INTRODUCTION

Childhood interstitial lung disease (ChILD) is a term used to describe a rare heterogeneous group of diffuse lung diseases that produce considerable morbidity and mortality ***(Deterding, 2007).***

Because of a lack of consensus on case definition until recently, the broad differential diagnosis and the lack of organized reporting systems, determining the precise prevalence of ILDs is impossible ***(Hagood, 2015).***

Interstitial lung disease (ILD) in children comprises a broader spectrum of disorders than in adults ***(ATS/ERS, 2002; Clement et al., 2004).*** This is certainly linked to the fact that the disease occurs in the context of lung growth at the various stages of alveolar development and maturation, with each of these stages being regulated by specific cascades of events ***(Clement et al., 2004).***

In lung, wound healing and fibrosis are considered as complex pathophysiologic processes that involve numerous cell types and cellular processes such as adhesion, proliferation, apoptosis and a vast array of soluble mediators and extracellular matrix (ECM) molecules ***(Bush, 2005).***

Fibulin-1 is known to play important roles in wound repair and is implicated in airway remodeling that is

specifically induced by TGF-β treatment of airway smooth muscle (ASM) cells ***(Liu et al., 2016).***

Across diseases in which fibrosis occurs there are similar mechanisms contributing to fibrogenesis. Hence, it was logical to explore whether fibulin-1 would also be important in a disease predominantly characterized by fibrosis such as ILD ***(Royce et al., 2012).***

Bronchoalveolar lavage (BAL) has gained widespread acceptance as a procedure that can be performed safely to retrieve respiratory secretions for the examination of cellular and a cellular components for both diagnostic and research purposes ***(Drent et al., 2007).***

When performed with a standardized technique, expertly examined and combined with clinical and imaging data, BAL differential cell counts and types can provide important information that contributes significantly to the diagnosis of specific ILDs ***(Baughman and Drent, 2001).***

Aim of the Work

Measurement of serum and BALF levels of fibulin-1 using fiberoptic bronchoscope in children with ILD and correlation of these levels with their clinical and radiological scoring.

Childhood Interstitial Lung Disease (ChILD)

Definition

Interstitial lung disease is a nonspecific term referring to disorders that feature remodeling of the lung interstitium and distal airspaces, with resultant abnormal gas exchange ***(Kurland et al., 2013).***

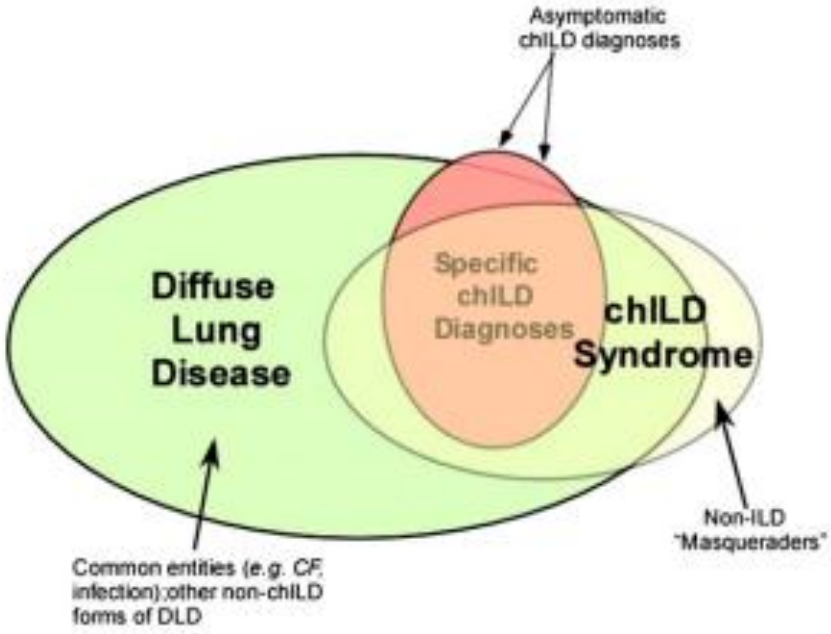


Figure (1): Venn diagram depicting a conceptual framework, which demonstrates the relationships among diffuse lung disease (DLD), childhood interstitial lung disease (chILD) syndrome, and specific chILD diagnoses ***(Kurland et al., 2013).***

Childhood interstitial lung disease (ChILD) syndrome is a clinical presentation comprising respiratory symptoms (e.g.

cough, tachypnea), signs (retractions, crackles), and diffuse radiographic abnormalities, with hypoxemia ***(Dell et al., 2012)***.

Epidemiology:

Prevalence:

The prevalence of Interstitial lung disease in children (chILD) is rare, It is likely <1 per 100 000 but there are no reliable estimates ***(Bush et al., 2015).***

Age:

The prevalence of ChILD is higher in the younger patients, more than 30% of patients are less than 2 years at diagnosis, as recorded by the recent ERS Task Force ***(Clement and Eber, 2008).***

Gender:

In ChILD, there is a male predominance with male: female ratio 4:1 ***(Clement and Eber, 2008).***

Morbidity and Mortality

A significant numbers of children have poor growth requiring nutritional supplementation, pulmonary hypertension and gastroesophageal reflux. A mortality rate of 30% has been reported in the literature for all children with the presence of pulmonary hypertension which is a considerable risk factor for mortality ***(Fan and Kozinetz, 1997)***.

Genetic Role in ChILD:

In ChILD cases, 7% have parental consanguinity and nearly 10% of case siblings were affected by similar diseases, the estimated prevalence ranging 1.3–5.9 per million ***(Grutters and du Bois, 2005; Clement et al., 2010)***.

i. Surfactant Dysfunction

Pulmonary surfactant is a multimolecular complex, secreted by type 2 AEC constituted of phospholipids and proteins into the alveolar space. It acts by reducing surface tension along the epithelial lining and this role involves mainly lipids and specific hydrophobic SP, SP-B and SP-C ***(Stevens et al., 2005).***

The ATP-binding cassette, sub-family A, member 3 (ABCA3) and the thyroid transcription factor 1(TTF-1) are important players in surfactant metabolism ***(Stevens et al., 2005).***

- **SP-B gene** has more than 40 distinct mutations that have been identified to date.

The histopathology shows alveolar proteinosis with foamy, eosinophilic, lipoproteinaceous material filling alveoli, thickened alveolar septa with alveolar epithelial hyperplasia, and abnormal lamellar bodies on electron microscopy (Fig. 2) ***(Wert et al., 2009).***

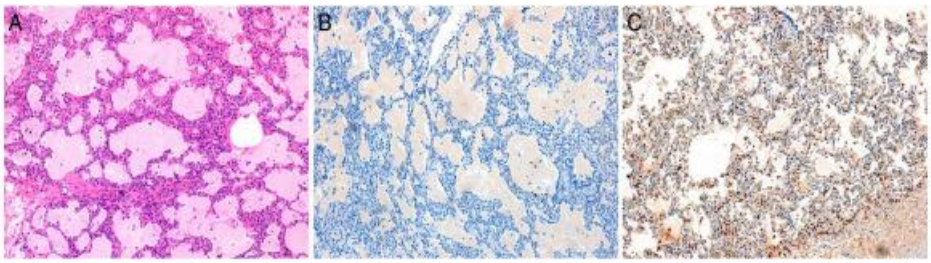


Figure (2): Surfactant protein B deficiency. (A) Interstitial thickening, and a striking quantity of granular, proteinaceous debris within alveolar spaces. (B) Immunohistochemical staining with antibody to surfactant protein B is negative. (C) Immunohistochemical staining with antibody to surfactant protein B in control lung tissue ***(Edwards et al., 2005).***

- **SP-C** gene was first described in 2001 in a full-term infant and mother with respiratory insufficiency. Patients with SP-C mutations can present with severe manifestations early in life or may develop symptoms in adulthood ***(Nogee et al., 2001; Schock and Perrimon, 2002).***

More than 40 distinct mutations in the *SFTPC* gene have been identified, with the majority of these mapping to the carboxyl terminus of proSP-C ***(Soraisham et al., 2006)***.

- **ABCA3 gene** mutation is an autosomal recessive disorder, more than 150 distinct mutations have been identified, and mutations in the ABCA3 gene consist of missense, nonsense, frame shift, and splice-site mutations, as well as insertions and deletions,the histopathological findings and the HRCT chest are seen in (Fig. 3) (Fig.4) ***(Gower et al., 2008)***.

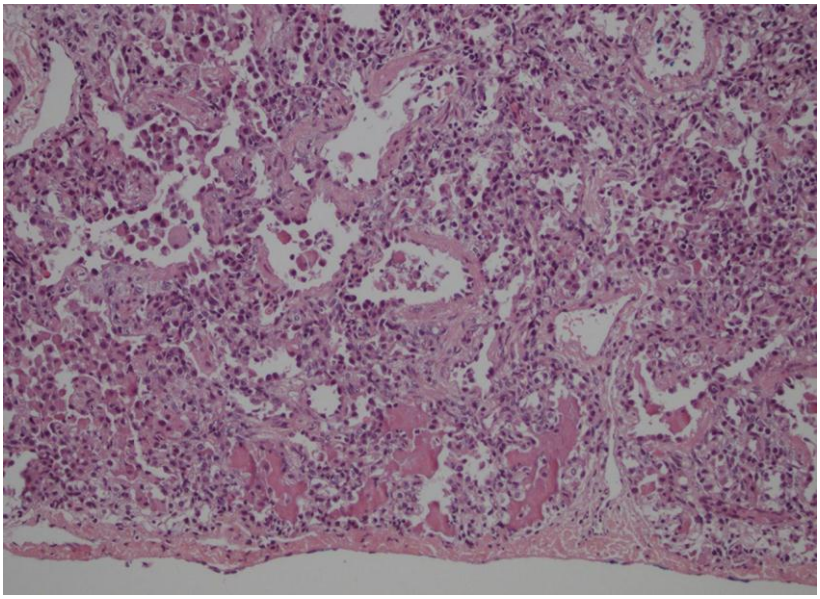


Figure (3): Histopathology of ABAC3 deficiency showing interstitial thickening with florid type II pneumocyte hyperplasia and pulmonary alveolar proteinosis due to genetically proven ABCA3 deficiency. The eosinophilic debris within the alveolar spaces has a characteristic 'glassy' appearance. There are abundant intra-alveolar macrophages. There is also hyperplasia of smooth muscle in the interstitium ***(Edwards et al., 2005).***

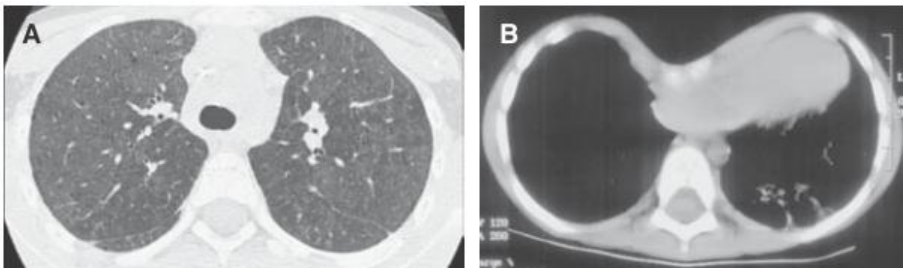


Figure (4): HRCT image (A) shows extensive ground-glass pulmonary opacities, small cysts, and a few thickened septa. Additional evaluation revealed ABCA3 gene mutations. Pectus excavatum also as illustrated on a CT image (B) of a case with ABCA3 gene mutations ***(Doan et al., 2008).***

ii. Brain-lung-thyroid syndrome: mutations in the thyroid transcription factor-1 (also known as NKX2-1) gene are associated with a syndrome of neurologic (cerebral

dysgenesis, chorea, developmental delay), thyroid (hypothyroidism), and pulmonary dysfunction ***(Krude et al., 2002).***

iii. Pulmonary alveolar microlithiasis:

This disease is an autosomal recessive gene encoding the type 2b sodium phosphate co-transporter SLC34A2, It is found in Turkish people in particular characterised histopathologically by the slow formation of microliths in the intra-alveolar spaces (fig. 5) ***(Castellana et al., 2002; Huqun et al., 2007).***

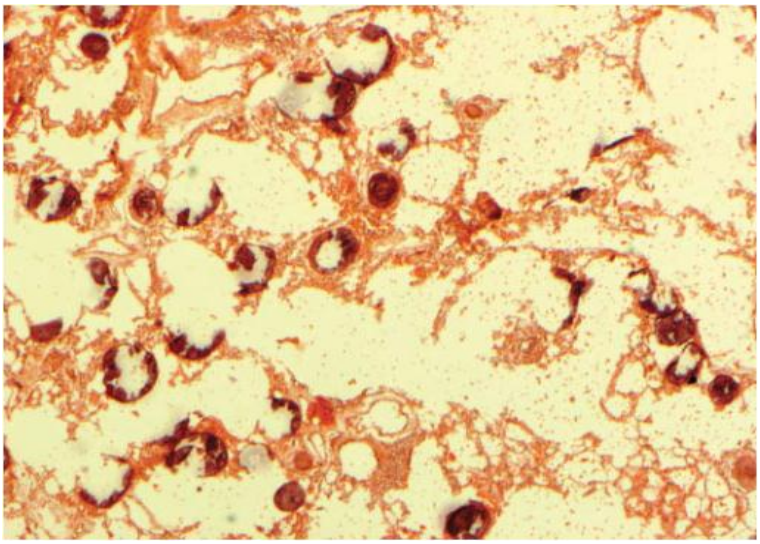


Figure (5): A case of alveolar microlithiasis shows abundant calcification lying both within alveolar spaces and in the interstitium ***(Castellana et al., 2002).***

iv. Hermansky-Pudlak syndrome:

Although rare in most areas with prevalence approximately one in 1,000,000, in some parts of the world

(e.g. Puerto Rico) the disease is common, attaining a frequency of one in 1,800. HPS is thought to be a manifestation of defective formation or trafficking of intracellular vesicles ***(Huizing et al., 2008).***

There are eight different HPS genes, some of which lead to a relatively mild phenotype. All exhibit some degree of pulmonary fibrosis, hypopigmentation and a bleeding diathesis ***(Gahl et al., 2002)***.

The pathophysiological mechanisms of ChILD:

Critical role of the alveolar epithelium

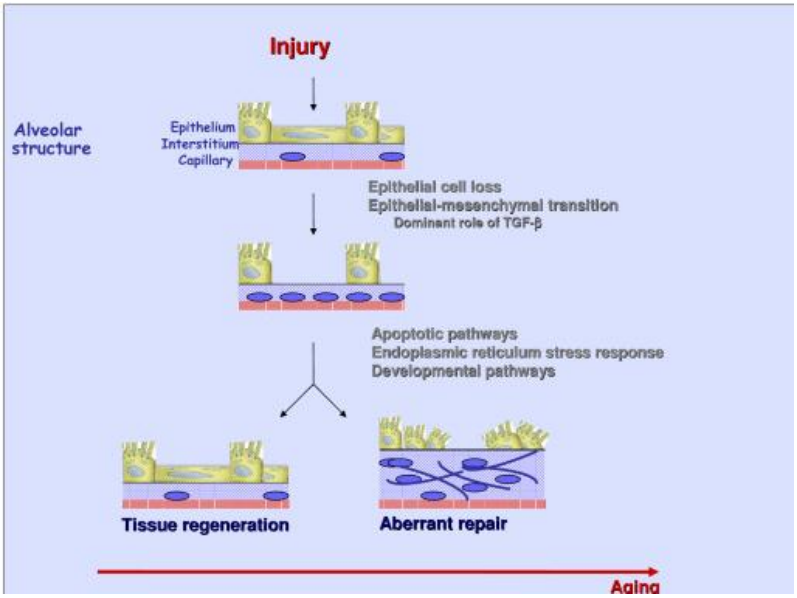
The mechanisms underlying the development and progression of ILD remain elusive ***(Corvol et al., 2009)***.

Indeed, for a long time, chronic ILD and pulmonary fibrosis were believed to result mainly from initial injury to the alveolar epithelial lining and through a process known as epithelial-mesenchymal transition (EMT) ***(Thiery and Sleeman, 2006; Bringardner et al., 2008).***

Consequently, the mechanisms underlying disease progression are through interactions of multiple pathways, which include apoptotic pathways, developmental pathways, and endoplasmic reticulum (ER) associated pathways (Fig.6) ***(Clement et al., 2010).***

A. Apoptotic pathways

Apotosis plays a central role in lung remodeling associated with ILD.TGF- β is an important molecule in the events associated with epithelial cell apoptosis, which is over expressed in ILD ***(Thannickal and Horowitz, 2006; Yamasaki et al., 2008)***.



TGF-β: Transforming Growth Factor

Figure (6): Mechanisms and pathways involved in the response of the alveolar structure of the lung to injury ***(Clement et al., 2010).***

B. Development pathways:

Recently, it has been suggested that genes associated with lung development and embryonic pathways could participate in the development of chronic ILD ***(Selman et al., 2008)***.

C. Endoplasmic reticulum (ER) associated pathways:

The ER stress may represent an important mechanism of the altered repair process, misfolding or mistargeting of the protein. These events trigger induction of intracellular aggregate formation and ER stress, which can lead to cell death observed in the alveolar epithelium of fibrotic lung (fig. 7) ***(Beers and Mulugeta, 2005; Mulugeta et al., 2007).***

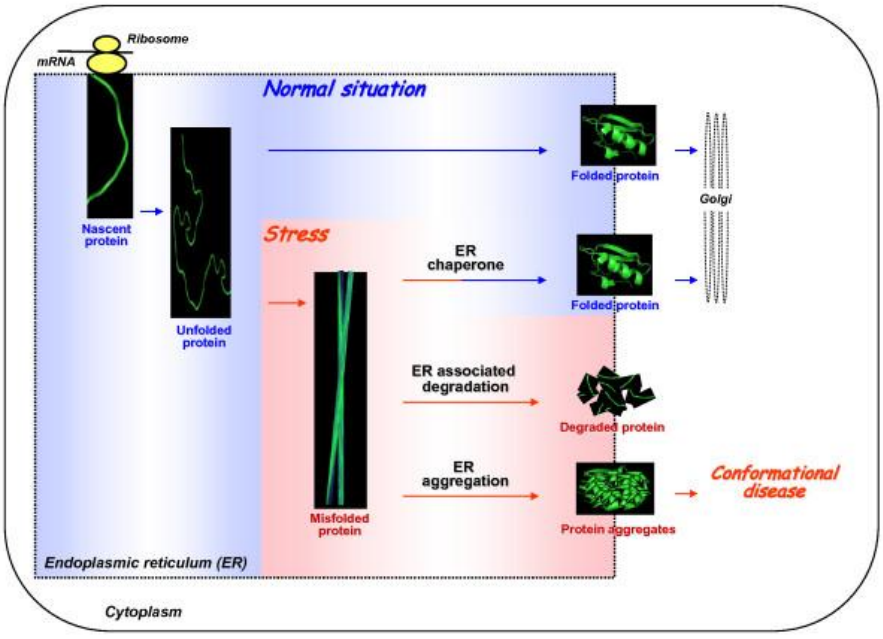


Figure (7): Alveolar structure disorder-associated ILD and ER stress ***(Clement et al., 2010).***

Histological Classification of ChILD

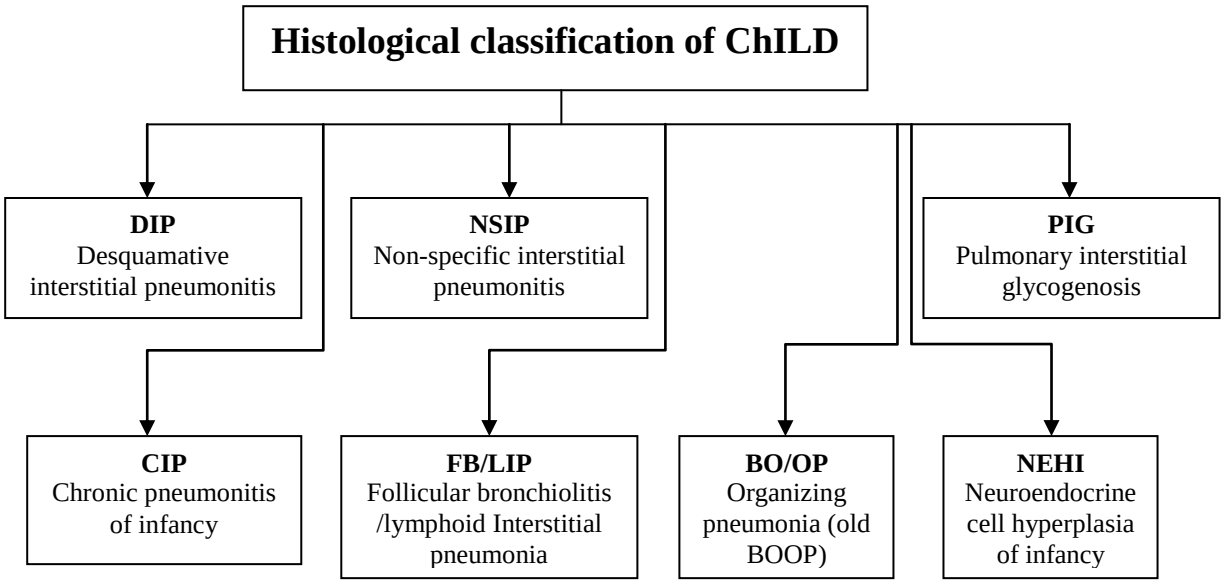


Figure (8): Histological Classification of ChILD ***(Shaheen, 2011).***

Types of Childhood Interstitial Lung Disease:

The "childhood interstitial lung disease" (ChILD) is a group of rare lung diseases that can affect babies, children and teens. Some types are more common in certain age groups (table 1) ***(NHLBI, 2014)***.

Table (1): Classification of ChILD

Diseases more common in children older than 2 years of age and teens include:
▪ **Primary disorders:**
- Alveolar hemorrhage syndromes. - Aspiration syndromes. - Hypersensitivity pneumonitis. - Infectious or postinfectious disease (bronchiolitis obliterans). - Eosinophilic pneumonia. - Pulmonary alveolar proteinosis. - Pulmonary infiltrates with eosinophilia. - Pulmonary lymphatic disorders (lymphangiomatosis, lymphangiectasis). - Pulmonary vascular disorders (haemangiomatosis).
▪ **ILD associated with systemic disease processes:**
- Connective tissue diseases. - Histiocytosis. - Malignancy-related lung disease. - Sarcoidosis. - Storage diseases.
▪ **Disorders of the compromised immune system:**
- Opportunistic infection. - Disorders related to therapeutic intervention. - Lung and bone marrow transplant-associated lung diseases. - Diffuse alveolar damage of unknown cause.
▪ **Idiopathic interstitial pneumonias:**
- Nonspecific interstitial pneumonia. - Cryptogenic organizing pneumonia. - Acute interstitial pneumonia. - Desquamative interstitial pneumonia. - Lymphocytic interstitial pneumonia.
Diseases more common in infancy include:
- Surfactant (sur-FAK-tant) dysfunction mutations. - Developmental disorders, such as alveolar capillary dysplasia. - Lung growth abnormalities. - Neuroendocrine cell hyperplasia of infancy (NEHI). - Pulmonary interstitial glycogenosis (PIG).

(NHLBI, 2014)

I. Exposure-related ILD:

Exposure-related disease is a disease caused by a sufficient level of dose exposure to components with target organ contact, and subsequent biologic changes and clinical expression (fig. 9) ***(Clement et al., 2010).***

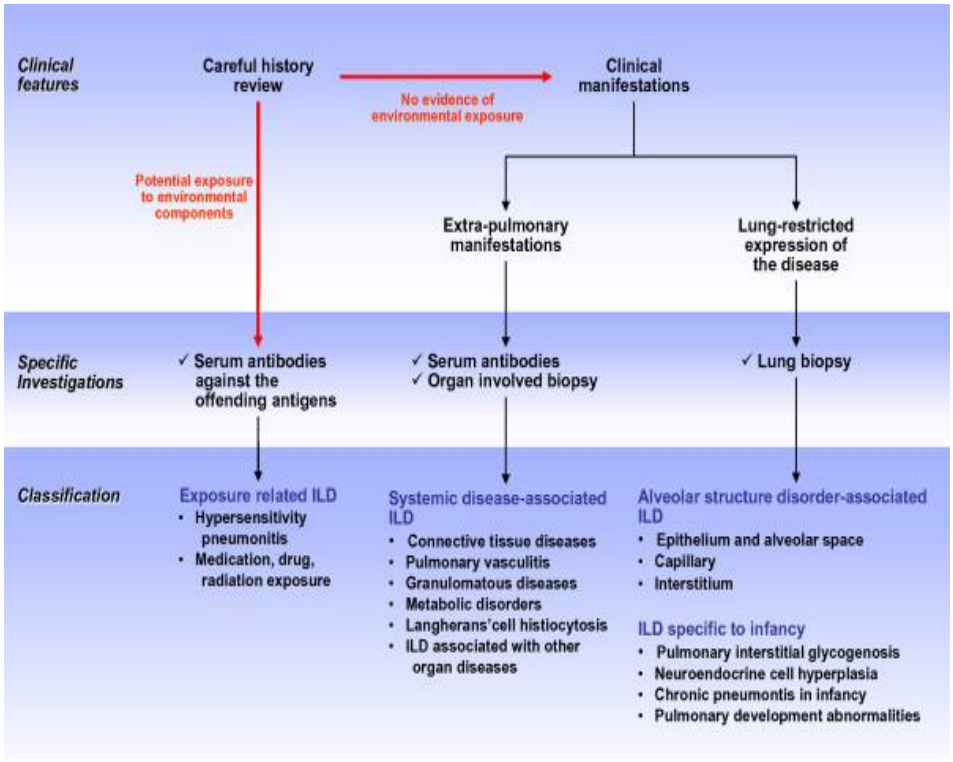


Figure (9): Search for ILD etiology in children ***(Clement et al., 2010).***

A. Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is "a cell-mediated immune reaction to inhaled antigens in susceptible persons" ***(Fan, 2002)***.