treatment is available, even over a longer period (45). Depending on the underlying cause, specific treatment option for PAP may include hematopoietic stem cell transplantation (46), oral methionine supplementation (47), atorvastatin (48), recombinant and exogenous GM-CSF (49), aerosolized GM-CSF (50, 51), or rituximab (52-54).

For surfactant protein dysfunction caused by genetic defects in ABCA3, promising *in vitro* results have been published regarding variant-specific small molecules including Ivacaftor, genistein and cyclosporine A (55–57). While no reports about the clinical use of ivacaftor and genistein have been published, a patient with chILD caused by systemic lupus erythematosus was successfully treated with cyclosporine A in combination with prifinidone (58). A recent observational analysis showed a positive effect of inhaled glucocorticosteroids and bronchodilators on the diseases severity and pulmonary function testing results in symptomatic children with PTI/NEHI (59). Preliminary data have also been published about

the clinical use of baricitinib in STING-associated vasculopathy with onset in infancy (SAVI) (60) and COPA syndrome (61), for which ruxolitinib may also be beneficial (62).

For patient with severely impaired pulmonary function who do not respond to therapy, lung transplantation is a treatment option, which has been successfully performed in infants and young children with genetic disorders of surfactant metabolism (63). One infant with chILD related to ABCA3 gene mutation was successfully treated receiving a living donor lobe transplant (64), while the first ABO-incompatible lung transplantation was performed in an infant with surfactant protein B deficiency (65). Good short- and long-term outcome of children and adolescents following lung transplantation were published recently, reporting a 5-year graft and patient survival of 72% and 79%, respectively (63).

SUMMARY

chILD is a rare group of respiratory rare respiratory disorders that typically present with non-specific clinical features. Clinicians should be familiar with these disorders as they are associated with high morbidity, mortality and healthcare resource utilization. The diagnosis and classification are challenging, while treatment options are limited. Growing data and knowledge of pathogenetic genetic variants as well as pathophysiological models increase therapeutic options for personalized treatments in chILD. Multi-center collaboration is the key for further research to improve the care for our patients.

COMPLIANCE WITH ETHICAL STANDARDS

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Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

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REFERENCES

1. Griese M. Etiologic Classification of Diffuse Parenchymal (Interstitial) Lung Diseases. J Clin Med. 2022;11(6):1747. doi: 10.3390/jcm11061747.

2. Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, et al; American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med. 2013;188(3):376-94. doi: 10.1164/rccm.201305-0923ST.

3. Cunningham S, Jaffe A, Young LR. Children's interstitial and diffuse lung disease. Lancet Child Adolesc Health. 2019 Aug;3(8):568-577. doi: 10.1016/S2352-4642(19)30117-8.

4. Bush A, Cunningham S, De Blic J, Barbato A, Clement A, Epaud R, et al. European protocols for the diagnosis and initial treatment of interstitial lung disease in children. Thorax. 2015;70(11):1078-84. doi: 10.1136/thoraxjnl-2015-207349.

5. Griese M, Haug M, Brasch F, Freihorst A, Lohse P, von Kries R, et al. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. Orphanet J Rare Dis. 2009;4:26. doi: 10.1186/1750-1172-4-26.

6. Cunningham S, Graham C, MacLean M, Aurora P, Ashworth M, Barbato A, et al. One-year outcomes in a multicentre cohort study of incident rare diffuse parenchymal lung disease in children (ChILD). Thorax. 2020;75(2):172-5. doi: 10.1136/thoraxjnl-2019-213217.

7. Seidl E, Schwerk N, Carlens J, Wetzke M, Cunningham S, Emiralioğlu N, et al. Healthcare resource utilisation and medical costs for children with interstitial lung diseases (chILD) in Europe. Thorax. 2022;77(8):781-9. doi: 10.1136/thoraxjnl-2021-217751.

8. Nathan N, Lauby C, Abou Taam R, Bessaci K, Brouard J, Dalphin ML, et al. Health-related quality of life in children interstitial lung disease (abstract). Eur Respir J. 2019;(54):PA5184. doi: 10.1183/13993003.congress-2019.PA5184.

9. Seidl E, Niemitz M, Stöhr S, Schwerk N, Wetzke M, Carlens J, et al. Health related quality of life in childhood interstitial lung disease–an ERS Clinical Research Collaboration (abstract). Eur Respir J. 2023;62(PA424). Available from: https://channel.ersnet.org/media-102121-health-related-quality-of-life-in-childhood-interstitial-lung-disease-an-ers-clinical-research-collaboration. Accessed: Sept 27, 2024.

10. Dinwiddie R, Sharief N, Crawford O. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. Pediatr Pulmonol. 2002;34(1):23-9. doi: 10.1002/ppul.10125.

11. Torrent-Vernetta A, Gaboli M, Castillo-Corullón S, Mondéjar-López P, Santiago VS, Costa-Colomer J, et al. Incidence and prevalence of children's diffuse lung disease in Spain. Arch Bronconeumol. 2021;58(1):22-9. doi: 10.1016/j.arbres.2021.06.001.

12. Kornum JB, Christensen S, Grijota M, Pedersen L, Wogelius P, Beiderbeck A, et al. The incidence of interstitial lung disease 1995-2005: a Danish nationwide population-based study. BMC Pulm Med. 2008;8(1):24. doi: 10.1186/1471-2466-8-24.

13. Clement A, Nathan N, Epaud R, Fauroux B, Corvol H. Interstitial lung diseases in children. Orphanet J Rare Dis. 2010;5(1):1-24. doi: 10.1186/1750-1172-5-22.

14. Griese M. Chronic interstitial lung disease in children. Eur Respir Rev. 2018;27(147):170100. doi: 10.1183/16000617.0100-2017.

15. Deutsch GH, Young LR, Deterding RR, Fan LL, Dell SD, Bean JA, et al. Diffuse lung disease in young children: application of a novel classification scheme. Am J Respir Crit Care Med. 2007;176(11):1120-8. doi: 10.1164/rccm.200703-393OC.

16. Griese M, Irnstetter A, Hengst M, Burmester H, Nagel F, Ripper J, et al. Categorizing diffuse parenchymal lung disease in children. Orphanet J Rare Dis. 2015;10:122. doi: 10.1186/s13023-015-0339-1.

17. Griese M, Seidl E, Hengst M, Reu S, Rock H, Anthony G, et al. International management platform for children's interstitial lung disease (chILD-EU). Thorax. 2018;73(3):231-9. doi: 10.1136/thoraxjnl-2017-210519.

18. Laenger FP, Schwerk N, Dingemann J, Welte T, Auber B, Verleden S, et al. Interstitial lung disease in infancy and early childhood: a clinicopathological primer. Eur Respir Rev. 2022;31(163):210-251. doi: 10.1183/16000617.0251-2021.

19. Nathan N, Griese M, Michel K, Carlens J, Gilbert C, Emiralioglu N, et al. Diagnostic workup of childhood interstitial lung disease. Eur Respir Rev. 2023;32(167):220-188. doi: 10.1183/16000617.0188-2022.

20. Griese M. Interstitielle Lungenerkrankungen. Monatsschr Kinderheilkd. 2023;171(11):985-94.

21. Bankier AA, MacMahon H, Colby T, Gevenois PA, Goo JM, Leung ANC, et al. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology. 2024;310(2):e232558. doi: 10.1148/radiol.232558.

22. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722. doi: 10.1148/radiol.2462070712.

23. Rauch D, Wetzke M, Reu S, Wesselak W, Schams A, Hengst M. PTI (Persistent Tachypnea of Infancy) Study Group of the Kids Lung Register. Persistent tachypnea of infancy: usual and aberrant Am J Respir Crit Care Med. 2016;193(4):438-47. doi: 10.1164/rccm.201508-1655OC.

24. Deterding RR, Fan LL, Morton R, Hay TC, Langston C. Persistent tachypnea of infancy (PTI)-A New Entity. Pediatric pulmonology. 2001;32(Suppl 23):72-3. PMID: 11886155.

25. DeBoer EM, Weinman JP, Ley-Zaporozhan J, Griese M, Deterding R, Lynch DA, et al. Imaging of pulmonary fibrosis in children: A review, with proposed diagnostic criteria. Pediatr Pulmonol. 2024;59(4):845-54. doi: 10.1002/ppul.26857.

26. Liang T, Vargas SO, Lee EY. Childhood Interstitial (Diffuse) Lung Disease: Pattern Recognition Approach to Diagnosis in Infants. Am J Roentgenol. 2019;212(5):958-67. doi: 10.2214/AJR.18.20696.

27. Sodhi KS, Sharma M, Lee EY, Saxena AK, Mathew JL, Singh M, et al. Diagnostic utility of 3T lung MRI in children with interstitial lung disease: a prospective pilot study. Acad Radiol. 2018;25(3):380-6. doi: 10.1016/j.acra.2017.09.013

28. Urbankowska E, Urbankowski T, Drobczyński \Lukasz, Griese M, Lange J, Brzewski M, et al. Lung ultrasound—a new diagnostic modality in persistent tachypnea of infancy. Pediatr Pulmonol. 2020;55(4):1028-36. doi: 10.1002/ppul.24654.

29. Coren ME, Nicholson AG, Goldstraw P, Rosenthal M, Bush A. Open lung biopsy for diffuse interstitial lung disease in children. Eur Respir J. 1999;14(4):817-21. doi: 10.1034/j.1399-3003.1999.14d16.x.

30. Schramm D, Freitag N, Kötz K, Iglesias-Serrano I, Culebras-Amigo M, Koblizek V, et al. Cryotherapy in the paediatric airway: Indications, success and safety. Respirology. 2022;27(11):966-74. doi: 10.1111/resp.14353.

31. Chandra T, Srikanta JT, Madhusudan M, Mohite K, Arigela K. Safety, utility and clinical efficacy of cryobiopsy of lung in paediatric population − A single centre experience. Lung India. 2023;40(5):418-22. doi: 10.4103/lungindia.lungindia_217_23.

32. Seidl E, Griese M. Standard Operating Procedure for lung biopsy. 2018. Available from: https://www.klinikum.uni-muenchen.de/Child-EU/en/child-eu-register/sop_checklists/index.html. Accessed: June 9, 2024.

33. Walsh SL, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, et al. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. Lancet Respir Med. 2016;4(7):557-65. doi: 10.1016/S2213-2600(16)30033-9.

34. Borie R, Kannengiesser C, Gouya L, Dupin C, Amselem S, Ba I, et al. Pilot experience of multidisciplinary team discussion dedicated to inherited pulmonary fibrosis. Orphanet J Rare Dis. 2019;14(1):280. doi: 10.1186/s13023-019-1256-5.

35. Saddi V, Beggs S, Bennetts B, Harrison J, Hime N, Kapur N, et al. Childhood interstitial lung diseases in immunocompetent children in Australia and New Zealand: a decade's experience. Orphanet J Rare Dis. 2017;12(1):133. doi: 10.1186/s13023-017-0637-x.

36. Bernardinello N, Griese M, Borie R, Spagnolo P. Emerging Treatments for Childhood Interstitial Lung Disease. Pediatr Drugs. 2024;26(1):19-30. doi: 10.1007/s40272-023-00603-9.

37. Seidl E. Acute exacerbations in children´s interstitial lung disease. Thorax. 2022;77(8):799-804. doi: 10.1136/thoraxjnl-2021-217941.

38. Griese M, Köhler M, Witt S, Sebah D, Kappler M, Wetzke M, et al. Prospective evaluation of hydroxychloroquine in pediatric interstitial lung diseases: Study protocol for an investigator-initiated, randomized controlled, parallel-group clinical trial. Trials. 2020;21(1):307. doi: 10.1186/s13063-020-4188-4.

39. Griese M, Kappler M, Stehling F, Schulze J, Baden W, Koerner-Rettberg C, et al. Randomized controlled phase 2 trial of hydroxychloroquine in childhood interstitial lung disease. Orphanet J Rare Dis. 2022;17(1):1-11. doi: 10.1186/s13023-022-02399-2.

40. Deterding R, Young LR, DeBoer EM, Warburton D, Cunningham S, Schwerk N, et al. Nintedanib in children and adolescents with fibrosing interstitial lung diseases. Eur Respir J. 2023;61(2):2201512. doi: 10.1183/13993003.01512-2022.

41. Griese M. Chronic interstitial lung disease in children. Eur Respir Rev. 2018;27(147):170100. doi: 10.1183/16000617.0100-2017.

42. Griese M. Pulmonary Alveolar Proteinosis: A Comprehensive Clinical Perspective. Pediatrics. 2017;140(2): e20170610. doi: 10.1542/peds.2017-0610.

43. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers. 2019;5(1):16. doi: 10.1038/s41572-019-0066-3.

44. Uchida K, Nakata K, Trapnell BC, Terakawa T, Hamano E, Mikami A, et al. High-affinity autoantibodies specifically eliminate granulocyte-macrophage colony-stimulating factor activity in the lungs of patients with idiopathic pulmonary alveolar proteinosis. Blood. 2004;103(3):1089-98. doi: 10.1182/blood-2003-05-1565.

45. Seidl E, Schramm D, Schön C, Reiter K, Pawlita I, Kappler M, et al. Pulmonary alveolar proteinosis due to heterozygous mutation in OAS1: Whole lung lavages for long-term bridging to hematopoietic stem cell transplantation. Pediatr Pulmonol. 2022;57(1):273-7. doi: 10.1002/ppul.25728.

46. Magg T, Okano T, Koenig LM, Boehmer DFR, Schwartz SL, Inoue K, et al. Heterozygous OAS1 gain-of-function variants cause an autoinflammatory

immunodeficiency. Sci Immunol. 2021;6(60):eabf9564. doi: 10.1126/sciimmunol.abf9564.

47. Lenz D, Stahl M, Seidl E, Schöndorf D, Brennenstuhl H, Gesenhues F, et al. Rescue of respiratory failure in pulmonary alveolar proteinosis due to pathogenic MARS1 variants. Pediatr Pulmonol. 2020;55(11):3057-66. doi: 10.1002/ppul.25031.

48. Büyükşahin HN, Yalçın E, Özdemir A, Haliloglu M, Orhan D, Griese M, et al. Successful atorvastatin treatment of pulmonary alveolar proteinosis in a child with GM-CSF receptor deficiency. Pediatr Pulmonol. 2024;59(6):1777-80. doi: 10.1002/ppul.26946.

49. Campo I, Mariani F, Rodi G, Paracchini E, Tsana E, Piloni D, et al. Assessment and management of pulmonary alveolar proteinosis in a reference center. Orphanet J Rare Dis. 2013;8:40. doi: 10.1186/1750-1172-8-40.

50. Papiris SA, Tsirigotis P, Kolilekas L, Papadaki G, Papaioannou AI, Triantafillidou C, et al. Long-Term Inhaled Granulocyte Macrophage–Colony-Stimulating Factor in Autoimmune Pulmonary Alveolar Proteinosis: Effectiveness, Safety, and Lowest Effective Dose. Clin Drug Investig. 2014;34(8):553-64. doi: 10.1007/s40261-014-0208-z.

51. Tazawa R, Ueda T, Abe M, Tatsumi K, Eda R, Kondoh S, et al. Inhaled GM-CSF for Pulmonary Alveolar Proteinosis. N Engl J Med. 2019;381(10):923-32. doi: 10.1056/NEJMoa1816216.

52. Amital A, Dux S, Shitrit D, Shpilberg O, Kramer MR. Therapeutic effectiveness of rituximab in a patient with unresponsive autoimmune pulmonary alveolar proteinosis. Thorax. 2010;65(11):1025-6. doi: 10.1136/thx.2010.140673.

53. Malur A, Kavuru MS, Marshall I, Barna BP, Huizar I, Karnekar R, et al. Rituximab therapy in pulmonary alveolar proteinosis improves alveolar macrophage lipid homeostasis. Respir Res. 2012;13(1):46. doi: 10.1186/1465-9921-13-46.

54. Nagasawa J, Kurasawa K, Hanaoka R. Rituximab improved systemic lupus erythematosus-associated pulmonary alveolar proteinosis without decreasing anti-GM-CSF antibody levels. Lupus. 2016;25(7):783-4. doi: 10.1177/0961203315627204.

55. Kinting S, Höppner S, Schindlbeck U, Forstner ME, Harfst J, Wittmann T, et al. Functional rescue of misfolding ABCA3 mutations by small molecular correctors. Human molecular genetics. 2018;27(6):943-53. doi: 10.1093/hmg/ddy011.

56. Kinting S, Li Y, Forstner M, Delhommel F, Sattler M, Griese M. Potentiation of ABCA3 lipid transport function by ivacaftor and genistein. J Cellular Molecular Medi. 2019;23(8):5225-34. doi: 10.1111/jcmm.14397.

57. Forstner M, Lin S, Yang X, Kinting S, Rothenaigner I, Schorpp K, et al. High-Content Screening Identifies Cyclosporin A as a Novel ABCA3-Specific Molecular Corrector. Am J Respir Cell Mol Biol. 2022;66(4):382-90. doi: 10.1165/rcmb.2021-0223OC.

58. Deng L, Chen Y, Hu X, Zhou J, Zhang Y. Case report: successful treatment of refractory interstitial lung disease with cyclosporine A and pirfenidone in a child with SLE. Front Immunol. 2021;12:708463. doi: 10.3389/fimmu.2021.708463.

59. Marczak H, Peradzyńska J, Seidl E, Griese M, Urbankowski T, Lange J, et al. The improved clinical course of persistent tachypnea of infancy with inhaled bronchodilators and corticosteroids. Pediatr Pulmonol. 2021;56(12):3952-9.

60. Kanazawa N, Ishii T, Takita Y, Nishikawa A, Nishikomori R. Efficacy and safety of baricitinib in Japanese patients with autoinflammatory type I interferonopathies (NNS/CANDLE, SAVI, And AGS). Pediatr Rheumatol. 2023;21(1):38. doi: 10.1186/s12969-023-00817-8.

61. Krutzke S, Rietschel C, Horneff G. Baricitinib in therapy of COPA syndrome in a 15-year-old girl. Eur J Rheumatol. 2020;7(Suppl 1):S78-81. doi: 10.5152/eurjrheum.2019.18177.

62. Frémond ML, Legendre M, Fayon M, Clement A, Filhol-Blin E, Richard N, et al. Use of ruxolitinib in COPA syndrome manifesting as life-threatening alveolar haemorrhage. Thorax. 2020;75(1):92-5. doi: 10.1136/thoraxjnl-2019-213892.

63. Iablonskii P, Carlens J, Mueller C, Aburahma K, Niehaus A, Boethig D, et al. Indications and outcome after lung transplantation in children under 12 years of age: a 16-year single center experience. J Heart Lung Transplantat. 2022;41(2):226-36. doi: 10.1016/j.healun.2021.10.012.

64. Kumata S, Matsuda Y, Oishi H, Sado T, Niikawa H, Watanabe T, et al. Living Donor Lobar Lung Transplant for a Patient With Lung Disease Caused by ABCA3 Gene Mutations: A Case Report. Transplant Proc. 2022;54(10):2803-6. doi: 10.1016/j.transproceed.2022.07.020.

65. Grasemann H, De Perrot M, Bendiak GN, Cox P, van Arsdell GS, Keshavjee S, et al. ABO-incompatible lung transplantation in an infant. Am J Transplant. 2012;12(3):779-81. doi: 10.1111/j.1600-6143.2011.03861.x.

66. National Health Lung, and Blood Institute. Interstitial Lung Diseases. Childhood Interstitial Lung Disease. Available from: https://www.nhlbi.nih.gov/health/childhood-interstitial-lung-diseases. Accessed: June 11, 2024.

Figure 1

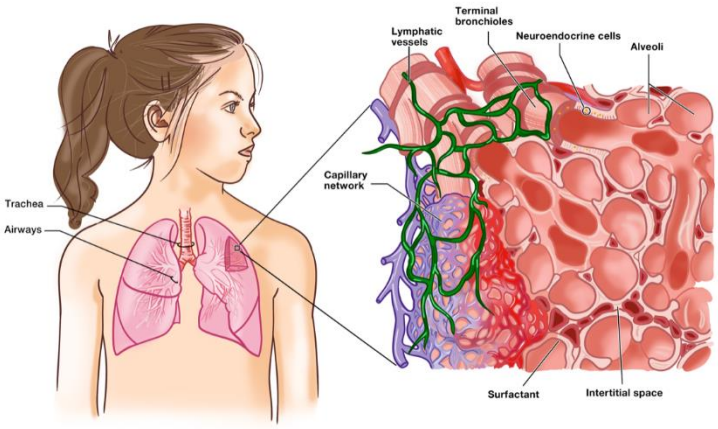

Figure 2

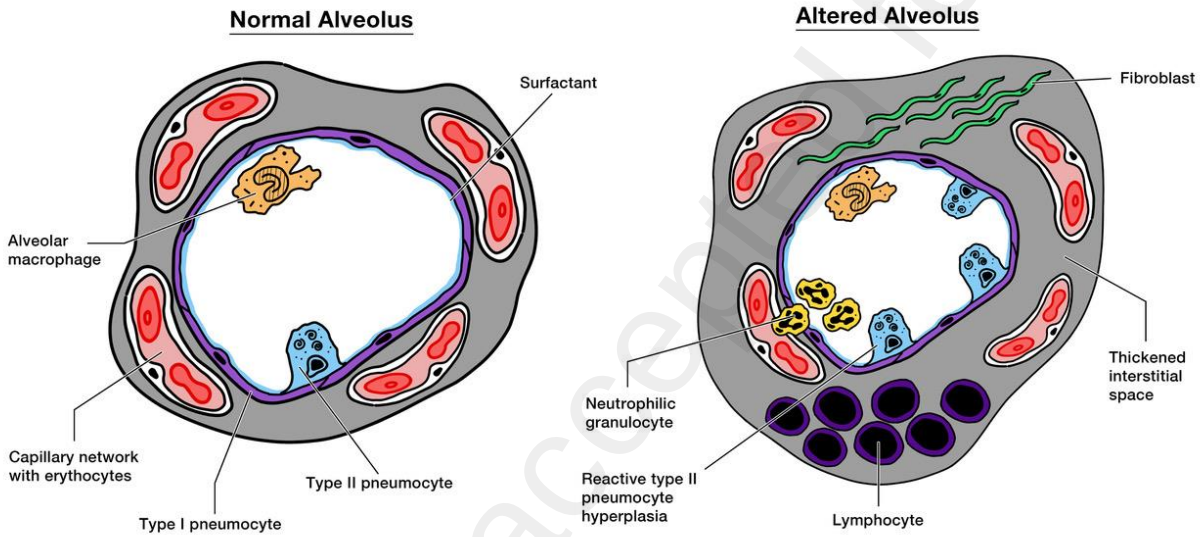

Figure 3

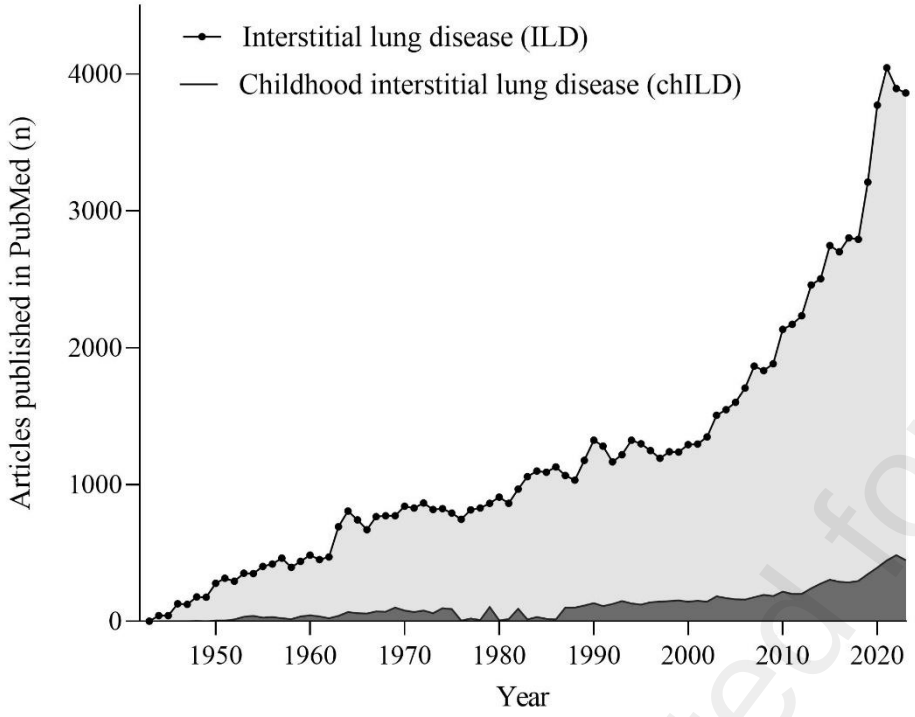

***Table 1**. Etiologic classification of childhood interstitial lung disease (chILD) as used in the chILD EU register (www.childeu.net) (1). The disorders are divided into four categories (1) lung-only/native parenchymal disorders, (2) systemic disease-related disorders, (3) exposure-related disorders and (4) vascular disorders. Specifiers and subcategories are used to describe the different disease characteristics.*

Category	Specifier	Subcategories (examples)
Lung-only/native parenchymal disorders	Developmental conditions manifesting in infancy	A1- Diffuse developmental disorders (ACD, acinar dysplasia, CAD) A2- Growth abnormalities deficient alveolarization (related to preterm birth, associated with diaphragmatic hernia, associated with oligohydramnios) A3- Infant conditions of undefined etiology (PTI, NEHI, PIG) A4- related to alveolar surfactant region (CPI)
	All ages	NSIP, DIP, LIP, PAP, genetic surfactant protein deficiencies.
Systemic disease-related disorders	Immuno-competent	Lane-Hamilton syndrome, EGPA, Hermansky-Pudlak syndrome
	Immuno-deficient	COPA syndrome
	Transplanted	CLAD
	Immune dysregulated	STING associated vasculopathy, interferonopathy
Exposure related disorders	Non-infectious	HP, drug induced interstitial lung disease, radiation pneumonitis
	Infectious	Postinfectious constrictive bronchiolitis
Vascular disorders		DAH, pulmonary capillary hemangiomatosis, VOD

Abbreviations: ACD: Alveolar Capillary Dysplasia; CAD: Congenital Alveolar Dysplasia; CLAD: Chronic Lung Allograph Dysfunction; CPI: Chronic Pneumonitis of Infancy; DAH: Diffuse Alveolar Hemorrhage; DIP: Desquamative Interstitial Pneumonia; EGPA: Eosinophilic Granulomatosis with Polyangiitis; HP: Hypersensitive Pneumonitis; LIP: Lymphocytic Interstitial Pneumonia; PAP: Pulmonary Alveolar Proteinosis; PTI: Persistent Tachypnea of Infancy; NEHI: Neuroendocrine Hyperplasia of Infancy; NSIP: Nonspecific Interstitial Pneumonia; PIG: Pulmonary Interstitial Glycogenosis; VOD: Vena Occlusive Disease.