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The term interstitial lung disease (ILD) refers to a broad category of lung diseases rather than a specific disease entity. They all affect the tissue and space around the alveoli (air sacs), called the interstitium, however they display diverse causes, treatments, and prognoses. These disorders are also collected together because of similarities in their clinical presentations, plain chest radiographic appearance, and physiologic features. Because there are more than 200 separate disorders, it is helpful to group them based on cause, disease associations, or pathology. First, the diseases are separated into those with known causes or associations and those of unknown cause. Diseases with known causes are further classified based on specific exposure, association with systemic disease, or association with a known genetic disorder. When responding to any injury, whether from a specific exposure (e.g., asbestos, nitrofurantoin, moldy hay), an autoimmune-mediated inflammation from a systemic connective tissue disease (e.g., rheumatoid arthritis), or unknown injury (e.g., idiopathic pulmonary fibrosis), the lung must respond to the damage and repair itself. If the exposure persists or if the repair process is imperfect, the lung may be permanently damaged, with increased interstitial tissue replacing the normal capillaries, alveoli, and healthy interstitium. These pathologic abnormalities can lead to profound impairment in lung physiology. Gas exchange is impaired due to ventilation-perfusion mismatching, shunt, and decreased diffusion across the abnormal interstitium. Work of breathing is markedly increased because of decreased lung compliance. Together, these physiologic impairments lead to the exercise intolerance seen in all of the ILDs. Unfortunately, if the initiating injury or abnormal repair from injury is not halted, progressive tissue damage can lead to worsening physiologic impairment and even death.


WHY IS ILD A DIFFERENT DISEASE IN CHILDREN? CLASSIFICATION OF chILD

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ILD: Adults vs. Children chILD is an order of magnitude rare than adult ILD, and comprises >200 entities. chILD and its treatment, especially in young babies, must be seen in the context of normal maturation of immune and epithelial function, and profound airway and alveolar growth changes. Any effects on lung function are likely permanent by school age. Genes dominate over environmental effects, and it is unsurprising that, for example, surfactant protein-C mutations have completely different manifestations over the age spectrum (pulmonary alveolar proteinosis-like picture in babies, usual interstitial pneumonia in adults even in the same family).

Classification of chILD Conventional these are split into 0-2 and 2-16 years, and initial papers have significantly advanced the field. However, it is becoming clear that many current biopsy-based classifications do not capture the full spectrum of chILD. Although one histological pattern may be dominant, others may co-exist, and overlaps between classes are not uncommon. Secondly, increasing numbers of conditions are appropriately diagnosed on genetic testing, and may not come to biopsy. Thirdly, conditions thought to be specific to infancy (pulmonary interstitial glycogenosis (PIG, increased mesenchymal glycogen positive cells) and neuroendocrine cell hyperplasia of infancy (NEHI, increased bombesin positive cells)) may overlap with other conditions, and the abnormal cells may in fact be markers of immaturity of the mesenchyme and airway respectively. Finally, novel entities are being discovered, in particular from low and middle income countries with different environmental exposures. In summary, chILD classification is a work in progress, and much is to be learned about the interactions between lung growth, immunological and epithelial maturation, and chILD disease manifestations.
INTERSTITIAL LUNG DISEASE CAUSED BY FILAMIN A GENE MUTATIONS: CLINICAL COURSE OF THREE PAEDIATRIC CASES

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Introduction: Diffuse parenchymal lung disease related to Filamin A (FLNA) mutation is a newly recognized disease entity in children's interstitial lung disease (chiLD). Only 3 single cases of FLNA associated chiLD have been reported. Information on the clinical course after the first years of life is lacking.

Aim: To describe follow up into childhood of 3 patients with FLNA-associated chiLD.

Methods: Retrospective chart analysis and prospective clinical and functional follow-up.

Results: The median age at first presentation was 9.2 (4.1 to 11.8) years. Pulmonary symptoms (tachypnea, hypoxemia, bronchial obstruction) developed at a median age of 3.3 (birth to 10) weeks. Chest CT revealed panlobular emphysema which was confirmed by histology of lung biopsies. Initial mean FEV1 was 35% predicted. 6-minute-walk-test distances were markedly reduced in all patients. Hypertension, which had persisted to presentation in only the youngest patient at age 4 years. Dystrophy improved in two patients with gastrostomy tube feeding. All patients had similar facial dysmorphic features and cranial MRI findings of subependymal heterotopia. Severe pulmonary exacerbations from respiratory tract infections occurred in all children in early childhood. Overtime, all...
patients clinically improved with fewer exacerbations, decreased oxygen requirement, stable lung function and improved quality of life.

**Conclusion:** FLNA associated chILD is a severe and potentially life threatening disease. In these 3 cases, the disease appears to have a critical phase in the first two years of life. With increasing age and under supportive medical care all patients stabilized, showing progressive functional improvement, decreased pulmonary hypertension and oxygen requirement.

**INTERSTITIAL LUNG DISEASE IN TWO PATIENTS WITH JUVENILE SYSTEMIC SCLEROSIS**

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Juvenile systemic sclerosis (JSS) is a rare but potentially life threatening chronic multisystem connective tissue disease. Interstitial lung disease (ILD) is one of the most common mortality and morbidity-causing factors in patients with JSS. Although various types of immunosuppressive therapies have been attempted for patients with JSS-ILD, no curative or effective treatment strategies have been developed yet. Here we report two cases of JSS-ILD with different grades of gastrointestinal (GI) involvement.

**Case 1:** A 14-year-old girl under methotrexate and prednisolon treatment with a two-year history of JSS and severe GI involvement with massive gastro esophageal reflex (GER) exhibited chronic cough. Her pulmonary function tests (PFT) revealed restrictive features. Carbon monoxide diffusing capacity (DLCO) and computerized tomography (CT) of thorax findings were compatible with ILD. Despite to treatment with cyclophosphamide and anti-GOR treatment for six months, her PFTs negatively correlated with the extent of ILD at thorax CT and cyclophosphamide was replaced by mycophenolate mofetile but anti-GER treatment maintained. After one-year of mycophenolate mofetile and anti-GER treatment, her PFTs are still worsening.

**Case 2:** A 12-year-old boy presented with cough and dysphagia with a five-year history of Raynaud phenomenon and sclerodactyly. He was diagnosed JSS-ILD and mild GI involvement according to thorax CT and upper GI endoscopy findings. He could not cooperate enough to perform PFTs and DLCO. As his cough resolved but thorax CT findings insisted after receiving prednisolon, iloprost, cyclophosphamide and anti-GER treatment for six months, cyclophosphamide was replaced by mycophenolate mofetile and anti-GER treatment maintained. He has been receiving mycophenolate mofetile for the last three months and he is still cough free.

**Conclusion:** Although the second case is a late diagnosed patient, his respiratory symptoms are moderate possibly due to mild GI involvement. GI involvement might have an important impact on respiratory problems.

**AN OBSERVATIONAL STUDY OF INCIDENT DIAGNOSES OF CHILDREN’S DIFFUSE PARENCHYMAL LUNG DISEASE (ChILDEU)**

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**Introduction:** The incidence and progression of ChILD have very limited data. We wished to understand the progression of ChILD in the year following diagnosis, in those identified as newly diagnosed within the ChILDEU trial.

**Methods:** Clinicians across Europe were invited to submit cases with a high suspicion of ChILD to the ChILDEU database (Secutrial). Potential cases underwent peer review to confirm a diagnosis. Baseline data were made available for peer review. Following
Results: In the period 01/2014 to 11/2016 (26 months), 128 cases of incident cases of ChILD were submitted to ChILDEU and were peer reviewed. Cases were included from 9 countries with most cases coming from Germany (48), UK (25) and Poland (21).

Cases were male (56%)/female (44%) and predominantly caucasian (90%). Children were a median age of 0.9 years (iqr 0.3-8.4 years). The time from local clinical diagnosis at site to database registration was a median of 0 days (iqr 0-14 days). Children had a median birthweight of 3170g (2 score -0.6, iqr -1.4, 0.1). At baseline weight was -1.4 z score (iqr -2.9, -0.4), height -0.8 (iqr -2.4, 0.3). Tachypnoea (69%) and dyspnoea (54%) were the most common symptoms at baseline.

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DECIPHERING THE MECHANISM OF QT45H SFTPC MUTATION UNMASKS A SPLICING DEFECT AND EXPLAINS THE SEVERITY OF THE PHENOTYPE

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Mutations in the gene encoding surfactant protein C (SFTPC) have led to a broad range of phenotypes from neonatal respiratory distress syndrome to adult interstitial lung disease. We previously identified the c.435G>C variant in the SFTPC gene associated with fatal neonatal respiratory distress syndrome in an infant girl. Although this variation is predicted to change glutamine (Q) at position 145 to histidine (H), its position at the last base of exon 4 and the severity of the phenotype suggested that it might also induce a splicing defect.

To test this hypothesis, we used hybrid minigene, biochemical and immunofluorescence tools to decipher the molecular mechanism of the mutation. Immunoblotting and confocal imaging showed similar maturation and localization of wild-type and QT45H proteins, but hybrid minigene analysis showed complete exon 4 skipping. Since the exon 4 is in frame, a putative truncated protein of 160 amino acids would be produced. We have shown that this truncated protein had an altered intracellular trafficking and maturation. The c.435G>C mutation is deleterious not because of its amino acid substitution but because of its subsequent splicing defect and should be referred to as r.325_435del and p.Leu109_Gln145del. The absence of residual full-length transcripts fully explained the severity of the phenotype we observed in the infant.

OPEN LUNG BIOPSY FOR CHRONIC PULMONARY DISEASE IN CHILDREN

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Introduction: This study aimed to evaluate the efficacy of open lung biopsy in children with chronic lung disease.

Methods: Patients underwent open lung biopsy in 2006-2017 at Hacettepe University Department of Pediatric Pulmonology were examined retrospectively.

Results: Twelve patients (6 boys, 6 girls) underwent open lung biopsy for diagnostic purposes. The mean age of the patients was 8.5 years (4 months-15.1 years). Four patients were followed up with immune deficiency. The diagnoses of these patients were chronic granulomatous disease (n:1), CVID (n:1) and hypogammaglobulinemia (n: 2). None of the patients had any malignancy. The mean time between the onset of respiratory symptoms and the open lung biopsies was 6 months (range 1 to 36 months). None of the patients developed
acute respiratory failure on follow-up. Nine of the patients (75%) required mechanical ventilation in the first 24 hours postoperatively. The mean chest tube withdrawal time in patients is 4.2 days (2 days to 7 days). Three patients were hypersensitivity pneumonitis, 1 patient was SPC deficiency, 2 patients were interstitial pneumonia, 1 patient was granulomatous lymphocytic interstitial lung disease, 1 patient was cryptogenic organizing pneumonia, 1 patient was follicular bronchiolitis, 1 patient was pulmonary hemosiderosis, 1 patient was giant air cyst and 1 patient was granulomatosis inflammation was diagnosed. Ten patients underwent a treatment change after biopsy results. According to biopsy results, steroid treatment was started for all these patients, 1 patient was given mycophenolate mofetil and 1 patient was given hydroxychloroquine treatment.

**Conclusion:** Our results suggest that open lung biopsy is safe and guiding for diagnosis in children with chronic lung disease.

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**METHODOLOGY TO DEVELOP AND VALIDATE A NEW QUESTIONNAIRE FOR MEASURING PATIENT REPORTED OUTCOMES (PROs) IN chILD**

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**Background:** In children with interstitial lung disease (chILD) there is the lack of standardized tools for measuring how the patient feels and quality of life. At the moment, the available patient symptom score is the Leland-Fan clinical scale for children with pulmonary hypertension. Indeed, quality of life is often impaired in chILD, and the best patient-reported outcomes (PROs) to monitor have not been explored.

**Objective:** To develop and validate new questionnaire-based scores for measuring PROs, for monitoring disease progression in chILD.

**Methods:** Psychologists will develop a questionnaire for assessing PRO in close cooperation with expert and parent groups. Children surveys requires appropriate and effective questions: short, straightforward syntax, low memory usage, appropriately ordered, few response options, labelled scales, visual images, no “I don’t know” answer.

The development phase will involve setting up of a starting pool of items covering the main dimensions related to quality of life, based on literature review, clinical experience, and unstructured interviews to children and parents. The items will be randomly listed and tested on a sample of consecutive outpatients, asking to indicate which item they had experienced and, for each selected item, its importance on a four-point scale (1 = not at all; 4 = very much). The data of this pilot survey will be used to assess quality and effectiveness of the questions: high levels of item non-response, unexpected findings, inconsistencies, items of low importance.

The questionnaire obtained after addressing the emerged issues and excluding the item of low importance will then be validated by assessing: internal consistency, identification of possible subscales, convergent validity (correlation with other validated scales), reproducibility (in stable patients), responsiveness (in patients whose clinical status has changed).

**Expected results:** To provide tools and instructions for monitoring disease progression by PROs in chILD.

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**RECOGNITION OF INTERSTITIAL LUNG PATHOLOGIES USING DEEP CONVOLUTIONAL NEURAL NETWORKS**

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**Introduction:** The detection of pathologies in HRCT scans with interstitial lung disease (ILD), is a basic component towards the automatic quantification of ILDs and a valuable identifier for the final diagnosis. Scope of this study is the development and evaluation of an automatic system for the recognition and segmentation of pathological ILD lung tissue. The system is based on deep learning techniques, which have recently achieved impressive results in a variety of problems. Specifically, we propose and evaluate a deep convolutional neural network (CNN), designed for the classification of ILD patterns.

**Methods:** Based on two multimedia ILD databases (University Hospital of Geneva, University Hospital of Bern) consisting of 172 unique HRCT scans, and a total area of annotated pixels, 2575 annotated slices were extracted. Six lung patterns were considered: normal, ground glass opacity (GGO), micronodules, consolidation, reticulation and honeycombing. To this end, a CNN that was designed...
particularly for ILD pattern classification was trained in an end-to-end and semisupervised manner. For the evaluation of the results a cross-validation scheme was adopted, where the cases were split on a patient level.

**Results:** The system reached a performance of nearly 82% in terms of accuracy, demonstrating the potential of CNNs in analyzing lung pathological tissue. The confusion matrix of the results is presented in Fig. 1. Examples of the output of the system is depicted in Fig. 2.

**Conclusion:** The CNN showed very promising results in lung pattern recognition, outperforming state-of-the-art methods. Future work includes the integration of this system into a pipeline that will provide a differential diagnosis for ILDs.

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**PULMONARY DISEASE IN CHILDREN WITH ACTA2 MUTATION**

Iglesias I.₁, Navarro A.₂, Albert D.₃, Carreño JC.₄, Torrent A.₁, Rovira S.₁, Mir I.₁, Gartner S.₁, Moreno A.₁

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**Introduction:** The α-actin 2 (ACTA2) is a protein of the smooth muscle cells (SMC) which is essential for its contraction. Patients with a mutation at the ACTA2 gen have diffuse vascular disease, with characteristic features such as arterial aneurysms, fixed bilateral mydriasis, intestinal and bladder dysfunction, besides of pulmonary hypertension and diffuse lung disease. We report four pediatric patients with confirmed ACTA2 mutation and pulmonary disease, showing their different evolution and age at the time of diagnosis, and similar radiologic pattern on the CT.

**Methods:** Retrospective observational study. Medical records from pediatric patients diagnosed with ACTA2 mutation during the last years were reviewed.

**Results:** Four patients with ACTA2 mutation were identified: 2 had heterozygous p.Arg179Cys mutation and 2 patients were found to have heterozygous p.Arg179His mutation. All of them had patent ductus arteriosus diagnosed in neonatal period, cerebral anomalies and respiratory symptoms with hypoxemia. ¾ had congenital mydriasis, intestinal malrotation, and pulmonary hypertension. Only one of the children was a premature newborn (35 weeks).

All of these patients had similar radiologic pattern, with septal thickenings, parenchymal bands, air-trapping and mosaic pattern on the thoracic CT. In one of the cases, we did a pulmonary biopsy, which showed striking peripheral alveolar enlargement, constrictive bronchiolitis and dilated both lymphatic and venous vessels.

Follow up wise, 2 of the children died being infants (2 and 7 months old); another passed away when she was a 15 year-old teenager, during the surgery for a lung transplant, due to an aortic dissection. The only patient alive is currently 8 years old, needs some oxygen intermittently and has limitation for physical activities, but is doing fine otherwise.

**Conclusion:** ACTA2 mutations cause multisystemic organ disease including significant lung involvement usually associated with pulmonary arterial hypertension.

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**CORTICOSTEROIDS IN chILD TREATMENT**

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Corticosteroids (CS) as a potent anti-inflammatory drugs have been used in the treatment of respiratory diseases since 1950. Their role in many pulmonary conditions is still controversial. CS exert their anti-inflammatory effect by binding to glucocorticoid receptor through three genomic independent mechanisms: 1. They induce the production of lipocortin-1; 2. They induce the mitogen-activated...
protein kinase phosphatase 1 and finally 3. They antagonize the transcriptional activity of NF-κB.

The exact mechanism of action of CS in a chILD is not well defined. CS exert a direct inhibitory effect on many inflammatory cells. The cellular effects of CS are generally immediate, but there is a time lag, usually hours before they produce a clinical response. The washout of effects is also prolonged.

Systemic GS are the traditional treatment for a wide variety of interstitial lung diseases, including hemorrhagic syndromes and surfactant protein deficiencies. There are no RCTs of treatment because of the rarity of the chILD.

Many pediatricians prefer to use pulsed methylprednisolone at the dose 10-30 mg/kg given for three consecutive days once a month for a period of at least three months. In the literature treatment with several pulses also have been presented.

Oral or intravenous prednisolone at the dose 1-2 mg/kg daily is also used as the main treatment or as a support treatment between pulses, especially in the most severe cases.

It is not so simple to extrapolate existing data from adults. It this group of patient GS are used in the treatment of ILD such as sarcoidosis and non-specific interstitial pneumonia, but they are not recommended in fibrotic disorders such as usual interstitial pneumonia.

The third route of treatment described in the literature is inhalation. There are few reports of the use of inhaled CS as the maintenance treatment, but the evidence that they are deposited sufficiently distally and in an effective dose is scanty. In sarcoidosis (stage I and II) or hypersensitivity pneumonia budesonide or beclomethasone HFA can be used as a method to spare systemic steroids. More new trials with inhaled steroids should be done for the clarifying their role in the chILD treatment. Because of not sufficient data they are not recommended.

HEALTH RELATED QUALITY OF LIFE IN INFANTS AND CHILDREN WITH INTERSTITIAL LUNG DISEASE: A NATIONAL PILOT SURVEY IN FRANCE

Lauby C.¹, Boelle PY.², Epaud R.³, De Blic J.⁴, Abou Taam R.⁵, Reix P.⁶, Dubus JC.⁷, Renoux MC.⁸, Fayon M.⁹, Giovannini Chami L.¹⁰, Thumerelle C.¹¹, Troussier F.¹², Brouard J.¹³, Tatopoulos A.¹⁴, Weiss L.¹⁵, Varni JW.¹⁶, Clement A.¹⁷, Nathan N.¹⁸

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Introduction: Interstitial lung disease (ILD) in infants and children is a heterogeneous group of rare respiratory disorders. Children suffering from severe ILD may develop hypoxemia and growth issues. They often require long-term treatments such as oxygen therapy, corticosteroids and nutritional support. Systematic follow-up and acute exacerbations lead to recurrent hospitalizations and visits. The disease by itself and the burden of the treatments may affect children quality of life (QoL). The aim of this study is to assess health related QoL in these children.

Methods: The study is on-going. We are prospectively including patients aged 1 month to 18 years diagnosed with ILD of known or unknown aetiology. We use a validated paediatric QoL questionnaire (PedsQL™ 4.0 Generic Core Scale) that is a generic QoL scale adapted to the age of the patient. It is divided into 3 parts: physical, emotional, social and school functioning. PedsQL is filled in by parents as well as children over 8 years old. Clinical data are collected using the national internet-linked based database for paediatric interstitial lung diseases (RespiRare). The mean QoL of the patients will be compared to the published data on mean QoL in healthy population.

Preliminary results: We already included 63 children recruited in 13 French paediatric centres. As 50 patients were needed to reach significance, the study should be able to reach the main objective. Only preliminary global QoL scores are available at this stage, and seem to be significantly lower than the mean QoL observed in a healthy population.

Conclusion: QoL seem to be highly impaired in children with ILD. Predictive clinical factors of a lower QoL score have to be determined. Families’ QoL should be a major concern, as they are the mains actors in the management of the disease.

A CHILD WITH DIGITAL CLUBBING

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We report on a case of a boy born at term from normal pregnancy. No respiratory distress or oxygen requirement at birth. At 18 months he was hospitalised with dyspnoea and cyanosis associated with fever. During the admission he presented few episodes of desaturation. Chest X-ray was referred to be normal. ECG showed incomplete right branch blockage. He was discharged, but in the following months he had several episodes of cyanosis with cough and also presented failure to thrive. At the age of 4 the situation seemed to be improved; however, during a normal paediatric follow up visit digital clubbing was noted in both hands.
Diffuse lung diseases (DLD) of infancy and children are heterogenous spectrum of lung disorders. There has been done an important progress in the approach to childhood interstitial lung diseases (chILD). It was recognized that interstitial lung disease (ILD) in infants is often distinct from the diseases occurring in older children and adults. Diagnosis is very challenging because ILD in children are rare disorders and presenting symptoms could often overlap with other common respiratory disorders. Diagnostic utility of lung biopsy in chILD syndrome were proved in several published studies. However, the potential benefits of lung biopsy must outweigh the risks in most children with acute respiratory deterioration, prolonged lung disease, or unresolved lung disease. Histopathologically, pattern-based approach to diagnosis of DLD of infancy with the aid of appropriate multidisciplinary input, including clinical and radiological expertise may lead to an accurate appropriate diagnoses. Moreover, recent studies have better defined the characteristics and molecular understanding of several different forms of children ILD. Histopathological pattern identification scheme of chILD was proposed and there is an evidence that morphology of ILD in children over 2 years could be similar to patterns seen in adult patients excluding UIP pattern which is very rare and only few cases namely with ABCA3 deficiency were described in the literature. Specific age-related DLD of infancy includes different patterns of alveolar changes, septa thickening, vascular lesions, surfactant protein deficiencies, and feet. For this reason he came to our attention and was then admitted to the ward. Blood tests (including α1-antitrypsin and ACE levels) and sweat test were normal. Genetic analysis for cystic fibrosis was negative. His chest X-ray showed an increased interstitial component. The chest CT scan showed atelectasis with bronchogram in the superior paracardiac region and diffused increased opacity with interstitial and alveolar involvement in the right upper lobe. Chest MRI showed no vascular malformations. A bronchoscopy was also performed showing secretions in the right upper lobe and Nelson’s lobe, and inflammation of the right middle lobe. Bronchoalveolar lavage gave negative microbiology results as well as negative cytology (including PAS staining). Considering his clinical and radiological features he underwent a pulmonary biopsy, which showed intra-alveolar cholesterol granulomas. The genetic analysis for SFTP-C gene showed a nucleotidic substitution 1876 T-C, responsible for the aminoacidic substitution 173T in the expressed protein reported to be associated with interstitial lung disease. This boy is now 15 years old and is stable. Written consent was obtained from his parents to report his clinical information. To our knowledge only three previous publications reported intra-alveolar cholesterol granulomas in children.

**LUNG ULTRASOUND – A RELIABLE TOOL IN ILD ASSESSMENT**

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**Objective:** This study evaluated the sonographic features of interstitial syndrome and compare them with the findings of chest high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs).

**Materials & methods:** High-resolution computed tomography (HRCT) is the method of choice in assessment of the extent and the pattern of pulmonary fibrosis. Sub-pleural reticulation in a basal predominance with honeycombing and bronchiectasis are HRCT findings of IPF. Lung sonography is a non-invasive, non-radiation technique, very sensitive to detect any alterations in the lung parenchymal density. Diffuse sub-pleural abnormalities as those occur in IPF are characterized by the presence of multiple B-lines and thickening of pleura line.

Twenty three patients with a multidisciplinary consensus IPF diagnosis underwent lung ultrasound (LUS) to assess the fibrotic index based on the evidence of B-lines and the characterization of the pleura line. These findings were compared with HRCT features (ground glass, reticulation and honey-combing) and with PFT: forced vital capacity (FVC), total lung capacity (TLC), diffusion capacity for carbon monoxide (DLCO).

**Results:** All patients had diffuse bilateral B-lines. The main distance between two adjacent B lines was 6.7 mm suggestive for a predominant reticular pattern. Number of total B-lines correlated directly with the severity of fibrosis on HRCT and inverse correlated with FVC, DLCO. A fragmented, irregular, blurred pleura line are the features of severe fibrosis.

**Conclusion:** ultrasound fibrotic index is correlated with HRCT fibrotic index, when the severity of the IPF is in counted. Therefore LUS is a non-radiation imagine technique reliable in IPF screening and monitoring.

**HISTOLOGICAL DIAGNOSIS OF chILD**

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Diffuse lung diseases (DLD) of infancy and children are heterogenous spectrum of lung disorders. There has been done an important progress in the approach to childhood interstitial lung diseases (chILD). It was recognized that interstitial lung disease (ILD) in infants is often distinct from the diseases occurring in older children and adults. Diagnosis is very challenging because ILD in children are rare disorders and presenting symptoms could often overlap with other common respiratory disorders. Diagnostic utility of lung biopsy in chILD syndrome were proved in several published studies. However, the potential benefits of lung biopsy must outweigh the risks in most children with acute respiratory deterioration, prolonged lung disease, or unresolved lung disease. Histopathologically,
neuroendocrine cell hyperplasia of infancy and other. Careful investigation of biopitic samples by specialized pathologist using appropriate spectrum of histochemical and immunohistochemical method is the most crucial step for final histopathological diagnostic report. In all cases, however, ultimate diagnosis is necessarily based on a multidisciplinary approach, including clinical, radiological and histopathological input.

**OFF LABEL TREATMENT OF cHILD**

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No randomized controlled trial about the treatment of interstitial lung diseases (ILD) in children have been performed. Current treatment is based only in the reports of individual clinical cases or small series and it is very much dependent on the treating physician’s experience.

A small number of drugs have been used off-label and can be considered for empiric treatment of some of the ILD in children. Systemic steroids are the most frequently used drugs. Other drugs often used are hydroxychloroquine and azithromycin.

Hydroxychloroquine have been used in something less than 100 hundred case report or small series of children with ILD, sometimes alone but most often in combination with other drugs. The effect of hydroxychloroquine in these patients has been variable with some of them improving and some not responding. It is currently not possible to predict with patient will benefit from this treatment. In addition to having anti-inflammatory properties, hydroxychloroquine has been shown to cause inhibition of the intracellular processing of the precursor of surfactant protein C. A phase IIa clinical trial is currently on development to assess its effect in surfactant dysfunction disorders and histologically related diseases.

Macrolides have anti-inflammatory and immunomodulatory actions. A beneficial effect has been described in some children with ABCA3 or surfactant protein C mutations.

In children with ILD ventilated or close to ventilation, both drugs have been used together with steroids. In a Delphi study no preference was established about using first as second line drug either hydroxychloroquine or azithromycin in children with ILD not ventilated.

Antifibrotic therapies, pirfenidone and nintedanib, used for the treatment of idiopathic pulmonary fibrosis, in adults could also have a potential role in the treatment of certain children, such as those with fibrosis resulting from surfactant mutations.

**SURFACTANT DISORDERS**

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Interstitial lung diseases (ILD) comprise a large and heterogeneous spectrum of rare and severe disorders. In the recent years, dramatic progresses have been done in ILD etiological diagnosis, leading to identify a monogenic cause of ILD in up to 20% of the cases. Whereas telomerase complex genes mutations are mostly involved in adult ILD, surfactant genes mutations are commonly related to children ILD.

The surfactant proteins (SP)-A1, SPA2, SPB, SPC, SPD are encoded by SFTPA1, SFTPA2, SFTPB, SFTPC, SFTPD respectively. SP-B deficiency caused by bi-allelic SFTPB mutations are described in neonates with fatal respiratory failure. SFTPC mutations are mainly heterozygous and their phenotypes are highly heterogeneous from asymptomatic carriers to neonatal respiratory failure and children and adults presenting with progressive ILD. Their transporter, ATP-binding cassette family A member 3 (ABCA3) are also associated with recessive severe neonatal ILD, but milder forms have been reported with patients diagnosed in late childhood and adulthood. Heterozygous ABCA3 mutations seem overrepresented in patients with neonatal respiratory failure, and in patients with ILD but the clinical significance of such observations remains to be elucidated. NKX2-1 plays a crucial role in SP-B and SP-C transcription. Its heterozygous mutations lead to a specific entity called brain-lung-thyroid syndrome. SP-A1 and SP-A2 are key factors of lung local immunity and surfactant homeostasis. SFTPA1 and SFTPA2 mutations have been involved in adult cases of ILD and lung cancers. Recently, pediatric cases were also described.

In the light of current studies, surfactant system genes are involved in ILD at any age. Their analysis seems therefore essential to the ILD etiological diagnosis with no regard to the age of the patient. This systematic approach together with a precise phenotypic description will provide new insights in ILD knowledge.
Inherited surfactant metabolism disorders represent 10 to 15% of respiratory syndrome associated with alveolar-interstitial lung disease in children. NKX2-1 (NK2 homeobox 1) is a critical regulator of transcription for the surfactant protein (SP)-A, B, C and D genes (SFTPA, B, C and D respectively) and ABCA-3. NKX2-1 is also expressed in the thyroid and the nervous system. In humans, NKX2-1 mutations have been reported in patients with respiratory disease usually in association with neurological symptoms and thyroid dysfunction (Brain-Lung-Thyroid syndrome) or, more recently, isolated.

The aim of this work is to improve our understanding of NKX2-1 mutations deleterious effect, which produces atypical phenotype of the Brain-Lung-Thyroid syndrome.

We studied two mutations of NKX2-1: DUP found in a patient with brain-lung-thyroid syndrome and DEL found in a family with isolated respiratory disease. The mutations were introduced by site-directed mutagenesis into the expression vector containing the wild-type cDNA of NKX2-1. Two cell lines (A549 and Nthy) were transfected.

The protein obtained from the wild-type and mutated NKX2-1 plasmids were analyzed by Western blot and subcellular localization was assessed by confocal microscopy. Transcriptional regulation studies of SFTPA, SFTPB, SFTPC, ABCA3 and thyroglobulin promoters were performed using these promoter luciferase reporter plasmids co-transfected with either mock vector, wild-type or mutated NKX2-1.

The two mutants produce a nonsense protein of 408, rather than 371, amino acids, with a loss of homeodomain. The mutant proteins were localized in both cytoplasm and nucleus, but with a different aspect than the wild-type protein. The DUP protein results in a loss of transcriptional activity on SFTPA, SFTPB, SFTPC and ABCA3 promoters. The DEL protein was able to activate thyroglobulin promoter but not surfactant promoters.

In conclusion, our results are in accordance with patient's phenotype. Ongoing studies will pinpoint the mechanism of action and elucidate phenotype/genotype correlation of NKX2-1 mutations responsible for pulmonary phenotype.
Visceral calcification is a common complication in long-term chronic renal failure. Clinical manifestations are usually minimal and chest radiography is non-specific, thus it is often underdiagnosed. The clinical course is slow although disease progression has been reported in a few cases. Treatments are debated and limited to symptomatic patients.

We report the case of a 12 year-old hemodialyzed girl, affected by Kibuki syndrome, with pulmonary opacities detected on chest radiography during pre-transplant analysis. After a cycle of antibiotics for suspected infection, the findings were unchanged and a computed tomography (CT) was done. A Bubble test and a perfusion pulmonary scintigraphy excluded arteriovenous malformation. An infective counselling was required in order to rule out difficult to treat lung infections (e.g. mycobacterium). Pulmonary agobiopsy was performed and histology, special stainings and molecular analysis excluded bacterial/viral infections and demonstrated a prevalent interstitial involvement with diffuse calcium deposition, mainly located in the alveolar epithelial basal membrane.

The diagnosis of metastatic pulmonary calcification (MPC) was achieved and the patient was finally included in kidney transplant waiting list. MPC is an interstitial process characterized by deposition of calcium in the lung, mainly in the alveolar epithelial membrane and less commonly in the bronchial and capillary walls. Fibrous septal widening and few lymphocytes are usually associated. High resolution CT (HRCT) is sensitive in detecting small calcifications. Despite a high incidence in end-stage renal disease, the diagnosis remains challenging.

MPC should be suspected in end-stage renal disease with unexplained radiological changes and respiratory symptoms in order to program a correct diagnostic approach with a HRCT, avoiding more invasive investigations in young compromised patients.

Interstitial lung disease (ILD) is a rare heterogeneous disorder of various etiology. In children it is much less prevalent than in adults and often has better response to treatment and even better prognosis. Unfortunately, as the onset of clinical symptoms is often rather slow and gradual, it may remain unnoticed for quite a long time and the diagnosis substantially delayed. The suspicion triggering the diagnostic work-up is mostly based on respiratory distress with hypoxemia that has no other explanation. This may be seen even in the neonatal period in a term baby suffering from some of the pathologies typical for this age, such as surfactant protein disorders. In children presenting with ILD within the first two years of age the leading symptoms may be tachypnea and failure to thrive. In older children, the first symptoms may be induced by exercise.

The differential diagnostic work-up starts always with detailed history including family history and assessment of environmental risks. Laboratory analysis follows with blood count, differential count and immunology tests to exclude immunodeficiency or autoimmune disease. Antibodies to environmental antigens may be present in hypersensitivity pneumonitis. Imaging, mainly high-resolution computed tomography (HRCT) performed in a centre with experience in chILD, may give clue to diagnosis based on the distribution and pattern of the interstitial pathology. Lung function testing in co-operative children with measurement of lung volumes, airway patency and diffusing capacity is mandatory and may also help to assess severity of the disease. Detailed cardiac investigation with echocardiography should exclude congenital heart defect and pulmonary hypertension.

Last step in the diagnostic algorithm are invasive tests, such as bronchoscopy with bronchoalveolar lavage and bronchial biopsy and parenchymal lung biopsy, often now performed by video-assisted thoracoscopy (VATS). Lung biopsy should be always perfectly prepared to make sure that all necessary staining and analyses will be performed and the material will be handled and transferred to the laboratory accordingly.
INTERSTITIAL LUNG DISEASES IN CHILDREN – SINGLE CENTER EXPERIENCES
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Background: Childhood interstitial lung disease (chILD) represents a highly heterogeneous group of rare disorders associated with significant morbidity and mortality. The etiology of chILD is multifactorial, in many cases it remains unknown. The prognosis is depending upon the specific diagnosis.

Aims and objectives: The objective of this study was to determine age at diagnosis and investigations in a group of patients with chILD younger than 18 yrs treated in the University Children’s Hospital in Ljubljana.

Methods: We conducted a retrospective review of children younger than 18 years. Relevant data from medical records were entered into an Excel database. We were following the North American classification system.

Results: We have identified 31 patients with chILD, 14 with »primary« ILD and 17 with disorders related to systemic diseases. At present data for 14 children with »primary« ILD are available for further analysis. There were 5 girls, mean age at diagnosis 25.5 months, SD 27.3. Most patients had tachypnea at diagnosis (9), failure to thrive (7), rales (11), hypoxemia (6). All patients had a chest X-ray performed, 11 ECHO and lung function measurement. In 12 BAL was performed and in the majority (13) HRCT. Open lung biopsy was done in 12 patients.

The specific diagnoses were as follows: NEHI 5, follicular bronchiolitis 1, undefined ILD 1, giant cell pneumonia 1, postinfectious BO 3, aspiration syndrome 1, eosinophilic pneumonia 1, lymphatic disorder 1. The outcome was good, with no mortality in the study population during observational period.

Conclusions: Although rare chILD do occur and thorough investigations are needed to establish a diagnosis. There is an urgent need to establish international chILD network to unify diagnostic and therapeutic opportunities for all children.

RECURRENT WHEEZING IN CHILDREN WITH HISTORY OF BRONCHOPULMONARY DYSPLASIA
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Aim: To evaluate recurrent wheezing among children with history of bronchopulmonary dysplasia (BPD).

Material and method: A 2 year retrospective study was performed in Paediatric Clinic of Constanta, Romania, including children previously diagnosed with long term chronic lung disease developed in neonatal period. The inclusion criteria consisted in previous neonatal therapy with oxygen, mechanical ventilation, surfactant administration, under BPD suspicion. Demographic data, gestational age, birth weight, clinical, radiological and therapeutic data were assessed among 22 children with ages from 2 months to 2 years – mostly boys. Clinical evolution of recurrent wheezing was followed-up and respiratory exacerbations were evaluated, taking into account the number and length of admissions, and the severity of exacerbation.

Results: Gestational age was between 25–30 weeks (8 cases), and 30–34 weeks (14 cases), with birth weight from extremely low birth weight (ELBW) (8 cases), to very low (VLBW) (9 cases), and low birth weight (5 cases). The severity of neonatal respiratory episodes was related with idiopathic respiratory distress syndrome and prolonged administered mechanical ventilation. Admissions varied from 2 to 6. Exacerbations were noticed in 17 cases with medium (14) to severe (3) respiratory failure. Recurrent wheezing appeared in 63.63% cases, more frequently in those infants, with shorter gestational age, ELBW or VLBW, who required ≥3 hospital admissions. Diagnosis of respiratory bronchiolitis interstitial lung disease was inconclusive. Mortality rate was 13.63%. All deaths had in common, severe respiratory failure, impaired neurological status and prolonged mechanical ventilation support.

Conclusions: Children with long term chronic lung disease developed in neonatal period and suspected BPD have a high risk of mortality. Recurrent wheezing is frequently reported in premature infants with ELBW or VLBW and BPD history.

INTERNATIONAL PERSPECTIVES ON chILD
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International efforts to improve outcomes for chILD are underway in different regions including North America (chILD Foundation US & chILDRN), Europe (chILD-EU), Britain (BPOLD), South America, Australia and New Zealand (chILDRANZ).

Australia is unique given disparate and remote populations. A recent study conservatively estimated the prevalence of chILD in Australasia at 1.5 per million. Although chILD is rare the health care impact of individuals with chILD has been demonstrated to be large. Unlike
Europe and the USA, the diagnosis and management of chILD are not standardised. Challenges for chILD include a general lack of funding, state-centred approaches and lack of national plan.

The Young Lungs group, comprised of a handful of paediatric respiratory physicians and consumer advocates was established in 2013 under the auspices of the Lung Foundation Australia (http://lungfoundation.com.au). The Young Lungs group launched support for families of children with chILD in the form of 1) a website that provides basic information on chILD and links to potentially useful websites and groups, and 2) a Young Lungs Parent Advisory Committee to raise awareness and advocate for chILD and help with fundraising.

**LUNG TRANSPLANTATION**

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Lung transplantation (Ltx) is an established treatment option for children and adolescents suffering from end stage lung diseases refractory to therapy. The primary aims, to prolong life and to improve quality of life, are reached in most cases. Cystic fibrosis is still the main indication for Ltx followed by pulmonary hypertension. It seems that the number of CF-patients who undergo Ltx decreased during the last years while other indications increased. Despite improvements in surgical techniques and perioperative care, long term survival remains significantly lower compared to other solid organ transplant outcomes. Infections and chronic lung allograft dysfunction (CLAD) are still the leading causes of death. Although these entities have not yet been systematically studied in the pediatric population, CLAD is associated with poor adherence which is especially often observed in adolescent patients and thus is a special challenge in pediatric care.

Due to limited numbers of patients, prospective controlled studies in pediatric lung transplant recipients are still missing even if they are urgently needed to improve patient care and long term outcome.

**INSTALLATION OF A MULTIDISCIPLINARY TEAM (MDT) REVIEW BOARD FOR CHILDREN’S INTERSTITIAL LUNG DISEASE (ILD)**

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**Introduction:** MDTs are standard in adult ILD, however there is little experience in children reviewing a case and involving a clinician, radiologist, geneticist and pathologist. Technically, a web-based peer review system was installed on the management platform for children’s interstitial lung disease.

**Aims and objectives:** To implement a MDT case review as part of the European management platform for ILD and to analyse the peer review process of all included patients.

**Methods:** Between 12-2013 and 11-2016 575 cases were evaluated with respect to 1) sufficiency of data for peer review, 2) number of peer reviews performed and 3) change of the given initial diagnosis.

A peer support platform for physicians who treat chILD was formed in order to share and develop expertise in chILD, to nurture interest for future research in chILD, and to generate and sustain enthusiasm for chILD amongst physicians. The peer support platform is well attended by increasing numbers of respiratory physicians as well as geneticists, histopathologists, radiologists, rheumatologists and immunologists. Peer support has resulted in change in clinical management for virtually all clinical cases discussed.

A major challenge has been to establish a national data registry for chILD. A recent assessment of the feasibility of a web-based registry for multiple orphan lung diseases was limited by under-reporting. International collaboration is needed if there is to be major advances in the field.
Conclusion: We have installed an international multidisciplinary web-linked tool for peer review of chILD-cases in the European management platform. Complex cases were rapidly and comprehensively reviewed. Diagnoses were confirmed to a large extent and about 13% were revised.

ROMANIAN EXPERIENCE IN DIAGNOSING INTERSTITIAL LUNG DISEASES (REGIS)

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The aim of the research was to determine the spectrum of Interstitial Lung Diseases (ILDs) in Romania. Study design consisted in a 3-year prospective study of diagnosing Interstitial Lung Diseases (ILD), supported by the ILD Working Group within the Romanian Society of Pneumology, from 2014 to 2016.

Material and method: A National Register was developed as an electronic data base of 104 patients, mean aged 63 years. ILD were diagnosed and reported, in the last 3 years, by physicians from 4 Romanian centers. Methods consisted in chest X-ray and HRCT scan, spirometry and DLCO (80.77%), broncho-alveolar lavage, lung biopsy, biomarkers (angiotensin-converting enzyme), and autoantibodies.

Results: Identified ILD were classified into idiopathic pulmonary fibrosis (IPF) diagnosed among 26 patients (25%), sarcoïdosis (n=25; 24.04%), collagen disease with interstitial lung involvement (associated ILD) (n=13; 12.5%), hypersensitivity pneumonitis (n=12; 11.54%), eosinophilic pneumonia (n=3; 2.88%). NSIP and undefined ILD were noticed among each 7 patients (6.73%). Only 2 cases of cryptogenic organizing pneumonia, polyarthritis granulomatosis and drug induced ILD and one single case of rare diseases as bronchiolitis related ILD, lymphangioeleomlyomatosis, Langerhans histiocytosis, and alveolar proteinosis were reported. Female gender was prevalent among NSIP (85.71%) and hypersensitivity pneumonitis (50%) versus male gender in IPF cases (69.23%) and sarcoidosis (56%). Restrictive ventilatory syndrome has an increased severity, expressed by a mean FVC of 60.26% predicted and mean DLCO 42.89% predicted. HRCT scan was performed in majority of cases (99.04%) facilitating UIP diagnosis. Lung biopsy was performed in 4 patients (15.38%). Smoking was associated in 65.38% ILD cases but all 24 sarcoidosis patients were nonsmokers.

Conclusions: Romanian experience is limited because ILDs are generally under estimated and/or reported. Delayed diagnosis is a characteristics, excepting sarcoidosis.

PULMONARY INTERSTITIAL GLYCOGENOSIS ASSOCIATED WITH ALVEOLAR GROWTH ABNORMALITY: LONG-TERM FOLLOW-UP

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Introduction: Pulmonary interstitial glycoegenosis (PIG) is a rare interstitial lung disease with an unknown pathophysiology that typically affects infants. PIG is characterized by an increase in the number of interstitial mesenchymal cells in the absence of inflammation and at the expense of immature cells, presenting as enhanced cytoplasmic glycogen and sometimes considered to represent the expression of an underlying lung development disorder.

Methods: This study describes the clinical, radiological, and functional outcome (median 12 years) of nine infants diagnosed with PIG associated with alveolar simplification in the absence of other diseases.

Results: All patients presented with tachypnea. Additionally, seven patients had respiratory distress and hypoxemia. Abnormalities on pulmonary high-resolution computed tomography with a pattern of ground-glass opacity, septal thickening, and air trapping were observed in all individuals, with images suggesting abnormal alveolar growth (parenchymal bands and architectural distortion). All lung biopsies showed alveolar simplification associated with an increased number of interstitial cells, which appeared as accumulated cytoplasmic glycogen. All patients were treated with corticosteroids or hydroxychloroquine. This therapy aimed to produce a favorable clinical evolution with the resolution of symptoms. Despite good clinical outcome, we continued to observe significant radiological alterations and sequelae in pulmonary function on the long-term follow up.
**Conclusion:** The presence of alveolar simplification, observed in all patients studied in the absence of another associated pathology, supports the hypothesis that PIG is a phenomenon caused by abnormal intrauterine alveolar development. This feature, marked mostly by major radiographic abnormalities and functional consequences, influences the clinical outcome of patients with this disease.

**TBX4 MUTATIONS DETERMINE HETEROGENEOUS INTERSTITIAL LUNG DISEASE**

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**Introduction:** T-box gene 4 (TBX4) is expressed during embryonic development and is essential for lung development. Heterozygous mutations in TBX4 have been associated with dysmorphic features and childhood-onset pulmonary hypertension other than diffuse lung disorder. However, literature is very scarce and TBX4-related clinical disease spectrum is still uncertain.

**Methods:** patients with either known family history positive for TBX4 genetic mutation or diffuse lung disease associated with skeletal malformations were genetically screened. Clinical history and phenotypic features were studied.

**Results:** Two patients (NM and CL), both females and of similar age, were identified with TBX4 heterozygous mutation (c.652G>C and c.792-1G>C respectively). Immunodeficiency and the major pulmonary disease such as: CF, PCD, surfactant disorders were excluded. Pulmonary hypertension was not found. However, the respiratory phenotypic presentation was significantly different.

NM, without respiratory problems at birth, developed soon a restrictive chronic respiratory failure, associated with multiple skeletal deformities. Clinical history was positive for recurrent severe respiratory exacerbations needing mechanical ventilation and persistent desaturation with 6 min walking test. Lung images showed an interstitial damage with diffuse nodules, three in bud, and parenchymal distortion (Fig.1A). Lung biopsy showed pulmonary fibrosis.

CL, presented monolateral spontaneous pneumothorax at birth. The mother is affected by bronchiectasis, pulmonary hypertension, chronic respiratory insufficiency and skeletal anomalies. At 7 months CL presented bronchiolitis followed by recurrent wheezing and pneumonia infections treated at home. CT excluded significant interstitial lung damage but only revealed an expiratory air trapping into the left lower lobe caused by bronchial collapse (Fig.1B). CL presents toes fingers malformations.

**Conclusions:** TBX4 gene mutation has been proven to be important for lung development and has been associated with pulmonary hypertension. However, our experience interestingly suggests a variable expression with heterogenous interstitial lung involvement. Larger studies, as result of international collaboration, are needed.

**Figure 1**
Interstitial lung diseases (ILDs) are characterized pathogenetically usually by mix of alveolar lesions, inflammation and fibroproliferative healing. Prognosis of ILDs is based on type of combination of these pathologic patterns. In adult age the ILDs have greater tendency to fibroproliferative healing with bad prognosis and one of the typical representatives of this is idiopathic pulmonary fibrosis (IPF). Interstitial lung diseases of childhood (chILDs) are rare lung diseases, which with exclusion of genetically based severe disorders of surfactant proteins, have usually better prognosis than most of adult ILDs. Less severe forms of genetic mutations of surfactant genes can be seen as genetic background in both chILDs and adult ILDs. The chILDs are rather age specific group of ILDs characterized by mainly inflammatory processes, fibroproliferation is not usual. However they can transfer to adult age and can change their behaviour to definite fibrotic processes. The adult respiratory physicians should take neat care for these patients on transition and demand and seek full and complex information on chILDs from referring pediatric pulmonary specialist including radiologic and histopathologic data. The follow-up mode, preventive measures and treatment considerations including lung transplantation should be adjusted to the disease course (lung function decline, radiologic progression), exposure (inducers in HP, inorganic drugs, smoking), and comorbidities. The respiratory physicians-ILD experts- should be aware of chILDs and whilst these are rare diseases demanding specialized care, a collaborating network of centers for both chILDs and adult ILDs should be created.

**PREDICTIVE FACTORS OF DRUG TREATMENT IN CHILDREN WITH ILD: FIRST INSIGHTS FROM THE chILD-EU REGISTRY**

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**Objectives:** Childhood Interstitial lung disease (chILD) is an umbrella term for more than 200 rare disease entities for which evidence on medical treatment regimens, healthcare utilization and clinical outcomes are broadly lacking. We therefore aimed to evaluate current drug utilization to benchmark European practice.

**Methods:** The ongoing chILD-EU registry was initiated in 2012 and currently includes children with ILD from 7 European countries. Next to baseline characteristics, the 5 most frequent drug treatments were analysed via logistic regression models adjusting for sex, age, country, disease severity and diagnosis.

**Results:** Among the 336 patients (56.3% male) median age was 3.9 years (interquartile range 0.8, 10.8) with a median disease severity of 3 on the FAN 5 point scale. 282 (83.9%) patients had final diagnosis with 72 different diseases on subcategory level. Within the 3 months prior to baseline or at baseline all patients received at least one kind drug treatment, thereof 35.1% steroids systemic, 27.1% long term macrolide, 22.9% steroids inhaled, 22.9 antibiotics, 20.8% hydroxychloroquine, 8.3% immunosuppressive conventional, 3.0% calcineurin inhibitors, and 2.1% biologicals. Regression models showed mostly significant influence of diagnosis (reference A4 – surfactant disorder, sign odds ratio (OR) 0.15 – 15.5) and a relevant influence of disease severity (reference asymptomatic, sign OR 3.9 - 20.8) on treatment. Females obtained less frequent inhaled steroids (OR 0.4). Country specific influences on treatment regime were seen in long term macrolide (reference Germany, Poland OR 0.16, UK OR 2.5), hydroxychloroquine (UK OR 3.6), and antibiotics (UK OR 0.3).

**Conclusions:** Corticosteroids are the most frequently used treatments. Longitudinal analysis of chILD-EU is needed to demonstrate whether corticosteroids or other medicaments can be linked to mortality and quality of life outcomes.

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Childhood interstitial lung disease (CILD) is a rare pulmonary condition mostly presented in the neonatal period as bronchopulmonary dysplasia or early feature of cystic fibrosis. However, the late diagnosis in childhood or even adolescent period is even likely to happen. Delayed diagnosis due to non-specific or mild symptoms for long time before deterioration often lead to high mortality rate. As well as clinical presentations and symptoms the causes are variable and underlied with some more frequent chronic conditions. Suspicion should be made upon pulmonary and extrapulmonary symptoms: cough, increased respiratory rate, exercise intolerance, hypoxemia and failure to thrive, loss of weight. Chest X-ray and CT scan should be the first step in diagnosis. Nowadays, the investigation for genetic mutations has been informative for surfactant malproduction. Classification of ILD should be determined by progression of respiratory symptoms, biopsy result and genetic confirmation when possible. The accurate diagnosis has been made in close collaboration of pediatric pulmonologist, radiologist, pathologist. The newly proposed differentiation of broad spectrum of CILD is tightly related to pathology findings (bronchoalveolar secretion or lung tissue specimens). Therefore, it should give the best opportunity to distinguish the problems of lung development (mostly hypoplasia or prenatal and early postnatal growth abnormalities) and surfactant deficiency which is genetically determined. The proper diagnosis lead to adequate treatment particularly in early childhood and for the first group of patients who will be transferred to adult physicians later in life.

The cure between these groups is substantially different such as outcome and life prognosis. In our practise, rare cases of true interstitial disease (pulmonary fibrosis with autoimmune background, various congenital genetic defects) has very poor clinical outcome mainly due to delayed diagnosis. So far, the better approach from the early stage the better outcome, should be the main point of our COST Action.