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Review Article

Navigating Interstitial Lung Disease: Overcoming Diagnostic Obstacles and Advancing Treatment Strategies

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Abstract

Childhood interstitial lung disease (ChILD) encompasses a diverse range of rare respiratory disorders in children that can ***result in significant morbidity and mortality****.*

The lung interstitium are connective tissue space, between the alveoli and the small blood vessels that surround the alveoli, that provide support to the components of the respiratory tract, such as bronchial division up to alveoli, blood vessels, lymphatics etc. Interstitial lung diseases are conditions that affect these structures, leading to inflammation and scarring of lung tissue. This impact hinders lung expansion, gaseous exchange, and can ultimately result in a restrictive lung disease. Symptoms of respiratory distress may develop gradually and might be subtle, highlighting the importance of a comprehensive clinical evaluation including thorough clinical history and physical examination.

The cause of ChILD is often unknown, with symptoms resembling more common conditions like pneumonia or asthma, making accurate diagnosis challenging. Genetic testing, bronchoalveolar lavage, or lung biopsy may be needed for confirmation. Treatment involves supportive care and anti-inflammatory, immunosuppressive, or anti-fibrotic medications. The delayed diagnosis can potentially lead to chronic respiratory failure. This review aims to provide key findings to assist in clinical evaluation and proper diagnostic decision-making, especially for children in developing countries like Bangladesh where specialized respiratory centers may not be available.

Keywords: interstitial lung disease, restrictive lung disease.

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Introduction

The interstitial space plays a vital role in supporting the airway extending from the main bronchus to the delicate alveolar sacs, blood vessels, and lymphatics. This space consists of three interconnected compartments: axial, parenchymal, and peripheral interstitium. [1]

- The **axial** interstitium (peribroncho-vascular space) surrounds the airways from the hilum to the alveolar ducts and the pulmonary artery, veins[2]
- The **parenchymal** interstitium (septal, alveolar) located along the interalveolar septa, and provides structural support for alveolar epithelial, capillary endothelium and lymphatics[2]
- The **peripheral** interstitium, situated along the visceral pleura into the interlobular septa, and supplies strong fibers to support the lung parenchyma.[2]

Functions of Interstitium

In a healthy lung, the interstitial space acts as a supportive connective tissue framework for the delicate alveolar sacs, allowing them to expand during inspiration. The space also plays a key role in the exchange of O_2 and CO_2 between the alveoli and the capillaries.[3] Additionally, the interstitium is full of lymphatic channels that help to remove filtered fluid from extra-cellular/extra-vascular space, to the mediastinal lymphatic vessels.[4]

Pathophysiology of ChILD

- ChILD includes a range of rare lung pathologies that stem from lung damage by various genetic, infectious, and inflammatory diseases.[5]

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- Damage to this supportive tissue can result in inflammation, overproduction of extra-cellular matrix leading to scarring, thickening, and stiffness of the connective tissue in interstitium.[6]

  What makes it difficult to understand this group of diseases is the confusing terminology. The pathogenetic consequence actually involves a series of inflammation & fibrosis that extends beyond disrupting the interstitial bed (as the name implies) to changing the lung parenchyma (alveoli, alveolar ducts, and bronchioles).[6]
- This restricts expansion of alveoli, impairing the exchange of O_2 and CO_2.
- Consequently, hypoxia, CO_2 retention, and manifestations of compromised respiratory functions like difficult breathing, fatigue, and weight loss appear slowly over several months and ultimately lead to a decline in lung function, resulting in a restrictive lung disease. [6]

The exact cause of ChILD is frequently unknown, and there is lack of comprehensive global epidemiological data due to the absence of systematic registries to monitor cases. Incidence rates vary from 0.13 to 16.2 cases per 100,000 children per year, but these figures may not accurately reflect the true prevalence of the disease.[7,8]

Diagnosing and treating ChILD also pose challenges as a result of the absence of standardized definitions and limited data derived from small patient groups.[9,10] Clinical guidelines have been formulated to aid in diagnosis and evaluation, involving imaging as well as genetic or histological analyses. However, it is important to note that these guidelines can be difficult to implement in developing countries with limited resources.[9,10]

Classification of Interstitial Lung Disease in Infants and Children

The most widely accepted classification of ChILD was published in 2007 by the Children's Interstitial Lung Disease Research Co-operative, based on clinical and histopathological characteristics.[11] Age at presentation is a key factor, dividing ChILD into that more common in children < 2 years of age and those > 2 years of age.[11]

A. ILD: more prevalent in children < 2 years

Most entities of this category manifest within the first year of life. Most affected infants cannot achieve acceptable oxygen saturations even by mechanical ventilation.[11,12] It is further divided into four main categories[11]

Classification Category	Example	Time of presentation
1. Diffuse developmental disorders leading to lung maturation arrest[11]	• Acinar/alveolar dysgenesis, congenital alveolar dysplasia	Birth or within the first weeks of life.
2. Lung growth abnormalities (incomplete or insufficient alveolarisation of prenatal or postnatal origin[3]	• Pulmonary hypoplasia, • Bronchopulmonary dysplasia • Chronic lung disease of prematurity • structural changes due to chromosomal anomalies (trisomy 21) or associated congenital heart disease • secondary to diaphragmatic hernia, oligohydramnios, thoracic skeletal dysplasia or neuromuscular disease;[12,14,15,16]	Birth or within the first weeks of life.
3. Surfactant dysfunction disorders (Mutation in surfactant protein)[11]	• Surfactant protein B (SFTPB), Surfactant protein C (SFTPC) • ATP binding cassette A3 (ABCA3) • NKX2.1 (thyroid transcription factor 1)	Birth or within the first weeks of life. Some forms of mutation present later in life.
4. Specific conditions of unknown or poorly understood etiology [11]	• Neuroendocrine cell hyperplasia of infancy (NEHI) - defined by the presence of neuroendocrine cells in at least 70% of all bronchi and a population of at least 10% in the epithelial lining of at least one bronchus[17,18]	Birth- 1 month
	• Pulmonary interstitial Glycogenosis (characterized by diffuse/ focal widening of septa, with predominance of intracytoplasmic deposition of glycogen[19,20])	Infancy to 24 month[12,21,22]

B. ILD: more prevalent in children >2 years

Most entities of this category manifest after infancy. It is further divided into four main categories

Classification Category	Example	Time of presentation
1. ILD of the normal host and due to environmental exposures	• Hypersensitivity pneumonitis (most common, results from repeated exposure to environmental organic antigens leading to type III and IV hypersensitivity reactions and secondary inflammation of the airways[23] • Infectious and post-infectious processes • Aspiration pneumonia • Eosinophilic bronchiolitis	Infancy to adolescence mainly affecting children aged >2 years [25]
2. ILD due to presence of a systemic disease process	• Immune-mediated collagen vascular disease • Storage disease- Niemann–Pick[24], Gaucher's[25], Glycogen storage disease, and mucopolysaccharidoses and mucolipidoses[26] • Sarcoidosis • malignant infiltrates • Langerhans cell histiocytosis	Childhood to adolescence
3. ILD of the immunocompromised host (trigger airway remodeling in the form of obliterative bronchiolitis[27,28,29]	• Acquired immunodeficiency- chemotherapy, stem cell transplantation, opportunistic infections, and lymphoid infiltrates [8,12,22]. • Immunodeficiency	Infancy to adolescence
4. ILD with structural vascular changes – (Pulmonary vascular remodelling leading to ILD	• Pulmonary hypertension • Vasculopathy • Pulmonary capillary haemangiomatosis, • Vasculitis, lymphatic disorders	Birth to adolescence

Clinical presentation

The age at which ChILD presents is crucial, with certain diagnoses more common in newborns, infants, or older children as depicted in the tables above[30,31]

When to suspect, how to suspect and why to suspect ChILD?

Children with ChILD do not have specific indicators; instead, their symptoms resemble other respiratory illnesses in children, making ChILD a secondary consideration after ruling out pulmonary infections, tuberculosis, recurrent aspiration, structural airway abnormalities, primary ciliary dyskinesia, bronchopulmonary dysplasia, congenital heart disease, immunodeficiencies, and cystic fibrosis.[9, 13]

The symptoms that raise suspicion of ChILD are:

- In newborns presenting with unexplained respiratory distress or respiratory distress beyond what is expected for their gestational age, further evaluation is warranted [32,33]
- Infants & children should exhibit at least 3 of the following 4 characteristics[22]:
  - Respiratory symptoms, such as dry cough, a gradual persistent shortness of breath either at rest or during physical activity, fatigue during feeding, and respiratory infections, poor weight gain and hemoptysis.
  - Respiratory signs including tachypnea, abnormal breathing sound-crackle/wheeze, visible chest retractions, digital clubbing, poor weight gain, and respiratory failure.
  - Hypoxemia.
  - Diffuse Parenchymal abnormalities on chest X-rays or high-resolution CT scans.

Evaluation: diagnostic approach of ChILD

History:

Certain important history should be emphasized:

- History of prematurity, cardiac disease, chromosomal abnormalities, and potential triggers such as severe respiratory infections or medications with pulmonary toxicity is crucial for a comprehensive assessment[22,34]

- Feeding difficulties, potentially leading to respiratory symptoms from micro inhalations
- Environmental exposure to organic dust, birds, hay, or mold, raising the risk for hypersensitivity pneumonia[35]
- Recurrent infections as a possible indicator of immunodeficiency
- Recurrent fevers, joint pain, and skin rashes suggesting a systemic disease
- Positive family history of interstitial lung disease indicated by need for O_2 therapy, neonatal respiratory distress, unexplained deaths[13]
- Details on family history of autoimmune diseases, fever, skin lesions, and joint pain help diagnosing connective tissue diseases.
- Consanguinity can increase likelihood of rare recessive Surfactant dysfunction disorders.

Examination

Children with ChILD can display nonspecific signs like chest wall retractions, abnormal breathing sounds. In advanced cases, cyanosis, clubbing, and a loud second heart sound due to pulmonary hypertension may be observed[36]. Extra pulmonary signs like joint disease, rashes, musculoskeletal manifestations, lymphadenopathy, and hepatosplenomegaly can narrow down the differential diagnosis[37,38].

Investigations

1. Radiology & Imaging

a) Chest radiography is the preferred initial imaging but rarely provides specific diagnosis.[39,40] It may appear normal in early stage or may show abnormalities like interstitial, alveolar, or mixed infiltrates, and hyperinflation, identify ChILD mimics (especially infection), and helps to define the extent and pattern of structural lung abnormalities.[41]

b) High-Resolution Computer Tomography (HRCT) is the cornerstone of diagnosis. A systematic approach to interpreting HRCT findings in suspected ChILD involves three practical steps[23]:-

- o First, lung volumes to determine whether they are high (with evidence of hyperinflation or air-trapping), normal, low, or variable.
- o Next, is to determine whether presence of ground-glass opacification and
- o Finally, to look for presence of cysts[23].

After these 3 steps, and in conjunction with the patient's clinical history, the radiologist should be able to narrow the differential diagnosis and help make a diagnosis appropriately. Additional characteristics include-

- o Septal thickening, honeycombing of bronchiectasis, mosaic attenuation, lung nodules and fibrotic changes[40,42]

The table summarizes HRCT findings specific to each diagnosis[23]

Step 1: Lung Volume	Step 2: Ground-Glass Opacities	Step 3: Cysts	Additional Characteristics[40,43]
High Lung Volume Disorders – Hyperinflation[23]			
Filamin A mutation	Absent	Absent	Atelectasis with coarse septal thickening
Neuroendocrine cell hyperplasia of infancy	Absent	Absent	extensive hyperlucency,No pulmonary nodules
Normal Lung Volume Disorders [23]			
Trisomy 21	Absent	Present	
NKX2-1 mutation	Present	Present/absent	Associated neurologic and thyroid abnormalities
Pulmonary interstitial glycogenosis	Present	Present / absent	Septal thickening Subpleural reticular changes
Low Lung Volume Disorders [23]			
Pulmonary hypoplasia	Absent	Absent	
Surfactant deficiency	Present	Present/ absent	Septal thickening
Variable Lung Volume Disorders[23]			
Chronic lung disease	Absent	Absent	bronchial wall thickening, coarse reticular pulmonary opacities, alveolar septal fibrosis, atelectasis

2. **Non-invasive laboratory tests** such as. Immune function tests, autoantibody studies, infection and inflammation markers, tests specific for environmental antigen exposure etc. can help rule out other systemic disorders associated with interstitial lung disease[11].

3. **To assess the severity of ChILD**

- Pulmonary function tests: Spirometry are often done in children over 4-5 years [9, 13, 39]. In older children, tests typically reveal a restrictive pattern with reduced FEV1 and FVC, and a normal or increased FEV1/FVC ratio[9]. Diffusing capacity of the lungs for carbon monoxide, DLCO (measurement to assess lung's ability to transfer gas from inspired air to the bloodstream) is usually decreased, which may be an early indicator of the disease.[43]
- Pulse oximetry: used to measure SPO_2, which is normal with mild disease but can lead to desaturation during sleep or exercise, and, further, hypoxemia at rest, and hypercarbia later in the disease course.[40,44]

4. **Echocardiography:** to exclude congenital heart disease, causing diffuse pulmonary diseases or pulmonary hypertension, which correlates with a worse prognosis[13]

5. **Bronchoscopy with broncho alveolar lavage (BAL):** to exclude anatomical abnormalities or active lung infections and to collect samples for microbiological studies.[7]

6. **Lung biopsy with histopathological study:** the final step in the diagnostic work-up. Ideally, the biopsy should be taken from two different lobes of the lung.[15]

7. **Genetic tests:** may confirm a defect in surfactant synthesis, surfactant metabolism or lung development.[42]

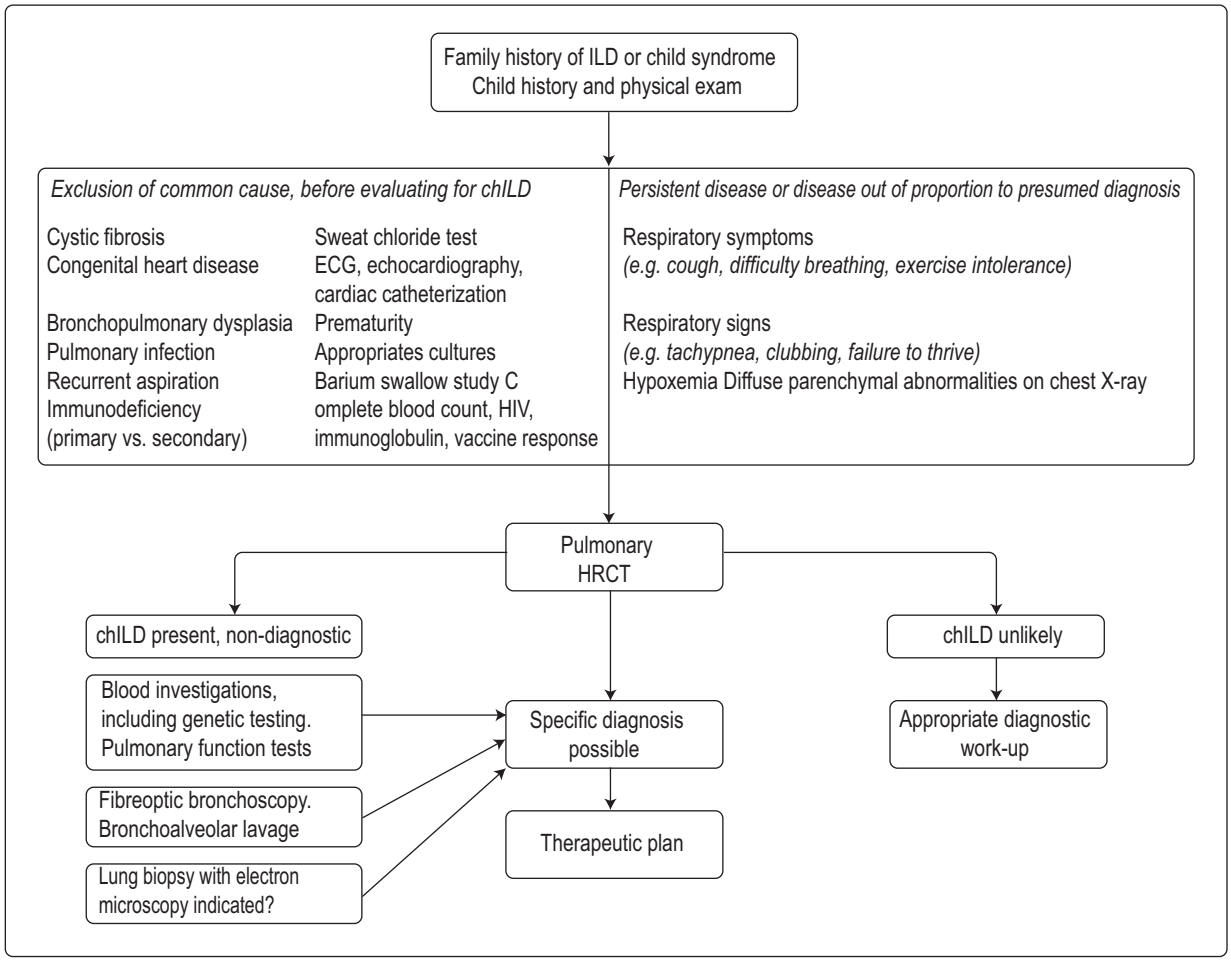

Figure 1: *The proposed general diagnostic design in ChILD*[45,46]

Current principles of treatment in ChILD

Therapeutic approaches for children with ChILD include supportive care and targeted pharmacological interventions [32]. Some children may recover spontaneously, while others may benefit from anti-inflammatory, immunosuppressive, or anti-fibrotic drugs[40]. Till date, there is no established guidelines for ChILD treatment; however, a European protocol called the **"Delphi method"** has been standardizing empirical treatment[9]

- The most common **anti-inflammatory drugs** used are corticosteroids- pulse dose of methylprednisolone 10–30 mg/kg/day for 3 days in the acute phase and oral prednisolone 1-2 mg/kg/day for 6-8 weeks with tapering in the chronic phase[9].
- Alternatively, **immunosuppressive agents** *e. g.* hydroxychloroquine as steroid-sparing drug
- Long-term Azithromycin at 10 mg/kg, administered three days a week can be given for its **antibiotic & immunomodulatory** properties[9].
- In refractory disease, **immunosuppressants** can be used *i. e.* Azathioprine, Cyclophosphamide, Methotrexate, along with **anti-fibrotic** drugs activity *i. e.* Pirfenidone or Nintedanib.[47]
- Children with severe diseases may consider lung or heart-lung transplantation.[54,48,49]

Supportive treatment, includes nutritional support, oxygen therapy, bronchodilators, treatment of infections, avoidance of environmental antigens in cases of hypersensitivity pneumonitis[48], and monitoring childhood immunizations with annual influenza vaccinations and respiratory syncytial virus prophylaxis as per guidelines[48], chemotherapy for malignancies, addressing swallowing dysfunction, managing gastroesophageal reflux in cases of chronic aspiration.

Conclusions-Points for clinical practice

- ChILDs are rare and diverse, with high morbidity and mortality rates.
- General pediatricians should keep ChILD in mind when evaluating children with persistent respiratory symptoms, especially after ruling out common lung diseases.
- It is recommended to follow a systematic diagnostic approach starting with routine tests before considering referral to specialized medical centers for further evaluation, such as CT scans, lab work, BAL, PFTs, genetic testing, and potentially a lung biopsy.
- Early detection and intervention are crucial in preventing the progression of pulmonary fibrosis
- A coordinated, multidisciplinary team approach along with clear diagnostic algorithms can help reduce delays in diagnosis and improve treatment and prognosis

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