



ZDRAŽENJE PNEVMOLOGOV  
SLOVENIJE  
SLOVENIAN RESPIRATORV  
SOCIETY

## Zbornik povzetkov: Book of Abstracts

**4th MEETING OF THREE  
RESPIRATORY SOCIETIES:**

**Slovenia, Croatia,  
Hungary**

Bled, Slovenia, May 22-23, 2015

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**PROGRAM 4th MEETING OF THREE RESPIRATORY SOCIETIES: Slovenia, Croatia, Hungary 2015**

<b>Friday 22 May</b>	<b>Workshops (parallel, 45 minutes)</b>	<b>9:00-11:00</b>
Matjaž Fležar Aleš Rozman Izidor Kern, Katarina Osolnik, Igor Požek	Difficult pulmonary function test results Bronchology workshop Interstitial lung diseases	
	<b>Lunch 12:00</b>	
<b>Respiratory infections</b>	<b>Chairs: Katarina Osolnik, Zoltán Balikó, Zinka Matković</b>	<b>13:00 -15:00</b>
Katarina Osolnik Zoltán Balikó Zinka Matković Natasa Fajfar, Denise O'Sullivan, Jernej Pavšic, Jim Huggett, Mojca Milavec, Viktorija Tomic Desa Nastasijević Borovac, Tatjana Pejčić <sup>1</sup> , Ivana Stanković, Tatjana Rađenović Petković, Biljana Vrbić, Ivanka Đorđević Dane Luznik, Viktorija Tomic, Mitja Kosnik Miklós Balázs Illés, M.B. Illés, I. Ruzsics, D. Sipos, B. Kovács, Z. Péterfi, V. Sárosi Rodman J, Praprotnik M, Mrvič T, Krivec U	Atypical pathogens in CAP Highlight of CAP. Antibiotic resistance in Hungary Chronic bronchial infection in COPD Evaluation of the efficacy of two DNA extraction methods from sputum samples in COPD patients The values of D-dimer in hospitalized patients with Community-acquired pneumonia according to the presence of comorbidities The frequency of <i>Streptococcus pneumoniae</i> in three distinctive groups of patients Q-fever outbreak in Baranya County Extrapulmonary manifestations of Mycoplasma pneumoniae infections: our experience in 2014	20' 20' 20' 10' 10' 10' 10' 10'
Satelite symposium Bayer		15:00
	<b>Coffee Break 15:20</b>	
<b>Hypoventilation syndrome</b>	<b>Chairs: Irena Šarc, György Losonczy, Hrvoje Puretić</b>	<b>16:00-18:00</b>
Irena Šarc Hrvoje Puretić András Bikov Kristina Ziherl Lea Leonardis Kristina Ziherl Hrvoje Puretić	NIV in stable COPD Obesity hypoventilation syndrome - positive airway pressure therapy The role of airway inflammation in the pathophysiology of obstructive sleep apnoea Survival in OHS patients Chronic respiratory failure in neuromuscular disorder Central sleep apnea – to treat or not to treat Reliability of the Epworth sleepiness scale and Berlin questionnaire in detecting sleep apnea patients	20' 20' 20' 10' 10' 10' 10'
Satelite symposium Chiesi Satelite symposium Novartis		18:00 20'
<b>Poster session with wine and snack</b>		<b>18:40</b>
Diner		20:00

**Saturday 23 May**

<b>Obstructive lung diseases</b>	<b>Chairs: Sabina Škrgat, Attila Somfay, Davor Plavec</b>	<b>9:00 - 11:00</b>
Sabina Škrgat	Biologic therapy in asthma	20'
Attila Somfay	Is there paradigm shift in COPD treatment?	20'
Davor Plavec	Asthma phenotypes, endotypes and network medicine	20'
Matjaž Turel	Lung transplantation in COPD	10'
Zsolt Komlósi	Innate lymphoid cells: novel players of the immune system, and their role in airway diseases	10'
Zsuzsa Csoma	Phenotypes of severe asthma	10'
Jernej Sitar	A patient with HIV infection and severe asthma	10'
János Varga	Functional and quality of life markers in pulmonary rehabilitation	10'
Satelite symposium Glaxo Satelite symposium Boehringer Ingelheim: The treatment roadmap for IPF	Veronika Mueller, dr. med. (Hungary): Idiopathic pulmonary fibrosis: terra incognita Katarina Osolnik, dr. med. (Slovenia): IPF therapy: Where we stand now?	11:00 20' 20'
<b>Coffee Break</b>		<b>20'</b>
<b>Rare lung diseases</b>	<b>Chairs: Marjeta Terčelj, Adrien Halász, Jasna Tekavec - Trkanjec</b>	<b>12:00-14:00</b>
Marjeta Terčelj	Introduction	10'
Borut Peterlin	Rare diseases in Slovenia and new diagnostic possibilities	20'
CYSTIC FIBROSIS		
Adrien Halász	Cystic fibrosis	20'
Marina Praprotnik	Treatment of early <i>Pseudomonas aeruginosa</i> infection in children with cystic fibrosis	10'
Matjaž Homšak	Shared care in children with cysic fibrosis	10'
PAH		
Barbara Salobir	Pulmonary arterial hypertension	20'
Janez Toplišek	Echocardiography as a screening tool for diagnosis of pulmonary arterial hypertension, what pulmonologists should know about that in modern era	10'
Vojka Gorjup	Right heart catheterization as a confirming tool for diagnosis of pulmonary arterial hypertension, what pulmonologists should know about that in modern era	10'
Katja Prokšelj	Eseimenger syndrome in adults: what pulmonogists should know about that	10'
MISCELLANEOUS		
Jasna Tekavec - Trkanjec	Dendriform pulmonary ossification	20'
Tatjana Peroš-Golubić	Smoking-related interstitial lung diseases	10'
Uroš Krivec	Interesting pediatric bronchology cases	10'

**Farewell snack 14:40**

**Poster session (Friday 18:40)**

**Chairs: Sabina Skrgat, Attila Somfay, Davor Plavec**

Zoltán Rózsavölgyi, K. Ugocsai	„Asthma phenotypes”?
V.Mircevska, M.Mladenov, S.Mircevska, I.Lazarevska, I.Gjorgoski	Concentration of specific IgE in serum in childhood
Anton Lopert	Polymorphism rs9910408 in TBX21 gene is a predictor of response to inhaled corticosteroids in adult asthmatics
Jovanovska Janeva E	How combined therapy ICS/LABA plus Montelukast affects on the inflammation in patients with severe asthma
Petra Krt, Irena Šarc	Clinical practice of non-invasive ventilation use in acute exacerbations of chronic obstructive pulmonary disease with respiratory acidosis
Petrova G. <sup>1</sup> , Miteva D. <sup>1</sup> , Lazova S. <sup>1</sup> , Andonova S <sup>2</sup> , Zafirovski L <sup>3</sup> , Matovska L <sup>4</sup> , Savov A. <sup>2</sup> , Perenovska P. <sup>1</sup>	ADAM33 single nucleotide polymorphisms and the asthma phenotypes in children
P.Perenovska <sup>1</sup> , G.Petrova <sup>1</sup> , L.Zafirovski <sup>2</sup> , T.Strateva <sup>3</sup> , N.Ulevinov <sup>1</sup> , L.Matovska <sup>4</sup>	Investigations of broncho-alveolar lavage in children with chronic respiratory diseases
S. Lazova <sup>1</sup> , Petrova G. <sup>1</sup> , Matovska L <sup>2</sup> , Rafailova Ch. <sup>1</sup> , Perenovska P. <sup>1</sup> , Zafirovski L <sup>3</sup>	Small airway indices in asthmatic children
Špela Pirtovšek Štupnik	Uporaba sedacije pri bronhoskopiji

**Chairs: Katarina Osolnik, Zoltán Balikó, Zinka Matković**

Ilonka Osrajanik	Young Female with Large Echinococcal Cyst in Lungs
Lj. Simonovska, M.Trajcevska, V.Mitreski, I.Simonovska	The causes of death among patients with tuberculosis
Istvan Ruzsics 2, Szabolcs Vigvari 1, Veronika Sarosi 2, Balazs Illes 2, Gabriella Kiss 3, Zsofia Verzar1	Pertussis whooping cough as a cause for collapse
David Lestan; Matjaž Turel; Miroslav Petrovec	Microbiological analysis of bronchoalveolar lavage from immunocompromised patients
Krokter Kogoj T, Osolnik K, Škrgat K, Košnik M.	Glucocorticoid-induced osteoporosis and adrenal insufficiency in 37 patients with interstitial pulmonary diseases
Jusuf Mehic	Aspiration of barium contrast

<b>Chairs: Marjeta Terčelj, Adrien Halász, Jasna Tekavec-Trkanjec</b>	
Barbara Salobir <sup>1</sup> , Marina Praprotnik <sup>2</sup> , Darja Kodrun <sup>1, 2</sup> , Marjeta Terčelj <sup>1</sup> , Uroš Krivec <sup>2</sup>	Successful transition of cystic fibrosis patient with low treatment compliance and frequent exacerbations of lung infections from pediatric to adult care – a case report
Majda Kočar <sup>1</sup> , Barbara Salobir <sup>2</sup> , Matevž Harlander <sup>2</sup> , Matjaž Turel <sup>2</sup> , Marjeta Terčelj <sup>2</sup> , Lucija Gabršček-Parežnik <sup>1</sup>	Individual shared-care for a cystic fibrosis patient with frequent exacerbations of Pseudomonas aeruginosa infection – a case report
G.Petrova <sup>1</sup> , S.Shopova <sup>2</sup> , L.Zafirovski <sup>3</sup> , L.Matovska <sup>4</sup> , P.Perenovska <sup>1</sup>	Children with cystic fibrosis – psychological problems and management pattern
Matevž Harlander	Cystic fibrosis and lung transplantation in Slovenia
Darja P. Kodrun, Vesna Potočnik-Tumpaj, Alejandro Rant, Marjeta Terčelj, Barbara Salobir	Coping strategies in patients with pulmonary hypertension
Tomaž Tajnšek <sup>1</sup> , Barbara Salobir <sup>2</sup> , Marija Dolenšek <sup>3</sup> , Marjeta Terčelj <sup>2</sup>	Combined pulmonary fibrosis and emphysema with pulmonary hypertension: Case presentation
Jože Pretnar <sup>1</sup> , Kiril Stojanov <sup>1</sup> , Marija Dolenšek <sup>2</sup> , Tomaž Goslar <sup>3</sup> , Janez Toplišek <sup>4</sup> , Barbara Salobir <sup>5</sup>	Pulmonary venoocclusive disease: case presentation
Barbara Salobir <sup>1</sup> , Jana Ambrožič <sup>2</sup> , Janez Toplišek <sup>2</sup> , Marija Dolenšek <sup>3</sup> , <sup>4</sup> Vojka Gorup, Marjeta Terčelj <sup>1</sup>	Late detection of chronic thromboembolic pulmonary arterial hypertension (CTEPH): case presentation
Matevž Harlander <sup>1</sup> , Barbara Salobir <sup>1</sup> , Janez Toplišek <sup>2</sup> , Vojka Gorup <sup>3</sup> , Marija Dolenšek <sup>4</sup> , Marjeta Terčelj <sup>1</sup> , Matjaž Turel <sup>1</sup>	Lung transplantation in severe idiopathic pulmonary arterial hypertension (iPAH): presentation of two similar cases with different outcome
Veljko Flego <sup>1</sup> , Sandra Glavaš <sup>1</sup> , Marina Kurpis <sup>1</sup> , Nives Jonjić <sup>2</sup> , Ljiljana Bulat-Kardum <sup>1</sup>	Adult multi-organ Langerhans cell histiocytosis with fatal outcome
Barbara Salobir <sup>1</sup> , Matevž Harlander <sup>1</sup> , Izidor Kern <sup>2</sup> , Tanja Bavčar <sup>3</sup> , Marija Dolenšek <sup>3</sup> , Matjaž Turel <sup>1</sup> , Marjeta Terčelj <sup>1</sup>	Pulmonary Langerhans cell histiocytosis – presentation of two consecutive patients
Sárosi Veronika MD	Langerhans cell histiocytosis and multiple malignant tumors
Marina Žakelj <sup>1</sup> , Barbara Salobir, Marija Dolenšek, Tomaž Rott, Marjeta Terčelj	Sporadic pulmonary lymphangioleiomyomatosis – a case report
Ana Hećimović	Lymphangioleiomyomatosis - experience with sirolimus
Edin Jusufovic	Amiloidosis CASE REPORT
Attila Nagy, Zoltan Erdodi, Maria Szilasi	An extraordinary thoracic tumour
Nadja Pucelj Koren <sup>1</sup> , Izidor Kern <sup>2</sup> , Marjeta Terčelj <sup>1</sup>	Pulmonary alveolar proteinosis - a case report
Balázs Odler <sup>1</sup> , Áron Cseh, Tamás Constantin, György Fekete, György Losonczy, Lilla Tamási, Kálmán Benke, Bálint Szilveszter, Veronika Müller	Effect of enzyme replacement therapy on the lung involvement in Fabry disease
Natalija Edelbaher	CVID in Female Patient with Pulmonary Granulomatosis (case report)
Marko Bombek	Drug Addict with Respiratory Insufficiency (case report)
Josipa Kokeza	Case report: Eosinophilic granulomatosis with polyangiitis associated with montelukast
Jurij Regvat	A patient with rheumatoid arthritis and obstruction in lung function
David Badovinac	Farmer's Lung with a high CD4/CD8 ratio lymphocytic alveolitis – a Case Report
Barbara Salobir <sup>1</sup> , Katja Seme <sup>2</sup> , Marjeta Terčelj <sup>1</sup>	Primary ciliary dyskinesia – a case report

## **Atypical pathogens in community acquired pneumonia**

Katarina Osolnik; University Clinic of Pulmonary and Allergic Diseases Golnik, Slovenia

Respiratory infections remain the most common illness in humans, the most prevalent reason why patients seek acute medical care. Lower respiratory tract infections, mainly community acquired pneumonia (CAP), are the most frequent and prevalent source of sepsis. Mortality is attributable primarily to bacterial pneumonia and severe influenza infections.

The atypical pathogens are an important and significant cause of CAP. The clinical and radiologic manifestations of CAP caused by these pathogens are modulated by the immunologic and physiologic status of the host, and there are not pathogen-specific. The range of frequencies found in various studies for the atypical pathogens among the causes of CAP is broad. These frequencies are affected by very important factors that should be recognized. In a significant percentage of patients, an atypical pathogen can be identified together with an additional cause. Till now, the significance of multiple causes has not been clarified sufficiently.

Causative microorganisms can be detected in only 10% to 20% of patients with respiratory infections (1).

In diagnostic procedure clinicians emphasised the importance of auscultation, fever, discoloured sputum and breathlessness, general impression of the illness course, familiarity with the patient, comorbidity, and age in informing their antibiotic prescribing decisions for CAP (2). Some of these factors may be overemphasised. Standardisation of assessment and integration of findings (national guidelines) may help reduce variation in management (3).

We retrospectively examined data from 735 patients hospitalized in University Clinic of Respiratory and Allergic Diseases, Golnik in year 2011 with diagnosis: pneumonia.

Causal organisms were determined using: blood and sputum cultures, PCR from respiratory samples (pharyngeal smear, sputum), antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* in urine and serology tests for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*..

206 (28%) of them had known etiology.

In group of patients with known etiology: 11,6% had atypical pneumonia (*Mycoplasma pneumoniae* 54%, *Chlamydophila pneumoniae* 4,5% and *Legionella pneumophila* 41,5% patients.). In 39% of patients *Streptococcus pneumoniae*, in 9% *Haemophilus influenzae*, in 8% *Staphylococcus*, in 7% *Pseudomonas* sp., in 13% other G- bacteriae (Klebsiella pn, E. coli), were diagnosed as causative agents.

We also retrospectively examined data of serological tests for atypical infections in 2011 in University Clinic of Respiratory and Allergic Diseases, Golnik:

serology for *Mycoplasma pneumoniae* was done in 180 patients: 8,3% of tested patients had positive IgM and 23,8% had positive IgG;

serology for *Chlamydophila pneumoniae* was done in 66 patients: 2,4% of tested patients had positive IgM and 32% had positive IgG;

serology for *Legionella pneumophila* was done in 137 patients: 2,1% of tested patients had positive IgM and 2,1% had positive IgG.

We retrospectively examined data from 2011 for:

Ag *Legionella pneumophila* test in urine: 189 tests were done: 9 (4,7%) were positive;

PCR test from respiratory samples (pharyngeal smear, sputum) for *Legionella pneumophila*: 340 tests were done: 4 (1,1%) were positive;

PCR test from respiratory samples (pharyngeal smear, sputum) for Chlamydophila pneumoniae:  
340 tests were done: 1 (0,2%) was positive;  
PCR test from respiratory samples (pharyngeal smear, sputum) for Mycoplasma pneumoniae:  
342 test were done: 19 (5,5%) were positive.

Serology for infections caused by *M. pneumoniae*, *C. pneumoniae* and *Legionella* is more useful in epidemiological studies than in the routine management of the individual patient. If aetiological diagnosis of the atypical agents is considered in the management of the individual patient, serological tests should not be performed as the only routine diagnostic test. A combination of IgM antibody detection and PCR may be the most sensitive approach.(4). Application of molecular tests for the detection of atypical pathogens (*Mycoplasma pneumoniae*) is useful, provided the tests are validated and the results can be obtained sufficiently rapidly to be therapeutically relevant (4).

Compared to patients with other definite and unknown etiologies, patients with atypical pneumonia were younger and had less co-morbidity. Patients with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were presented with a less severe disease and had better outcomes, including a shorter length of hospitalization, nobody requiring mechanical ventilation and nobody had died.

We retrospectively examined data from 29 patients hospitalized in University Clinic of Respiratory and Allergic Diseases, Golnik in winter 2014/2015 with diagnosis: Mycoplasma pneumonia (10 M, 19 F) (avg. 41 year), 37% smokers, 58% without any co-morbidity, 27% with asthma, COPD, bronchiectasis, 1 patient with arterial hypertension, diabetes and pregnancy. All of them had fever, coughed, had dyspnea and general malaise.

50% of them need oxygen, 20% of them had hemoptyses and by 20 % of them we diagnosed bronchiolitis. 50% of them had antibiotic therapy before admission: all beta-lactam.

Although pneumonia has been a hallmark of *Mycoplasma pneumonia* infection, it has been revealed that this infection can cause a number of extrapulmonary manifestations in the absence of pneumonia. It is proposed that extrapulmonary manifestations due to *M. pneumonia* infection can be classified in three categories: 1. A direct type in which inflammatory cytokines locally induced by lipoproteins contained in the bacterial cell membrane must play a role. 2. An indirect type in which immune modulation such as autoimmunity cross-reaction between the bacterial cell components and human cells must play a role. 3. A vascular occlusion type in which vasculitis and/or thrombosis with or without hypercoagulable state induced by bacterium must play a role (5).

Patients with legionellosis in 40% required intensive care, mechanical ventilation and longer hospitalization. Combination of PCR test with urinary Ag test for *Legionella pneumophila* is useful in patients with suspected legionellosis and might allow the early detection (6). Antigen detection in urine is the most rapid method to diagnose or exclude the infection. A negative test makes legionella unlikely, but does not exclude legionella infection (4).

There have been significant developments in molecular diagnosis (7), there are still diagnostic challenges in distinguishing carriage from infection, and in the field of macrolide-resistance. An increased understanding of the epidemiology and presentation of atypical pneumoniae will result in more targeted antimicrobial therapy.

## Literature

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## **Highlight of CAP. Antibiotic resistance in Hungary**

Zoltán Balikó, 1<sup>st</sup> Department of Internal Medicine, Pulmonology, University of Pécs, School of Medicine, Pécs, Hungary

According to the introductory words of Tobias Welte (European Respiratory Monograph 63, March, 2014) Community Acquired Pneumonia (CAP) is the leading cause of death due to infectious disease worldwide. Despite the enormous progress in the understanding of the disease the mortality rate is as high as it was 50 years ago. The key factor for the increased mortality is, along with the rising age and the increased number of comorbidities of the patients, the virulence of the pathogens.

The lecture demonstrates the most important details of the European Respiratory Monograph 63 dealing with CAP regarding epidemiology, microbiology using traditional and molecular techniques, severity assessment tools, the cornerstones of antibiotic treatment and finally the non-antibiotic therapies for CAP.

Unlike hospital-acquired pneumonia, however, the increasing development of resistance of the most important respiratory pathogens does not play a significant role. Yet to avoid the antibiotic pressure and thereby protect our common antibiotic treasure we have to know the actual resistance pattern of the usual bacteria causing CAP. Table 1. will present the antibiotic resistance of these microbes in 2013 in Hungary. The most important causative agent of CAP is *Streptococcus pneumoniae*: among around 3000 outpatient samples its sensitivity for penicillin was 85.8%, resistance 2.3%, sensitivity for macrolids (erythromycin) was 73.7%, resistance 26.2%; among around 1400 inpatient samples sensitivity for penicillin was 79.7%, resistance 3.8%, sensitivity for macrolids 75.3%, resistance 24.6%. *Streptococcus pneumoniae* is still highly sensitive for the respiratory flurokinolons which is around 99%.

These data attract attention not to overuse one specific antibiotic, but we should rotate the empirically administered presumably effective antibiotics to prevent generation of new antibiotic resistant strains (see high macrolid resistance of *Streptococcus pneumoniae* due to overuse of macrolids for many years).

## **Chronic bronchial infection in COPD**

Zinka Matković, University Hospital Dubrava, Zagreb, Croatia

Impaired host defences allow the establishment and proliferation of potentially pathogenic microorganisms (PPMs) in lower airways of patients with chronic obstructive pulmonary disease (COPD), both in stable state and during exacerbations. Repeated isolation of PPMs in bronchial secretions in stable patients has been previously defined as colonisation. However, it is well documented that the presence of PPMs in the lower airways is associated with chronic low-grade inflammation (local and systemic), increased exacerbation frequency and severity, accelerated lung function decline and impaired health-related quality of life. Therefore, it has been suggested to use the term chronic bronchial infection (CBI), instead of colonisation, when PPMs are repeatedly isolated from the respiratory specimens of patients with stable COPD.

Risk factors for CBI are smoking, impaired lung function, comorbidities, frequent exacerbations and bronchiectasis. Purulent sputum and an increased degree of dyspnoea have been recognised as clinical indicators of positive sputum cultures for PPMs in stable COPD.

Microbiological studies have demonstrated that the CBI is a dynamic process with changes in pathogens, their strains and loads occurring over time. It has been suggested that the acquisition of new strains of bacteria or antigenic change in pre-existing strains with subsequent rise in the bacterial load and enhancement of airway inflammation are crucial in the pathogenesis of bacterial exacerbations.

The concept of CBI in COPD has therapeutic implications because long-term antibiotic therapy might be effective in reducing the bacterial load and in modulating inflammation, resulting in a reduction in the frequency of exacerbations. Introduction of antibiotics in stable COPD is still a controversial issue with pros and cons, and further studies are clearly needed. Previous studies suggest that patients with the chronic bronchitis phenotype and frequent exacerbations might be the potential candidates for the long-term administration of antibiotics in stable COPD.

## **Evaluation of the efficacy of two DNA extraction methods from sputum samples in COPD patients**

Natasa Fajfar, Denise O'Sullivan, Jernej Pavšic, Jim Huggett, Mojca Milavec, Viktorija Tomic;  
*University Clinic of Pulmonary and Allergic Diseases Golnik, Slovenia*

**Background:** Efficient extraction of microbial DNA from various kinds of sample materials is crucial for sensitive detection of microorganisms by molecular methods. Currently there is only very limited knowledge on the best method for DNA extraction from sputum samples.

**Objectives:** This study is a part of the European JRP HLT08 INFECT-MET. The aim was to evaluate the efficacy of two different extraction methods, manual and automated, in treated and untreated sputum samples from COPD patients.

**Methods:** A total of 49 good-quality sputum samples from COPD patients between March 2014 and December 2014 were included in the study. Thirty-one samples were left untreated and 18 were treated with NALC-NaOH. All samples were split in two aliquotes and DNA was extracted with manual (QIAamp DNA Mini Kit, Qiagen GmbH, Germany) and automated (DNA Extraction Kit, DiaSorin, Italy on NorDiag Arrow instrument) method. Concentration of DNA was quantified (Qubit Fluorometer, Invitrogen, USA).

**Results:** Out of 49 sputum samples 42 (85,7%) had higher DNA concentration with automated extraction method. Among 31 untreated sputum samples automated method had a higher DNA yield in 25 samples by 46,1% and lower in 6 by 51,5%. In 18 NALC-NaOH treated sputum samples automated extraction method had a higher DNA yield in 17 samples by 57,6% and lower in 1 sample by 23,5%.

**Conclusions:** Automated extraction method proved to be more efficient in extracting DNA from untreated and treated sputum samples. Automated extraction method is much easier to perform and is less time consuming.

## **Extrapulmonary manifestations of *Mycoplasma pneumoniae* infections: our experience in 2014**

Rodman J<sup>1,2</sup>, Praprotnik M<sup>1</sup>, Mrvič T<sup>2</sup>, Krivec U<sup>1</sup>

<sup>1</sup>*Unit for Pulmonary Diseases, University Children's Hospital, University Medical Centre, Ljubljana, Slovenia*

<sup>2</sup>*Department of Infectious Diseases, University Medical Center, Ljubljana, Slovenia*

**Introduction:** Although pneumonia is a hallmark of *Mycoplasma pneumoniae* (MP) infection, a number of extrapulmonary manifestations (EPM) involving all the major organ systems can occur due to immune mechanisms, even without signs of respiratory tract infection (RTI).

**Aim:** To assess the characteristics of children that presented with EPM to our pediatric departments in 2014.

**Methods:** We analyzed data of patients with EPM diagnosed with acute MP infection by positive PCR from pharyngeal swabs or serology.

**Results:** Out of 509 children with acute MP infection, 60 (11.8%) presented with EPM (mean age 8.0 yrs, SD 4.0 yrs; 43.4% boys). Out of those 21.7% showed no signs of RTI. A higher percentage of patients with EPM required hospitalisation (48.3% versus 33.9% of other patients, p=0.032). The majority presented with exanthema (76.7%). Eight patients (13.3%) presented with a central nervous system infection however MP was not detected in CSF by PCR. All patients with EPM received antibiotic treatment. Only two patients received additional immunomodulatory treatment and one non-steroidal anti-inflammatory drugs.

**Conclusions:** Patients with EPM of MP infections tend to present with a more severe clinical picture and require hospitalisation more often. Treatments targeted at the immune response should be considered.

## The values of D-dimer in hospitalized patients with Community-acquired pneumonia according to the presence of co-morbidites

Desa Nastasijević Borovac<sup>1</sup>, Tatjana Pejić<sup>1</sup>, Ivana Stanković<sup>1</sup>, Tatjana Rađenović Petković<sup>2</sup>, Biljana Vrbić<sup>1</sup>, Ivanka Đorđević<sup>1</sup>

Clinic for Lung Diseases, Knez Selo, Clinical Centre Niš, Serbia<sup>1</sup>

Clinical Biochemical Laboratory, Clinical Centre Niš, Serbia<sup>2</sup>

D-dimer represents a degradation product of fibrin. High values of D-dimer were not found only in venous thrombosis and pulmonary embolism. Elevated values of D-dimer levels were found in patients with community-acquired pneumonia (CAP). Furthermore elevated values of D-dimer were found in arterial hypertension, renal insufficiency, diabetes and malignant diseases. The effects of uneven coagulation and fibrinolysis in the lung parenchyma during infection are regulated by various pro-inflammatory cytokines. The interaction between inflammation, infection, and coagulation is multidirectional.

The prospective clinical study was done on 129 patients with diagnosed CAP (mean age  $64.83 \pm 13.32$  years). The control group consisted of 30 healthy subjects (mean age  $47.34 \pm 12.13$  years). Patients were treated at the Clinic for Lung Diseases, Knez Selo, Serbia, in the period April 2012 - August 2014. The aim of this study was to determine the value of D-dimer in patients with CAP, according to the co-morbidities presence and outcome of CAP. The values of D-dimer levels were determined by quantitative latex method at Analyzer Coagulometar ACL 2000. According to the co-morbidities presence, patients with CAP were divided into the following groups: CAP with co-morbidities (*CAP Group I*) ( $n = 106$ ) and patients with CAP without co-morbidities (*CAP Group II*) ( $n = 23$ ). We analyzed the value of D-dimer in the group of non survived patients ( $n = 13$ ), and in the Group of survived patients ( $n = 116$ ). In 6 patients with CAP who had a high value of D-dimer CT pulmonary artery was ruled out the presence of pulmonary embolism.

The majority of the patients with CAP had cardiovascular disease. Concomitant diseases were found in the following proportion: Hypertensio arterialis (48.11%); COPD (39.66%); Diabetes mellitus (29.63%); Arrhythmia cordis (19.81%); Insuffitientio cordis (11.32%); Insuffitientio respiratoria (9.43%); Ulcus ventriculi (7.55%); Neoplasma (8.49); Status post infarctus cerebri (8.49%); Insuffitientio renuum et asotemia (6.61%); Other diseases have occurred in less than 5% of cases. In the *CAP Group II* the value of D-dimer was 1288.36 ng/mL (with a median of 859.5 ng/mL), and was higher than in the *CAP Group I* (406.02 ng/ml, with a median of 350.0 ng/ml) ( $p < 0.001$ ). Value of D-dimer in the *Control Group* was  $192.5 \pm 39.2$  ng/ml. All patients with CAP who had not survived ( $n=13$ ), had co-morbidities. Values of D-dimer in non survived patients were higher (2498.38 ng/mL with a median of 2188.0 ng/mL) than in the *Group of survived patients* (966.44 ng/ml with median of 968 ng/ml).

D-dimer test is influenced by many factors. High levels of D-dimer occur not only in venous thrombosis and pulmonary embolism. We have found significantly high values of D-dimer in patients with CAP and co-morbidities. Elevated values of D-dimer in patients with CAP and co-morbidities are the consequence of the imbalance of the coagulation response to infection, and previous vascular remodeling in part associated with the disease. Disturbances in the mechanisms of coagulation during organ dysfunction correlate with the severity of CAP and risk of mortality.

## **The frequency of *Streptococcus pneumoniae* in three distinctive groups of patients**

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A study was conducted to determine the frequency of *Streptococcus pneumoniae* (*S. pneumoniae*) colonization in three groups of patients (106 patients with community acquired pneumoniae (CAP), 55 patients with COPD and 159 patients, hospitalized due to non-infectious reasons). To determine presence of *S. pneumoniae* in clinical samples we carried out cultivation of respiratory samples, test Genprobe Accuprobe from culture, in-house real-time PCR, specific to *S. pneumoniae*, in-house multiplex PCR, specific to *S. pneumoniae* and urinary antigen test. Method with the highest sensitivity was in-house real-time PCR. All other methods had less positive results than in-house real-time PCR.

With combined results of all 5 methods we determined frequency of *S. pneumoniae* in each distinctive group of hospitalized patients. 37,7% samples of patients with CAP tested positive for *S. pneumoniae*. Result was expected due to the high rate of pneumococcal pneumoniae in that group of patients. Samples from patients with COPD were positive in 14,6% and samples from patients, hospitalized due to non-infectious reasons, were positive in 18,2%. That result was rather surprising; we expected higher percentage of positive samples in group of patients with COPD than in group of patients with non-infectious illness.

## **Q-fever outbreak in Baranya County**

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Q fever is a zoonosis with an obligation to report to public health organisations in Hungary since 1967. Between May and July 2013, Q fever, a type of community acquired pneumonia was diagnosed in a cluster of cases presenting as acute lower respiratory tract infections in the township of Siklós in Baranya county. 27 patients of the reported 124 cases required admission to either the respiratory or the infectology department of our university hospital. Diagnosis was confirmed by serologic testing in each case. The course of the outbreak implicated that the first wave of the infection occurred following a significant exposure. The number of Q fever cases in Hungary reached up to 149 in the first six months of the year due to the outbreak in this geographical area. The increase was almost tenfold compared to the summed-up median from 2007 to 2011. According to the identification results of bacteria isolated from livestock and human samples, transmission resulted through inhalation of aerosols from contaminated soil and dried animal waste. Medical history, epidemiological and demographical data were investigated in our retrospective analysis. Our findings were examined together with the clinical picture and the results of radiographic and laboratory tests in order to search for interrelations between the susceptibility of this rare zoonosis and the risk of developing disease.

## Hypoventilation syndrome

**Chairs: Irena Šarc, György Losonczy, Hrvoje Puretić**

### NIV in stable COPD

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There is robust data supporting the use of non-invasive ventilation (NIV) in acute hypercapnic respiratory failure due to an exacerbation of COPD. The evidence for the use of long-term NIV in stable COPD is less convincing. Several randomized controlled trials conducted in the past have concluded that there is no strong evidence to recommend NIV to be regularly used in patients with chronic hypercapnic respiratory failure due to COPD. However, these studies used NIV with low pressure settings, which could explain that partial arterial pCO<sub>2</sub> and other physiological parameters were not markedly influenced. Several more recent studies indicated that higher pressure settings provide marked physiological benefits (especially reducing the level of hypercapnia) in stable hypercapnic COPD patients. This technique has been labelled "high-intensity NIV" and has been shown by some studies to be superior to the conventional approach using lower inspiratory pressures ("low-intensity NIV") not only in terms of more substantial reduction of pCO<sub>2</sub>, but also in improving health-related quality of life and possibly survival of patients. However "high-intensity NIV" has also been linked to increased air leakage and poor patient tolerance.

A recent randomized controlled study has demonstrated that an addition of long-term NIV to standard treatment of COPD significantly improves survival of patients with hypercapnic, stable COPD when NIV is targeted to significantly reduce hypercapnia – by at least 20% (1-year mortality in the NIV group was 12% vs 33% in the control group). However, another recent large study demonstrated no impact on survival when NIV was initiated indiscriminately in hypercapnic patients shortly after an exacerbation of COPD. Hence, the technique of how NIV is applied and the appropriate selection of COPD patients are crucial and decisively influence the outcomes of long-term NIV, especially survival of patients.

## **OBESITY HYPOVENTILATION SYNDROME – POSITIVE AIRWAY PRESSURE THERAPY**

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Obesity hypoventilation syndrome (OHS) is present when an obese individual ( $BMI >30 \text{ kg/m}^2$ ) develops chronic awake alveolar hypoventilation ( $\text{PaCO}_2 >45 \text{ mmHg}$ ) not explained by other causes of hypoventilation. Hypercapnia occurs only when normal compensatory ventilatory mechanisms fail to maintain adequate ventilation. The main physiologic abnormalities of OHS are obesity, sleep disordered breathing (obstructive sleep apnea-OSA), impaired pulmonary mechanics and ventilatory control. Prompt diagnosis and therapy are necessary in order to avoid high mortality rates due to cardiovascular and metabolic consequences in untreated patients. The main therapeutic measures are lifestyle modifications aimed at weight loss (supervised and controlled) and nocturnal positive airway pressure (commenced and titrated during attended overnight in-laboratory polysomnography). Two major categories of positive pressure therapy are continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NPPV) with two available modes: bilevel (BPAP) and volume cycled (VCPPV). The pressures are delivered during sleep via nasal or oronasal mask mostly. CPAP is considered a prime therapy for patients with coexisting OHS and OSA. In the case of CPAP failure, NPPV (predominantly BPAP) presents a successful alternative. According to the studies so far, positive pressure therapy improves long-term survival of OHS patients regardless of the modality of pressure administered.

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## **The role of airway inflammation in the pathophysiology of obstructive sleep apnoea**

Andras Bikov, Ildiko Horvath, Gyorgy Losonczy, Laszlo Kunos

**Introduction:** Obstructive sleep apnoea (OSA) is a prevalent disorder with an increasing socioeconomic and healthcare-related burden. Its pathophysiology is not completely understood, but recent studies suggest that lower airways also contribute to decreased patency of the upper airways which is a key element in OSA. Exhaled breath is a potential method to study airway inflammation with numerous studies investigating exhaled biomarkers in OSA.

**Methods:** Exhaled breath volatile compound pattern was measured before and after night in 26 patients with suspected sleep-disordered breathing (SDB,  $53 \pm 15$  years) who underwent polysomnography and in ten control subjects ( $37 \pm 15$  years), by whom SDB was excluded with a screening device. Exhaled volatile compound pattern was processed with a Cyranose 320 electronic nose.

**Results:** Exhaled volatile compound patterns recorded in the evening and in the morning were different in patients with OSA ( $p=0.01$ ) but not in non-OSA habitual snorers ( $p=0.49$ ) or in control subjects ( $p=0.23$ ). The electronic nose distinguished patients with OSA from control subjects based on the breath samples collected in the morning ( $p<0.001$ ) but not in the evening ( $p>0.05$ ).

**Conclusions:** The molecular fingerprint of exhaled volatile substances is different in OSA and changes during night. This suggests a possible role of airway inflammation in OSA.

# Survival of patients with obesity hypoventilation syndrome

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## ABSTRACT:

**Objectives:** The prevalence of obesity hypoventilation syndrome (OHS) is increasing. OHS is associated with considerable comorbidity, morbidity and health costs. Data on mortality in OHS patients and survival benefit of positive pressure therapy (PAP) are lacking.

**Methods:** Medical records of all patients discharged with OHS diagnosis from 2005 to 2010 from University Clinic Golnik were reviewed. Patients with body mass index (BMI)  $\geq 30$  and daytime hypercapnia in the absence of any other cause of hypoventilation, were included. Prescription of PAP and adherence to treatment was recorded. Vital status was obtained from Central Population Registry.

**Results:** A total of 250 patients with OHS were included. Two groups were identified, 134 (54%) patients were admitted in acute exacerbation (aeOHS) and 116 (46%) under stable condition (sOHS). aeOHS patients were older ( $63.8 \pm 12.1$  vs.  $56.3 \pm 9.7$  years,  $p < 0.01$ ), more often female (59.7% vs. 37.1%,  $p < 0.01$ ), had higher BMI ( $46.3 \pm 9.7$  vs.  $41.8 \pm 8.9$ ,  $p < 0.01$ ), more often had heart failure (58.9% vs. 25.8%,  $p < 0.01$ ), arterial hypertension (92.5% vs. 73.3%,  $p < 0.01$ ), atrial fibrillation (29.4% vs. 5.1%,  $p < 0.01$ ), pulmonary hypertension (14.1% vs. 5.1%,  $p < 0.01$ ), diabetes mellitus (41.8% vs. 24.1%,  $p < 0.01$ ) and were less often prescribed with PAP (41% vs. 88%,  $p < 0.01$ ). In a mean follow-up of  $5.0 \pm 1.9$  years 70 (28%) patients died, 56 (41.8%) aeOHS and 14 (12.1%) sOHS (log rank  $p < 0.01$ ). On Kaplan-Meier analysis, 1-, 2-, 3-, and 5-year survival probabilities were 88%, 78%, 71%, and 62% for aeOHS group and 98%, 95%, 90%, and 89% for sOHS group, respectively. When comparing survival of patients who were prescribed with PAP, 1-, 2-, 3-, and 5-year survival probabilities were 85%, 72%, 64%, and 55% for the group without PAP and 97%, 93%, 89%, and 87% for PAP treated group, respectively (log rank  $p < 0.01$ ). Survival probabilities for users and non-users of PAP therapy in sOHS and aeOHS patients are presented in Figure 1 and 2, respectively.

**Conclusions:** We found significant difference in mortality rates between aeOHS and sOHS group. Patients with aeOHS were older, more obese and had more comorbidities. Patients who were prescribed with PAP therapy and used it had higher survival rates in both OHS groups.

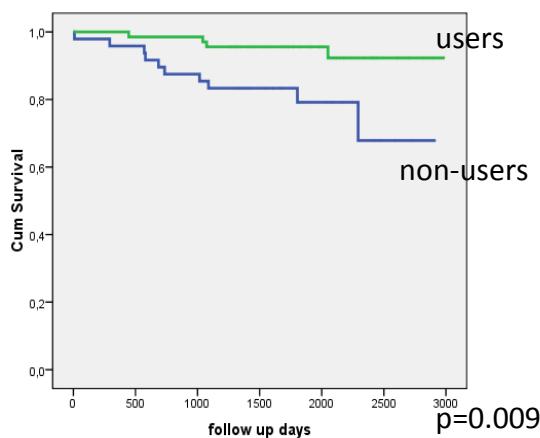


Figure 1: Survival of sOHS patients, comparing users and non-users of PAP

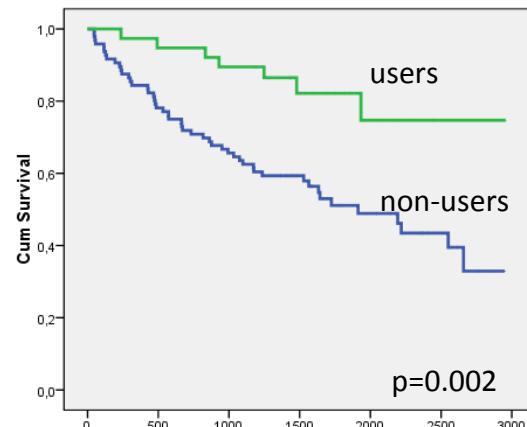


Figure 2: Survival of aeOHS patients, comparing users and non-users of PAP therapy

## **Chronic respiratory failure in neuromuscular disorder**

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Abstract:

Due to weakness of the respiratory muscles, respiratory insufficiency is a common complication in neuromuscular disorders. Its symptoms and signs generally start during the night time sleep, especially during its rapid eye movement (REM) phase when postsynaptic inhibition of somatic motor neurons causes reduction or total loss of the muscle tone in the rib cage- and other accessory respiratory muscles. Respiration in REM depends only on the diaphragm function. If the diaphragm is weak, respiratory efficiency is markedly reduced, and progressive hypercapnia and hypoxemia ensue. Careful monitoring of symptoms and regular assessment of pulmonary function with arterial gas analyses must be performed, since symptoms of the respiratory involvement are not always obvious, especially in patients who are still mobile. In respiratory failure, mechanical ventilation should be considered. The noninvasive mechanical ventilation reduces daytime symptoms, improves alveolar ventilation, quality of sleep and life, as well as prolongs survival. Compared to the invasive ventilation, the noninvasive form offers better comfort and acceptance, decreases the risk of pulmonary complications and reduces hospitalization. Already in the early phases of their diseases, patients should be well acquainted with the possibilities of respiratory treatment so as to enable them for the informed advance decisions. Long-term oxygen therapy is not recommended in patients with nocturnal hypoventilation as it may enhance hypercapnia and abolish hypoxic ventilatory drive. Oxygen is only acceptable in conjunction with the invasive ventilation or in palliative care. Weak respiratory muscles make coughing, and thus clearing mucus from the respiratory tract, ineffective; consequently, patients are put at risk of recurrent respiratory infections and chronic lung disease. Cough assisting techniques should be used when peak cough flow is less than 270 l/min.

Hypoventilation is not the only respiratory problem in neuromuscular disorders. Obstructive and central apneas as well as abnormalities in respiratory pattern and central respiratory drive can also be found.

## **Central sleep apnea – to treat or not to treat?**

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### **ABSTRACT:**

Central sleep apnea syndromes (CSAS) are a heterogeneous group of sleep-related breathing disorders. We all experience a few central sleep apneas during each night which is physiological. Sometimes central apneas (e.g. CSAS due to high altitude, apnea of prematurity) are classified as a disease, although it is hard to view them as pathological, since they represent a normal response in certain circumstances (high altitude, extreme prematurity). Pathophysiology of CSAS is heterogeneous – some are the consequence of low and others of high central drive. The most common of all CSAS is Cheyne-Stokes Respiration (CSR).

There are no clear guidelines on when and whether to treat CSAS in the absence of symptoms. If symptoms are present, treatment is warranted. Sometimes observation might be an appropriate first step and in some circumstances treatment of underlying disorder is the first line therapy (e.g. descent from high altitude, optimization of heart failure therapy). Treatments aimed specifically at CSAS include positive pressure therapy, oxygen, phrenic nerve stimulation, some medications (acetazolamide, theophylline, Z-drugs).

There is little evidence for adverse outcomes in CSAS due to medical disorder without CSR (e.g. post stroke CSAS) and primary CSAS. CSAS due to medications (e.g. opioids) and treatment emergent CSAS should be treated, however there is some controversy on how to treat them.

There is sufficient evidence to recommend treatment of CSR patients, and protocols on how to treat them exist. Currently the question whether we should use sophisticated positive pressure therapy machines (e.g. adaptive servo ventilation) to treat CSR and the extent to which patients benefit from this treatment is unresolved. In the summer of 2015 we are expecting preliminary results of SERVE-HF study, which promises to provide an answer to this question.

CSAS are diverse and before commencing any treatment, exact and correct diagnosis is mandatory. Treatment should be patient-tailored.

## **Reliability of the Epworth sleepiness scale and Berlin questionnaire in detecting sleep apnea patients**

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**Objective:** The Epworth Sleepiness Scale (ESS) and Berlin questionnaire (BQ) are used as screening tool for sleep apnea (SA) patients since the overnight polysomnography (PSG) is an expensive and time consuming procedure. Aim of this study was to reevaluate ESS and BQ compared to the PSG results.

**Methods:** 105 subjects suspected of SA were given ESS and BQ followed by PSG. The ESS and BQ values were compared to PSG apnea hypopnea index (AHI) with sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) calculated for ESS and BQ. The positive cut-off value for ESS was >10, for BQ 2 positive categories out of 3 and for AHI  $\geq 5$ .

**Results:** SA was confirmed by PSG in 85 subjects (81%). For ESS SE was 24.7%, SP 75.0%, PPV 80.0%, NPV 18.9% and DA 34.3%. For BQ SE was 81.9%, SP 65.0%, PPV 89.3%, NPV 33.0% and DA 68.6%. 80.9% of ESS positive subjects had severe SA. BQ better detected mild and moderate SA (30.5 %).

**Conclusion:** We consider BQ more useful than ESS as a screening tool for diagnosing SA. However, negative results do not exclude SA. Further studies on that issue are needed.

## Biologic therapy in asthma

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**Introduction:** Severe difficult-to-control asthma represents a small minority of the whole asthmatic population but this subset of the disease has a major impact on the direct and indirect asthma healthcare costs and the overall burden of asthma. Although most asthmatics can be managed with a combination of anti-inflammatory drugs and bronchodilators, patients who remain symptomatic despite maximum combination treatment represent a complex and heterogeneous group of patients. Our current understanding of the immune pathology of asthma has identified multiple mediators as potential therapeutic targets, and these are currently under development.

**The role of biologic therapy in asthma:** To date, most of monoclonal antibodies have focused on the Th2 asthma phenotype (e.g., interleukin-4, interleukin-13, and interleukin-5), since these proteins are thought to be major drivers of the inflammatory component of asthma.

Up until now, the first and as yet only biological agent licensed for the treatment of asthma is **omalizumab**, specifically for severe allergic asthma. Omalizumab is a humanized monoclonal antibody that binds to the Fc of free IgE molecules, reducing free circulating IgE and blocking its binding to the receptors present on mast cells, basophils, and dendritic cells, which prevents inflammatory cells from releasing mediators when in contact with allergens. Omalizumab decreases the density of Fc $\epsilon$ RI and Fc $\epsilon$ RII expression on basophils, mast cells, and dendritic cells, and decreases airway inflammation. A reduction in expression of Fc $\epsilon$ RI on dendritic cells and its binding to IgE may decrease the allergen presentation process. It has a steroid sparing effect. We have had experience in omalizumab treatment of 44 severe asthma patients since 2007 in Slovenia. As in other reports we have demonstrated a reduction in the rate of asthma exacerbation, improvement in asthma control and the quality of life.

**Mepolizumab** is a humanized monoclonal antibody against IL-5 and selectively and effectively inhibits eosinophilic inflammation in the airways. It is reasonable to consider anti-interleukin-5 therapy for patients with severe asthma who are receiving high doses of systemic glucocorticoids and who continue to have an elevated eosinophil count in sputum or blood regardless of their atopic status. Although persistent blood eosinophilia may be sufficient to identify patients who are likely to have a response to this treatment, whether this biomarker is sufficient or is as effective as airway eosinophilia in monitoring the response to treatment remains to be seen.

**Lebrikizumab anti IL-13.** Interleukin-13 induces bronchial epithelial cells to secrete periostin, a matricellular protein. It is a cytokine of type2 helper T cells (Th2) and has been thought to contribute to many key features of asthma. The enhanced effects of lebrikizumab on lung function in patients with high periostin levels or high FeNO are consistent with the hypothesis that phenomena driven by interleukin-13 are clinically important in such patients.

**Conclusion:** A multidisciplinary team is needed to do a good asthma phenotyping and choosing the right biologic therapy for severe asthma patients. Asthma register and asthma network would be good tools in this approach and follow up of these patients.

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## Is there paradigm shift in COPD treatment?

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Assessment of patients with COPD according to new GOLD categories (A-D) may contribute to a more effective and safer therapy for patients with stable disease. Avoidance of smoking, maintenance of physical activity and regular inhaled bronchodilator(s) create the cornerstone of the management for most patients with moderate - very severe diseases (GOLD 2-4). Long acting bronchodilator monotherapies - either LAMA-s or LABA-s – reduce both symptoms and risk of exacerbations and are preferred over short acting formulations. There is no evidence to prefer one class of long acting bronchodilator over another for initial treatment. If symptom relief is not sufficient, combination of LAMA/LABA may offer additional benefit. Inhaled corticosteroids (ICS) should be more carefully prescribed in the future in order to avoid side effects (e.g. pneumonias) in this polymorbid population. Main indication of ICS (practically in combination with LABA) in COPD is co-existence of asthma (ACOS) and patients remaining at high risk of exacerbations or in unstable condition despite previous bronchodilator therapy.

There is no clearcut evidence how to step up or step down in the treatment, so careful assessment of clinical data and symptomatic response (e.g change in CAT > 2 points or risk of exacerbations, change in lung function) are the best options to evaluate the effect of previous – pharmacologic and non-pharmacologic - interventions. In this heterogeneous disease, there are some clinically meaningful phenotypes (like asthmatic, bronchitic, emphysematic, exacerbators) which may help our decision how to prescribe more personalized treatment with more efficacy and fewer side effects.

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## **Davor Plavec    Asthma phenotypes, endotypes and network medicine**

## **Matjaž Turel    Lung transplantation in COPD**

### **Innate lymphoid cells – novel players of the immune system and their role in airway diseases**

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Innate lymphoid cells (ILCs) play distinct role in mucosal immunity. As key members of the innate immune system they are able to respond promptly to the environmental signals and participate in shaping of the adaptive immune responses. Besides the natural killer cells – the principal of the ILCs – there are some newly recognized members of the innate lymphoid cell family: ILC1, ILC2 and ILC3 cells share numerous biological characteristics and transcription factor expression with their adaptive T helper cell counterparts: Th1, Th2 and Th17/Th22 cells, respectively. ILC1s need T-bet for the differentiation, and they may contribute to the pathogenesis of some autoimmune disorders (e.g. Crohn's disease) via IFN- $\gamma$  production. ILC2s are depending on GATA3, and they substantially contribute to the IL-5 and IL-13 production in allergic airway responses. ILC3s are ROR $\gamma$ t dependent cells. Their signature-cytokine is the IL-22, an important mediator of the mucosal immune defence, tissue repair and maintenance of epithelial barriers. The discovery and characterization of the different ILC subsets substantially modify our current understanding of allergy, asthma, autoimmune diseases and other immunological disorders. The recent developments of this scientific field and their relevance to the airway diseases will be summarized.

## **Phenotypes of severe asthma**

Csoma Zsuzsanna

Asthma is a heterogeneous disease driven by a mix of genetic and environmental factors. The disease is defined as a clinical syndrome of intermittent respiratory symptoms triggered by different stimuli, and is characterized by non-specific bronchial hyperresponsiveness and airway inflammation. Asthma heterogeneity is most easily recognized in severe asthma (SA), where patients have diverse symptom profiles and altered responses to medications. Despite the intensive research focused on the field of SA for more than a decade, many aspects of this disease remained unclear. Data on prevalence of SA are quite heterogeneous, phenotypes have been only partly characterized and data on the natural course of disease are also limited. Clinical and statistical efforts have assigned patient phenotypes, with recent emphasis on statistical efforts. Recently, several studies have used cluster analysis in different groups of asthma patients to identify clinically well-recognized phenotypes of disease. By using these multivariate techniques, several adult phenotypes could be identified with clinically important differences. On the one hand, they found phenotypes of asthma that started in childhood including early onset atopic asthma, benign asthma and symptom-predominant asthma. On the other hand, the cluster analysis also revealed clusters of asthma starting mainly in adulthood: the noneosinophilic obese female cluster and a cluster with predominantly males with eosinophilic asthma. In cluster analyses, severe asthmatics were distributed among several clusters supporting the heterogeneity of this subgroup of asthmatics. The ultimate clinical usefulness of the severe asthma phenotypes will be determined by their therapeutic consequences.

## **ABPA in asthma patient with HIV infection. Case report**

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Allergic bronchopulmonary aspergillosis (ABPA) is an IgE mediated hypersensitivity response to *A. fumigatus* colonization of the tracheobronchial tree. It occurs most often in conjunction with asthma and cystic fibrosis. Clinically it presents with asthma-like exacerbations and can lead to irreparable lung damage such as bronchiectasis and fibrosis. ABPA is extremely rare in HIV infected individuals. We present a case of a 49-year old male with allergic asthma and HIV. Asthma was stable for 20 years on corticosteroid and bronchodilator inhalation therapy. Without clear cause he had several life threatening deteriorations. His asthma was not stable despite oral glucocorticoid treatment. We decided to initiate treatment with omalizumab but contrary to expectations his condition worsened. Due to resistance to high dose bronchodilator and oral steroid treatment he needed intubation and invasive mechanical ventilation. He was unstable until we were finally able to gather enough evidence to support the diagnosis of ABPA and introduce itraconazole treatment. Antifungal treatment led to evident clinical improvement despite precursory prolonged high dose steroid therapy. This is the second reported case of a successful antifungal treatment of ABPA in HIV affected patient.

## Different functional markers in pulmonary rehabilitation in COPD

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**Rationale:** Chest wall dynamic hyperinflation and rib cage distortion can be a contributor factor to breathlessness in patients with COPD. The procedure to increase chest mobility includes specific chest stretching and mobilization. Complex pulmonary rehabilitation, including physiotherapy, breathing- and exercise training has favourable effect. The effectiveness of pulmonary rehabilitation can be more detectable by activity monitoring compared to maximal exercise capacity. The functional capacity, including physical activity can evaluate the risk of thoracic surgery.

### Materials and methods:

50 patients (FEV<sub>1</sub>: 44±16 %pred, age: 63±9 years) was involved in the first study. Chest wall-stretching exercises were composed of thoracic rotation and anterior compression with stretching in sitting position, trunk extension and rib torsion in supine lying. Patients were performing personalized exercise training including cycling and treadmill exercise 2-3 times for 20-30 minutes per day at 60-80% of peak work rate for 6 weeks.

In the perioperative rehabilitation study, 45 lung cancer patients with COPD (FEV<sub>1</sub>: 56±10 %pred) was involved into 3 groups. Preoperative group (PE: rehabilitation before thoracic surgery): 23 patients, postoperative group (PO: rehabilitation after thoracic surgery): 11 patients, and pre- and postoperative group (PEO: rehabilitation before and after thoracic surgery): 11 patients. Activity monitoring was detected by Omron Walking Style Pro pedometer, 72h measurement was performed at start and end of the rehabilitation. Six minutes walking test (6MWD) was measured before and after rehabilitation. Patients were performing breathing training and physiotherapy for 30 minutes and personalized exercise training, including cycling and treadmill exercise 2-3 times for 20-30 minutes per day at 60-80% of peak work rate for 3 weeks.

**Results:** In the first study rehabilitation resulted improvement in six minutes walking distance (6MWD: 310±44 vs. 409±33m, p<0,05), chest expansion (3,9±1,0 vs. 5,9±0,8cm, p<0,05) and modified Borg scale (Borg (D): 7,5±2,4 vs. 4,7±1,2, p<0,05). FEV<sub>1</sub> did not change significantly (45±18 vs. 47±20 %pred), and there was no correlation between FEV<sub>1</sub> and chest expansion. The change of inspiratory- (IRV) and expatatory rezerv volume (ERV) values did correlate wit chest expansion (IRV: R<sup>2</sup>=0,39; ERV: R<sup>2</sup>=0,31, p<0,05).

In the perioperative rehabilitation study, lung function did not change significantly after rehabilitation. Daily steps (PE: 4318±3177 vs. 5588±4035; PO:3486±2637 vs. 6799±2743\*; PEO: 5136±2343 vs. 5446±2403 before and 2118±1516 vs. 4187±1533 steps\* after surgery; \*p<0,05) improved. As an tendency, 6MWD increased (PE: 412±97 vs. 447±85m; PO: 347±139 vs. 443±121m; PEO: 423±95 vs. 473±87m before and 376±112 vs. 427±85m after surgery). Daily steps did correlate with 6MWD.

**Conclusion:** Chest wall expansion, dyspnea, hyperinflation and 6MWD significantly improved. Chest expansion was correlated with IRV and ERV. Measurement of chest expansion may add valuable information for complex evaluation of pulmonary rehabilitation. Our results support the hypothesis of pulmonary rehabilitation improves physical activity and maximal exercise capacity, as well. Our results underline the importance of physical activity in pre- and postoperative, and complex perioperative rehabilitation.

## **Rare lung diseases Chairs: Marjeta Terčelj, Adrien Halász, Jasna Tekavec - Trkanjec**

### **Rare and orphan lung diseases**

Marjeta Terčelj; *Clinical Department for respiratory diseases and allergy, University medical Centre Ljubljana*

Rare and orphan diseases are not widely researched, specific treatment is not often available, and which may only be limited to scientists and doctors. Consequently, patients feel abandoned and "orphaned" in the world of healthcare. A disease is defined as rare in Europe if it affects less than one in 2,000 persons. Approximately 8,000 different rare diseases have been identified, 80% of which are considered to be genetic origin.

Primary care physicians or pulmonologists may sometimes feel that they are not directly concerned by rare diseases; dealing with such diseases is usually reserved for specialists working in university centers. However, patients with such diseases are distributed throughout the country, and can begin their diagnostics close to the place where they live. Patients with rare disease feel orphaned in the healthcare world and often feel lack of solicitude. They are often disappointed and angry by failure to diagnose or misdiagnosis and it may take months or even years before they eventually find an experienced clinician. Diagnosis is especially difficult when the disease imitates a more common disorder. Furthermore, as teaching in medical schools cannot cover the many rare diseases it is unavoidable that general practitioners could not recognize all of the estimated 8,000 rare diseases. Therefore, the specialist must have the capacity at least to suspect the diagnosis of rare disease in his or her own field.

The interest of pulmologists for rare/orphan diseases has increased, over recent years, for several reasons. These include the advancement of diagnostic tools available these days. Associations for the patients with rare diseases continue to play a role in supporting patients, dealing with daily difficulties, distress and isolation.

The time has come to develop efficient care, especially through more appropriate diagnosis and research, including drug development. Major principles include the following: healthcare pathways for the patients should be organized, patients may be treated as near as appropriately possible to their home, improved clinical and basic science knowledge in the field of rare diseases should be an ethical duty for respiratory physicians.

### **Rare diseases in Slovenia and new diagnostic possibilities**

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Rare diseases, including rare pulmonary diseases, share some common features. Diagnosis is often established late in the evolution of the disease resulting in significant burden for patients and health system. Consequently, treatment and prevention possibilities are reduced. Slovenia developed National plan for rare diseases in 2012 prioritising epidemiological survey, early diagnostics, complex provision of medical and non - medical care and development of information resources for professionals and lay public in the field of rare diseases. Furthermore, the Centre for undiagnosed rare diseases and Centre for Mendelian Genomics were established at Clinical Institute of Medical Genetics, University Medical Centre Ljubljana. In the later centre, we implemented Next generation technology in the Slovene health system to improve genetic diagnostics. Indeed diagnostic yield of over 30% was demonstrated in 2014 with significant improvement of patients' access to genetic testing as well as cost efficacy.

## Cystic fibrosis - new knowledge, new pathogens

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The presentation overviews the pathogenesis of cystic fibrosis (CF), the types of mutations of cystic fibrosis transmembrane conductance regulator (CFTR) gene resulting in the alteration of airway surface liquid volume. Evaluate the inheritance of cystic fibrosis, the clinical symptoms and the social burden of the disease.

To summarize the myriad of treatments used in CF and the new developments in gene therapy researches offering promise of a cure for cystic fibrosis.

*Beside Pseudomonas aeruginosa that had already been known to colonise the lower airways of CF patients, a growing number of different pathogens such as Burkholderia cepacia complex, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, methicillin-resistant Staphylococcus aureus and nontuberculous mycobacteria can be found in the patient's sputum. Nowadays a new multidrug-resistant species, Inquilinus limosus could be isolated from a few cystic fibrosis patients, too. The eradication of the respiratory pathogens in cystic fibrosis would be an integral component to the increase survival of CF patients.*

## Treatment of early *pseudomonas aeruginosa* infection in children with cystic fibrosis

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### Introduction

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive hereditary disease in Caucasians (1). It is caused by mutations in a single gene of chromosome 7, which encodes CF Transmembrane Conductance Regulator (CFTR). This protein is a chloride channel that regulates ion and water transport across the apical membrane of epithelial cells in the respiratory, gastrointestinal, hepatobiliary and reproductive tracts (2). In the lungs, CFTR dysfunction cause a decrease in the airway surface liquid, thickened and viscous mucus that serves as a nidus for chronic respiratory infection and inflammation. Airway microbiology may change over the lifetime of a person with CF. *Pseudomonas aeruginosa* (PA) is more likely to be cultured from adolescents and adults (3).

### The significance of PA infection

PA is the most important lung pathogen in cystic fibrosis lung disease and is associated with declining pulmonary status in children and poorer prognosis (4). Initial colonisation may be transient. This stage of infection is not associated with a change in the patient's clinical status (5). PA strains initially colonising the CF airways, are single non-mucoid cells which only after some time change their phenotype into mucoid biofilms which are very difficult to treat with antibiotics (6). There is increasing evidence that anti-pseudomonal antibiotics initiated early after the onset of PA infection (non-mucoid phenotype, antibiotic sensitivity, and low density) is an effective strategy to eradicate the organism in the majority of cases and postpone chronic colonisation (3). Aggressive treatment prevented or delayed chronic PA infection in 78% of the patients for 3 ½ years and maintained or increased pulmonary function (7).

Although several protocols for eradication of PA after the first isolation are in use, no consensus exists regarding the optimal antibiotic protocol (8).

In the recent EarLy Inhaled Tobramycin for Eradication (ELITE) study patients were treated with tobramycin inhalation for 28 or 56 days. The primary endpoint was the median time to recurrence of PA and it was similar between the two groups (9).

The Early Pseudomonas Infection Control (EPIC) randomized trial was designed to evaluate the impact of four different anti-pseudomonal treatment regimens in CF children with recent isolation of PA from respiratory cultures. All participants received an initial antibiotic course consisting of 28 to 56 days of tobramycin inhalation solution (TIS) with or without oral ciprofloxacin. The trial revealed no differences between treatment regimens with respect to key microbiologic and clinical outcomes including PA recurrence, pulmonary exacerbations and hospitalisations (10). Recently published Cochrane database on antibiotic strategies for eradicating PA in people with CF included 49 trials with 744 participants. They found that nebulised antibiotics, alone or in combination with oral antibiotics, were better than no treatment

for early infection with PA. There is still insufficient evidence from this review to state which antibiotic strategy should be used for the eradication of early PA infection in CF (11).

#### **Our experiences with eradication therapy for *Pseudomonas aeruginosa* in CF patients**

At the CF centre Ljubljana, 60 children and adolescents till their 19th birthday are seen quarterly. In a six years period (during 2006-2011) all PA-negative CF patients who become PA positive as evidenced by one positive respiratory culture ((11 girls, 13 boys, age at first colonisation was median 62.5 months (range 3-196)) were immediately treated with 3 weeks of oral ciprofloxacin in combination with 1 month of inhaled tobramycin.

Eradication of PA was achieved in 20 patients (87%) which is comparable with published data. The median time to recurrence of PA for 7 out of these 20 patients was 27 (range 12-34) months. The remaining 13 are still PA negative.

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#### **Shared care for pediatric patients with cystic fibrosis in Slovenia**

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Cystic fibrosis (CF) is a complex disease. The care for people with CF demand specialist, medical and health care expertise. The expected lifetime and quality of life for patients with CF has improved significantly due to appropriate care in CF centers. CF centers have become a model of care for CF patients or have local directed care supervised by CF center. The key to successful treatment is a multidisciplinary team approach, which include consultant, clinical nurse specialist, microbiologist, physiotherapist, dietitian, pharmacist, psychologist, social worker, clinical geneticist and allied healthcare professionals, all experienced in CF care.

Slovenian children with CF could be treated in the national center for CF at Pediatric Clinic in Ljubljana or »shared care« center in the Department of Paediatrics in Maribor. The last one has all facilities for successful diagnostic procedures, treatment of acute worsening or regular patient controls. The team included experienced CF specialist with gastroenterologist, radiologists, physiotherapist and psychologist, partially also a dietitian and social worker. This center gives support for 12 children with CF which visit the CF center in case of special diagnostic procedures and treatment. All annual visits are performed in the CF center in Ljubljana (bone density, CF related diseases like diabetes, hepatic failure, dietitian advice...). Our satellite unit is in closer contact with the CF center for children and we have equivalent standards to that delivered in the center.

Shared care could be an appropriate option of care only for CF children and must be considered for patients, which cannot (or will not) travel to another part of the country for routine visits or in case acute clinical worsening. The shared care center must deliver all standards as in CF center and could not result in suboptimal care.

## Pulmonary arterial hypertension

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Pulmonary hypertension (PH) is common and associated with bad prognosis. Most commonly it is associated with left heart diseases and lung diseases. In this kind of PH it is important to recognize and treat basic diseases of the left heart and the lungs. On the other hand, rare types of pulmonary arterial hypertension (PAH) characterized by progressive remodeling of the distal pulmonary arteries (idiopathic/familialPAH and PAH associated with some drugs, connective tissue diseases, HIV, portal hypertension, congenital heart diseases and schistosomiasis) might be specifically treated with several types of targeting drugs (prostanoids, endothelin antagonists, and agents that increase nitric oxide bioavailability and in calcium channel blockers – only for <10% of patients who has positive acute vasodilator test during right heart catheterisation). In addition, we have several treatment options for PAH due to inadequate recanalization of the pulmonary circulation after pulmonary thromboembolism (chronic thromboembolic pulmonary arterial hypertension-CTEPH). Surgical pulmonary endarterectomy (PEA) is the mainstay of CTEPH treatment and has the potential to be curative. In inoperable CTEPH patients, new targeting drug that increase nitric oxide bioavailability by stimulation of soluble guanylate cyclase, has been beneficial. In addition, balloon pulmonary angioplasty (BPA) could also be a promising alternative. For all PAH patients a supervised rehabilitation program, psychosocial support, and referral to palliative care might also lead to improvements not only in outcome but also in quality of life. Lung transplantation remains the last option for suitable patients in whom other therapy was ineffective. Given the multitude of treatment options for PAH, early recognition and differentiation of type of PH is crucial for treatment decision and consequently for long-term management and outcome.

## Echocardiography as a screening tool for diagnosis of pulmonary arterial hypertension, what pulmonologists should know about that in modern era

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Pulmonary arterial hypertension Group 1 according to the classification of Nice is a disease associated with a poor prognosis and increased mortality. Early detection and early treatment with specific medications can improve not only the quality of life, but also the prognosis and survival. International guidelines recommend annual echocardiography screening in patients with systemic sclerosis and the BMPR2 mutation (idiopathic or familiar form). Screening methods used routinely have limitations. Echocardiography is performed by many echocardiographers, not all have sufficient skills in assessment of early form of disease. Routine echocardiography report should include complete hemodynamic assessment - stroke volume, minute volume, filling pressures of the left and right ventricle, as well as absolute value of systolic pulmonary artery pressure and pulmonary vascular resistance, especially in case of abnormal stroke volume. A combination of echocardiography and clinical parameters may improve the sensitivity and selectivity of current screening programs. In addition, early forms of disease might also be detected by exercise testing – ergospirometry and bicycle exercise echocardiography, currently used in research purposes also in our institution.

**Keywords:** pulmonary arterial hypertension, systemic sclerosis, early detection, echocardiography, bicycle exercise echocardiography

## **Right heart catheterisation (RHC) as a confirming tool for diagnosis of pulmonary arterial hypertension (PAH) – what pulmonologists should know**

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Right heart catheterization (RHC) is currently the gold standard for confirming pulmonary hypertension (mean pulmonary arterial pressure  $\geq 25$  mmHg), differentiating PAH from pulmonary-venous-hypertension associated with left heart diseases (pulmonary artery wedge pressure  $\geq 15$  mmHg), assessing disease severity and prognosis. However only on the basis of RHC it is not possible to differentiate patients with PAH associated with lung diseases and hypoxemia from patients with rare idiopathic/familial PAH and rare PAH associated with some drugs, connective-tissue-diseases, HIV, portal-hypertension, congenital-heart-diseases and schistosomiasis. Since this differentiation is essential for treatment decision, comprehensive diagnostic procedure including several imaging techniques and laboratory investigations should be done together with RHC. Nevertheless, before decision for treatment with targeting drugs for PAH (which are not indicated in patients with lung diseases), complete RHC including also acute vasodilator test (usually with nitric oxide) is needed. Positive test is associated with better prognosis and responsiveness to calcium-channel-blockers. Although the RHC has been shown to be safe (procedure-related mortality of less than 0.055% and morbidity of 1.1% when conducted in specialized centers) follow-up and monitoring of PAH management by noninvasive techniques is progressing and might replace invasive procedures. Such evaluations are currently in progress also in our institution.

## **Eisenmenger syndrome in adults: what pulmonologists should know about that**

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Pulmonary arterial hypertension (PAH) is a common complication of congenital heart disease (CHD). In CHD with left-to-right shunt (e.g. ventricular and atrial septal defect, patent ductus arteriosus, truncus arteriosus,...), increased pulmonary arterial blood flow may lead to vascular remodelling and progressive rise of pulmonary pressures and vascular resistances. When severely increased, they may lead to shunt reversal and the development of central cyanosis. This is clinically considered as Eisenmenger syndrome (ES). Patients with ES have multiorgan involvement (secondary erythrocytosis, bleeding and thrombotic diathesis, intrapulmonary thrombosis, hemoptysis, right ventricular failure, arrhythmias, renal and hepatic dysfunction, gout, infections,...). The morbidity and mortality of these patients is severely increased.

ES should be differentiated from other forms of PAH and central cyanosis. For example, in patients with severe pulmonary hypertension or right ventricular dysfunction and persistent foramen ovale (PFO), cyanosis may develop due to right-to-left shunting through PFO, however this should not be regarded as ES.

Patients with ES are inoperable and the only possible treatment nowadays, besides general measures and supportive therapy, is introduction of advanced PAH therapies (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclins). In rare cases lung or lung-heart transplant is an option. Due to complex management, patients should be referred to tertiary centers for adult CHD.

## **Dendriform pulmonary ossification**

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Dendriform pulmonary ossification (DPO) is a rare condition of unknown origin defined by widespread heterotopic bone production within the pulmonary tissue.

Pathogenesis is not precisely understood. Presumably ectopic ossification is the result of multiple factors that interact enhancing each other, including cell and tissue injury, alkaline environment, impaired pulmonary blood flow, presence of collagen and profibrogenic cytokines, extravasation, and metallic deposition. DPO is usually associated with preexisting underlying disorders such as idiopathic pulmonary fibrosis, adult respiratory distress syndrome, chronic obstructive pulmonary disease, alveolar hemorrhage, organizing pneumonia, pneumoconiosis , heavy metal exposure, and passive congestion due to chronic heart failure.

Although the majority of cases had been diagnosed on autopsy, the diagnosis may be simply established during the patients' life. In addition to transbronchial or open-lung biopsy, DPO can be diagnosed by HRCT scan using mediastinal window settings that may reveal multiple nodular and branching lesions of bone density.

Clinical course of disease seems to be indolent or slowly progressive. Prognosis depends upon age and underlying conditions of patient.

Although DPO seems to be uncommon disease, it is probably under recognized and rarely considered in differential diagnosis. However, clinical recognition of this disease is important, not only to avoid mistake in further treatment, but also to help in differential diagnosis of underlying preexisting diseases. Applying the HRCT scan, clinicians have a sensitive tool to detect DPO in earlier stage, which will enable a better understanding this entity and its relation to associated diseases.

## **Smoking-related interstitial lung disease**

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Smoking is a risk factor for the genesis of number of interstitial lung diseases. Smoking-related interstitial lung diseases (SR-ILD) comprise of entities known to have a strong epidemiological association with smoking, like respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP) and pulmonary Langerhans cell histiocytosis (PLCH). Smoking-related interstitial fibrosis (SRIF) is a distinct form of chronic interstitial fibrosis, denoted by thickening of alveolar septa by collagen deposition with minimal inflammation. It is important to separate SRIF which has a relatively benign course from both usual interstitial pneumonia and fibrosing nonspecific interstitial pneumonia.

The histologic appearance of lung injury secondary to cigarette smoke is diverse and consist of smokers' macrophages within airspaces, which may be airway centered (RB-ILD) or diffuse (DIP) in distribution, emphysema, small airway injury with fibrosis, remodeling that results in distortion, thickening of walls of small arteries, stellate cellular and fibrotic lesions of PLCH and alveolar wall fibrosis.

SR-ILD are considered as distinct clinical entities but they share a number of clinical, radiological and pathological features, suggesting that they represent a spectrum of patterns of interstitial lung diseases occurring in predisposed individuals who smoke.

The patient suspected to suffer from SR-ILD should be referred to the pulmonologist. Early treatment with novel, even targeted therapies like in some PLCH cases, and smoking cessation can improve clinical outcomes.

## **Interesting pediatric bronchology cases**

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### **Pediatric bronchoscopy**

Flexible bronchoscopy is an important diagnostic and therapeutic tool in pediatric pulmology. It allows for dynamic visualization of the airway and microbiological, cytological or histological sampling in all age groups, including premature and mechanically ventilated babies.

Thin instruments (outer diameter 2.8 mm) allow for procedures to be performed even in premature babies, with limited instrumentation suitable for working channel 1.2 mm. Instruments with other diameter over 4.9 mm have standard with working channel and allow for any endoscopic instrumental procedure.

The main indications for bronchoscopy in children are: evaluation of airway obstruction (stridor, suspected foreign body aspiration, severe recurrent bronchitis, recurrent pneumonia, persistent consolidation, and localized hyperinflation), infectious disease (severe unremitting pneumonia, tuberculosis and assessment of infection in immunocompromised patients), hemoptysis, and interstitial lung disease.

Flexible bronoscopies in children are many performed under general anesthesia, with spontaneous breathing preserved and ventilation through facial mask. Laryngeal mask or endotracheal tube is used only in specific cases, because they hinder a large airway segment, important in pediatric respiratory pathology.

### **Interesting cases**

#### **Persistent infiltrate in a 7-month-old boy**

A 7-month-old boy was admitted shortly after Christmas. He was his mother's forth child with no important prior medical history. He was febrile for several days; lab tests reviled elevated leucocytes and C-reactive protein. An infiltrate was seen in the left lower lobe.

Amoxicillin/clavulanic acid was started and he gradually improved over the next week, but remained subfebrile. Other family members got ill with signs of atypical pneumonia and the boy had pharyngeal swab PCR positive for Mycoplasma pneumoniae and received a course of midecamycine. Afterwards, he still did not make a full recovery, but his paleness and inapetence were attributed to mycoplasmal infection. The mother continued to be concerned because of his ill-looking appearance and a feeling of a "trill" over his left thorax when lying beside her. Persisting infiltrate on the CXR prompted bronchoscopy. Granulation tissue obstructing bronchus for the left lower lobe was seen. Biopsy was taken and histology reviled a surprising finding: incarcerated foreign body, most probably of vegetal origin. Rigid bronchoscopy was performed and granulation tissue removed together with a 4 cm long spruce branch with some needle-shaped leafs still attached. The boy made a full recovery, nobody know of or witnessed an episode of possible inhalation.

#### **A difficult to intubate neonate**

A term baby-girl was transferred to the neonatal intensive care unit immediately after delivery due to respiratory distress and central cyanosis. Transposition of the great arteries was diagnosed and patent ductus arteriosus sustained with prostaglandin E1. Intubation prior to atrial septostomy was very difficult. Prominent resistance to passage of the narrowest endotracheal tube (ID 2.0) was felt just below the glottis and congenital subglottic stenosis was suspected. The girl was extubated in the operating theater with thoracic and ENT surgeon present. Bronchoscopy reviled a long segment of full tracheal rings, starting 3 rings below the cricoid and extending to the lower trachea. The girl was reintubated bronchoscopically. Chest computed tomography confirmed very tight tube- tracheal fit, consistent with full tracheal rings extending almost to the carina, there was no associated left pulmonary artery sling. The girl had arterial switch performed and was breathing without prominent effort after extubation, no tracheal intervention was performed. Despite her condition, her growth is within normal limits, she shows no signs of exercise intolerance.

#### **Post-extubation stridor in a seven weeks old boy**

Seven weeks old boy was transferred to the pediatric intensive care unit because of severe respiratory distress. He got ill with coryza and mild fever a few days before, similarly to his older siblings. Due to imminent respiratory failure he was intubated in a regional hospital prior to

transfer. Infection with respiratory syncytial virus was confirmed and he made a fast recovery. Unexpectedly, two consecutive extubation attempts failed due to severe stridor. The third attempt was successful, but due to pronounced stridor and obstructed inspiration he remained on systemic steroids in very frequent local antiedematous treatment. Post-intubation subglottic stenosis was suspected and bronchoscopy scheduled. The inspection reviled prominent laringomalacia and a polipoid granulation tissue protruding from the right sinus of Morgani, dangling over the vocal cords and obstructing the airflow on inspiration. The tissue was removed with biopsy forceps, there was no bleeding. The boy recovered, tolerated oral feeds well and was discharged home. Control endoscopy after a month time showed no scar or local abnormalities, his laringomalacia persisted.

# Poster session

## „Asthma phenotypes”?

Zoltán Rózsavölgyi, Katalin Ugocsai; *Hosp. of Chest Diseases, Deszk*

Although nowadays using modern technologies are popular and widespread, but we have to be aware of that it is crucial to examine and take the patient's history carefully to diagnose their medical conditions, especially, in case the clinician has any doubt about the diagnosis. I'd like to demonstrate that with 2 thoughtful examples.

1.case: a middle-aged woman had been transferred to the A&E department with wheezing and haemoptysis. Lacking signs of inflammation in lab tests and on chest x-ray the patient was released from hospital with suggestions to have further pulmonology examination. The patient turned up in a specialty clinic where COPD was determined and bronchodilator therapy was prescribed. In addition to this she also had an appointment in our hospital. After the physical examination an urgent chest CT scanning was organised and a new direction of diagnostics was revealed.

2.case: a young woman, who was diagnosed with asthma bronchiale and annually monitored by the competent dispensary. She used a complex antiasthmatic therapy and was complaint-free. Unexpectedly, she got in A&E department because of a significant relapse in her general condition. A chest x-ray and an ENT-consultation was performed with negative results, so the patient was directed to our hospital for further care. As the applied treatment (high-dose intravenous steroids, short-acting bronchodilators, adrenaline, antihistamine) proved to be unsuccessful and we detected inspiratory stridor, we decided to act rapidly that brought an unforeseen result/twist.

## Concentration of specific Ig E serum in childhood

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**Introduction:** Antibodies are specific proteins - globulins, which are synthesized in the body in response to the parenteral introduction of the antigen and are capable of in vitro and in vivo to react with specific antigens. They are initiated by the Ig E mediated allergy.

**Purpose:** Determination of serum concentrations of specific Ig E in childhood.

**Materials and Methods:** Examined were children from 90 to 16 years old, of whom 26 had an increased concentration of specific allergens, 18 were men (69.2%) and 8 (30.8%) of them female. An evaluation of retrograde material was made in 3rd month period (April-June) in 2014 where the concentration of spec.IgE was measured in serum.

**Results:** The results obtained showed that during that period were examined a total of 90 children who were referred to our laboratory for determining the concentration of specific IgE in serum. The distribution of children according to their age who had elevated serum spec.IgE was 7 children up to 3 years, 12 children up to 7 years and 7 children under 11 years.

Of all the samples examined in 26 (28.8%) had elevated levels of some of the specific IgE in serum. So by the inhaled allergens:Dermato.pt. 30.7% x13.0 IU/mL class 3, Dermato.far. 38.4% x 10.9 IU/mL class 3, Mixed grasses early 34.6% x 16.8 IU/mL class 3, Mixed grasses late 46.1% x 14.0 IU/mL class 3 ; Mixed grasses late 30.7% x 5.3 IU/mL class 3.

**Conclusion:** EIA test is highly application method, simple to perform. The determination of specific IgE is of great importance. They provide information on whether the process started sensitizing. It reflects the degree of the allergic sensitization . It confirms the presence of a particular allergen, which initiated the process in the absence of clinical entity that can provide later development of allergic disease. This leads to the conclusion that the specific IgE is an important bio marker of clinical expression of the atopy among our asthmatics patients.

## **Polymorphism rs9910408 in TBX21 gene is a predictor of response to inhaled corticosteroids in adult asthmatics**

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**Background.** The aim of our study was to evaluate the success of long-term inhaled corticosteroids (ICS) controller therapy in adult asthmatics. Polymorphisms in genes important for the biologic action of corticosteroids might be responsible for different treatment response.

**Patients and methods.** This is a prospective study involving 208 adult patients with newly diagnosed ("glucocorticoid naïve") mild to moderate asthma. The chosen treatment outcome parameters were: changes in FEV1, PD20 for methacholine, Asthma Control Test (ACT) and Asthma Quality of Life Questionnaire (AQLQ) scores. We also wanted to evaluate correlations between changes in all four parameters after 3-6 years of treatment with ICS. In the genetic part of the study polymorphism rs9910408 in TBX21 was genotyped in all 208 patients. Genotypic distribution and allelic frequencies in »good« and »poor« responders were compared.

**Results.** Despite the fact that all four parameters of asthma treatment outcome showed a significant improvement, we only found significant correlation between change in asthma control and change in asthma-related quality of life.

Polymorphism rs9910408 was associated with response to ICS treatment. In good responders, assessed by increase in PD20, the frequency of AA genotype was significantly higher than in poor responders. With regard to changes in PD20 and in FEV1 this genotype related response was even more evident in the subgroups of non-smokers and non-atopic patients. Furthermore in non-atopic patients AA genotype was overrepresented among good responders regarding changes in AQLQ score.

**Conclusion.** There is only weak correlation between changes in subjective and objective treatment outcome parameters after long-term treatment with ICS in adult asthmatics. Our results showed that treatment response to ICS is associated with polymorphism rs9910408 in TBX21 gene.

## **How combined therapy ICS/LABA plus montelukast affects on the inflammation in patients with severe asthma**

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**Introduction:** Asthma is a chronic inflammation disease in which many cells play a role with secreting a variety of mediators. IL-5 is a cytokine necessary for the development, differentiation, recruitment, activation, and survival of eosinophils during inflammation.

**The aim of this study** was to determine the effect of triple combined therapy: anti-leukotrienes Montelukast plus ICSs / LABAs in patients with severe asthma by analyzing of level of IL-5 and blood eosinophils after 6 months of therapy.

**Method:** The study included 29 patients, treated with ICSs/LABAs (500/50mcg-twice daily) plus anti-leukotrienes - Montelukast (10mg-daily). In each of them were measured serum IL-5 by the ELISA method and blood eosinophils were measured in a peripheral blood smear, the beginning and after 6 months of therapy.

**Results:** The results were statistically elaborated according to the Wilcoxon Pairs Test. The obtained results of IL-5 showed that their level before the start of therapy were much higher and treatment statistically significantly reduced their value ( Z=4,64; p=0,000004; p<0,05). After 6 months of treatment the eosinophils were statistically significantly reduced in peripheral blood (Z=2,99; p=0,0028; p<0,05).

**Conclusion:** In this study, the addition of anti-leukotrienes – Montelukast in regular preventive therapy with ICSs/LABAs in patients with uncontrolled severe asthma leading to reduced inflammation and airway remodeling, certainly clinical and subjective improvement which is a therapeutic option and a step towards achieving total control of asthma and certainly able to reduce the dose of ICSs/ LABAs or discontinued the anti-leukotriens.

## **Clinical practice of non-invasive ventilation use in acute exacerbations of chronic obstructive pulmonary disease with respiratory acidosis**

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**Background:** In acute exacerbation of chronic obstructive pulmonary disease (AECOPD) non-invasive ventilation (NIV) is advised as treatment in patients with respiratory acidosis (RA) and strongly advised in patients with pH<7.30 due to its benefit - it decreases length of hospitalisation, need for endotracheal intubation with its complications, in-hospital mortality, incidence of exacerbations and the need for long term oxygen treatment (LTOT) initiation. Overoxygenation can cause or worsen RA and therefore adjustment of oxygen therapy on admission can on itself cause improvement in some cases.

**Aim:** Evaluation of clinical practice of NIV use in AECOPD patients in RA at University Clinic Golnik respiratory centre.

**Methods:** A two year retrospective analysis of medical charts of all consecutive AECOPD patients treated in a tertiary respiratory centre in 2013 and 2014 was performed. Patients with the discharge diagnosis of AECOPD were included.

**Results:** Final sample included 434 acute exacerbations in 335 patients (age 71±10 years, 64% men and 36% women, 74% with FEV1<50%, 22% on LTOT, 5,1% on chronic NIV, 87,5% with comorbidities). On admission 74 patients (27%) were acidotic. After initial treatment additional 25 (5.8%) patients became acidotic and 25 (5.8%) acidotic patients improved with pH raising above 7.35, of which 10 (2.3%) improved mainly due to decreased oxygen flow. 82 (19%) patients were overoxygenated (oxygen saturation >95%) at the time of arrival to the emergency unit. 221 (51%) patients were admitted hypercapnic and in 131 (30%) pCO<sub>2</sub> on admission was above 7kPa. Overall 38 (8.8%) patients received NIV (42% in intensive care unit and 58% in NIV unit). In patients who were not intubated NIV was received by 67% (4/6) patients with pH<7.2, 40% (8/20) with 7.2<pH<7.3 and 18% (11/60) with 7.3<pH<7.35 ( $p<0.001$ ). 5 (1,2%) patients needed NIV and intubation. Overall intubation rate was 2% and in-hospital mortality 5.3%.

**Conclusions:** Use of NIV as AECOPD with respiratory acidosis treatment was lower than expected according to guideline recommendations. Emergency oxygen treatment was inappropriate in some patients and contributed to RA.

## **ADAM33 single nucleotide polymorphisms and the asthma phenotypes in children**

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Genetic association studies have demonstrated that multile SNP variants in ADAM33 are associated with airway remodeling and hyperresponsiveness in different ethnic groups. The objective of this study was to determine whether some ADAM33 polymorphisms are associated with asthma in a population of asthmatic children from Balkans.

**Method:** A crosssectional pilot study comparing the polymorphisms of asthmatic patients from Bulgaria over a period of 1 year according the asthma severity.

**Patients:** 71 asthmatic children and 29 healthy children of 5 to 17 years old were assessed for allelic association of ADAM33 T1 (rs2280091), T2 (rs2280090), V4 (rs2787094) and S1 (rs3918396) SNPs to asthma. Genotyping was done by real timePCR. For all asmatic patients detailed asthma history,treatment regimen, bronchodilator response, eosinophil count in nasal smear, asthma control level and ACQ were performed

**Results:** These SNPs were strongly associated with childhood asthma compared to healthy controls ( $P< 0.05$ ). V4 is associated with eosinofilic inflamation.

**Conclusion:** The ADAM33 gene polimorfisms play an important role in facilitating susceptibility to childhood asthma not only in Western Europe populations but also in the population of South-East Europe. **Acknowledgements:** This work was supported by a grant from the Medical University of Sofia (Council of Medical Science, project no. 71/2014, grant no. 65/2014).

## **Investigations of broncho-alveolar lavage in children with chronic respiratory diseases**

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**Background:** Bronchoscopy and examination of bronchoalveolar lavage (BAL) are useful and reliable tools for an objective monitoring of the respiratory tract in children with chronic pulmonary diseases. BAL studies allow cells, pathogens and soluble components from the distal parts of respiratory tract to be examined.

**Aim:** The purpose of this work is to evaluate the clinical significance of BAL in children with asthma, bronchiectasis and cystic fibrosis

**Methods:** For period of 5 yearswe performed bronchoscopy with obtaining broncho-alveolar lavage of 60 children with chronic respiratory disease. The children were divided in three groups: Group I - 10 children with bronchiectasis; Group II - 20 with bronchial asthma; Group III - 30 with cystic fibrosis (CF). The children aged 4 to 17 years underwent a fibrobronchoscopy with BAL aspiration. BAL is performed with 10-15 ml warm 37°C physiological serum. Microbilogical, cytological and immunological examinations of the BAL liquid were performed. All results were compared between the groups and with healthy controls from our previous studies and world literature data.

**Results:** The contents of the cellular elements reflected the character of the inflammation process in the respiratory tract. The presence of eosinophils leucocytes was typical in the patients with asthma with or without inflammatory changes. Neutrophil-dominated endobronchial inflammation was a major characteristic of cystic fibrosis and non-CF bronchiectasis. Especially for children with CF the levels of polymorphonuclear cells were 30-79%, and was noted deformation of the cells of ciliary epithelium, even some of them with metaplasia signs.

Immunoglobulin levels in bronchial secret depended of nosologic entity and special features of the clinical progress of the disease. In children with bronchiectasis with catarrhal endobronchitis high level of SIgA and IgG was found; in purulent endobronchitis, found predominantly in children with cystic fibrosis IgG levels even were higher with demonstrative low levels SIgA; for children with bronchial asthma low level of SIgA and high level of IgE in BAL fluid is a characteristic finding. As a contrast of the other groups all CF patients had significantly low levels of  $\alpha_1$ -antitripsin. In some of the patients ECP was estimated and found in higher level in children with bronchial asthma. Most common microbiology finding in patients with CF was *P.aeruginosa* – in 16 children, followed by *S.aureus* – in 7. The patients with asthma predominantly hadn't had any clinical relevant pathogen isolated. The patients with bronchiectasis had diverse microbial flora, without any prevalent pathogen.

**Conclusions:** If used properly, BAL can be a useful clinical tool that can assist in the diagnosis and follow up in children with asthma, bronchiectasis and cystic fibrosis, for it reflects the extent of the chronic inflammation and chronic infection in the lungs.

## **Small airway indices in asthmatic children**

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**Introduction:** Pulmonary function testing allows assessment of the severity of airflow constriction, its reversibility and variability and confirmation of asthma diagnosis. In contrast to adult, children often have normal pre-bronchodilator spirometry, even when they are symptomatic. The bronchodilator responsiveness (BDR) is safe and widely used in the clinical practice tool for detecting active asthma.

**Objectives:** To determine the value of bronchodilator response (BDR) in asthmatic children; to evaluate parameters of pre- and post-bronchodilator spirometry according to control treatment; to determine the degree of BDR and MMEF 75 and MMEF 25/75 in children with normal baseline spirometry.

**Materials and methods:** In a 24 month period pre- and post-bronchodilator spirometry was conducted in 70 children with asthma, aged 5 to 17 years, admitted in our clinic. 56 of examined children (80%) showed positive BDR ( $\Delta FEV1\% pred \geq 12\%$ ). Half of the examined children are atopic, 44% have diagnosed allergic rhinitis. Without control therapy in last eight weeks are 57% of examined children, 20% of them are treated with ICS, 12% in combination with leukotriene antagonist and 11% on monotherapy with antileukotriene agents.

**Results:** Normal pre-bronchodilator spirometry (FEV1% pred  $\geq 80\%$ ) was observed in 57 children (73%), 89% of them have MMEF25-75 <67%. In the group with positive BDR 30 children (54%) demonstrated normal baseline spirometry, 93% of them have shown low MMEF25-75 (<67%). Between the two groups (positive and negative BDR) had a statistically significant difference between the mean values of MMEF70%pred., MMEF 25/75%pred, FEV1% pred. and FEV1/FVC. In the positive BDR group was established a statistically significant difference in the mean MMEF25/75% Pred. between the groups with normal baseline spirometry and those with FEV1% pred <80%. In children that were hospitalized in the previous year is found a greater likelihood of positive BDR. A positive correlation was observed between MMEF75%pred. and BMI, history of previous year hospitalization and the age of wheezing appearance.

**Conclusion:** Asthmatic children often have normal pulmonary function when not exacerbated, but that does not exclude airway hyper-responsiveness and severe airway obstruction during an acute attack. MMEF25/75% Pred. is a good indicator of bronchial obstruction and airway dysfunction despite the presence of normal FEV1.

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## **Uporaba sedacije pri bronhoskopiji**

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Bronhoskopija z upogljivim bronhoskopom je pogosta in nujna preiskava za diagnostiko in terapevtske posege pri bolnikih z boleznimi dihal. Z razvojem tehnologije so intervetni posegi pri bronhoskopiji vedno bolj napredni, predvsem pa kompleksnejši in pogosto zahtevajo daljše postopke.

Za lajšanje neugodja bolnika ob bronhoskopiji, poleg lokalne/topične anestezije, več leta vedno pogosteje uporabljamo sedacijo. Standardni postopki sedacije se med bolnišicami zelo razlikujejo, ker so priporočila o uporabi premedikacije in izboru zdravil za sedacijo nasprotujoča. Prav tako ni zaključena razprava na temo kdo naj in lahko vodi sedacijo; anesteziolog ali endoskopist.

Za objektivizacijo globine sedacije in zadostnosti ohranjenega spontanega dihanja je morda ob običajnem nadzoru vitalnih parametrov (EKG, SpO<sub>2</sub>, pulz, NiBP) ustrezejša kapnografija, oziroma neinvazivno merjenje parcialnega tlaka CO<sub>2</sub> v izdihanem zraku.

Poleg uveljavljenih učinkov za sedacijo, kot so midazolam, kratkodelujoči opioidi in propofol, v novejših študijah v ospredje prihaja uporaba Dexmedetomidina, lipofilnega alpha-2 agonista s sedativnimi in analgetičnimi učinki, brez pomemne depresije dihanja.

## **Young female with large echinococcal cyst in lungs**

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We report a case of young female with echinococcosis. Echinococcosis, also called hydatid disease, is a parasitic disease caused by infection with tapeworms of *Echinococcus* type. Echinococcosis is classified as either cystic echinococcosis or alveolar echinococcosis. Persons with cystic echinococcosis often remain asymptomatic until hydatid cysts containing the larval parasites grow large enough to cause discomfort, pain, nausea, and vomiting. The cysts grow over the course of several years before reaching maturity and the rate at which symptoms appear typically depends on the location of the cyst. The cysts are mainly found in the liver and lungs but can also appear in the spleen, kidneys, heart, bone, and central nervous system, including the brain and eyes.

Imaging techniques, such as CT scans, ultrasonography, and MRIs, are used to detect cysts. After a cyst has been detected, serologic tests may be used to confirm the diagnosis.

In the past, surgery was the only treatment for cystic echinococcal cysts. Antiparasitic therapy, cyst puncture, and PAIR (percutaneous aspiration, injection of chemicals and reaspiration) have been used to replace surgery as effective treatments for cystic echinococcosis.

28-year-old female was admitted to our department due to a dry cough and chest pain for past 3 months. She was previously never ill, she never smoked. Physical examination on admission was normal.

Chest x-ray showed a large left upper lobe mass and CT scan confirmed fluid-filled cystic mass 18,7x11x15 cm in left hemithorax. The mass infiltrated pleura on the left side and displaced heart and mediastinum to the right side. Abdominal CT scan showed partially calcified cystic mass 5 cm in diameter in liver.

Laboratory tests showed mild leucocytosis, elevated CRP of 63 mg/L and positive hydatid serologic tests. She was born in country where hydatid disease is endemic.

Her case was discussed on multidisciplinary board, where several treatment options were discussed, including albendazol, PAIR and surgical resection of the cyst. She was first treated with albendazol in hope of lessening the cyst. After 4 weeks of treatment she was admitted to the department of thoracic surgery because of worsening of chest pain and dry cough. She underwent posterolateral thoracotomy and pneumonectomy had to be performed due to the size of the cyst and infiltration of the whole left lung.

24 hours after the surgery patient became extremely tachypnoic and needed orotracheal intubation with ventilation with 100% oxygen. CT scan showed right lung pneumonia. She was treated with imipenem, fluconazol and albendazol. To improve oxygenation nitric oxide was added to oxygen. After four days she was extubated and 14 days after surgery she could leave the hospital. She continued treatment with albendazol for 4 more weeks.

Almost 1 year after lung surgery patient underwent a surgical resection of liver cyst, which measured 5x4,5 cm, with albendazol treatment pre- and post-operatively.

## The causes of death among patients with tuberculosis

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**Introduction:** Tuberculosis is one of the main causes of morbidity and mortality in different societies. In 2010, there were an estimated 12 million people living with active TB, including 8.8 million new cases and there were an estimated 1.4 million deaths. Identifying causes for death following diagnosis of TB is important for planning effective interventions to reduce death rates.

**Aims and objectives:** The aim of this study was to assess and determinate main causes of death in TB patients in our Institute.

**Materials and methods:** It is a retrospective descriptive study conducted in Institute for lung diseases and tuberculosis, Skopje, Macedonia, from 2010 to 2013. Medical records of died tuberculosis patients over 4 – year period were reviewed and death data were analyzed.

**Results:** Twenty two deaths ( 15% from all hospitalized patients ) with mean age of 58+- 10.3 years were detected, 69.6% were male and 30.4% were female. The frequency rate for cigarette smoking, alcoholism, diabetes, intravenous drug usage, as risk factors were 54.5%, 22.7%, 4.5% and 4.5% respectively.

12 deaths ( 54.5%) were directly attributed to tuberculosis, among them overwhelming TB disease with respiratory failure, massive haemoptysis and MDR-TB accounted as the cause of death in 75%, 8.3% and 16.6% respectively.

10 deaths (45.5%) were due to other medical problems, which included, COPD, cardiovascular diseases, high blood pressure, cirrhosis, dementia i.e. 18.2%, 31.8%, 18.2%, 4.5% and 4.5% respectively.

The median time of survival was 28 days. 77.2% of patients died during the initial-2- month intensive phase of anti - TB treatment. 36.4% died in the first 10 days of treatment.

Those who died of tuberculosis had statistically significant ( $p < 0.001$ ) a shorter median survival (14.9) days in comparison with group who had other medical problems ( 27days ).

**Conclusion:** This study showed that overwhelming TB disease, with respiratory failure, haemoptysis, cardiovascular diseases, COPD, cirrhosis are main cases of death. Smoking, alcoholisms, diabetes, intravenous drug usage are frequent risk factors for TB mortality.

## Pertussis whooping cough as a cause for collapse

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Re-emerging Disease is a condition, usually an infection, that had decreased in incidence in the global population and was brought under control through effective health care policy and improved living conditions, reached a nadir, and, more recently, began to resurge as a health problem due to changes in the health status of a susceptible population. In our case history we would like to show a 67-year old men's story. His complaints were coughing, which was followed by headache, vomiting and syncope. During Otorhinolaryngology examination was found nothing special. His complaints reoccurred, and one shub was in the emergency department before the eyes of an infectologist. His idea was to examin the patient for Pertussis disease. In laboratory values we found high leukocyte level, with high lymphocyte number, and low CRP level. In the pulmonology department all other causes of coughing and syncope were excluded, Sumetrolim was given for the patient. Serology tests proofed high pozitivity for *Bordetella pertussis* toxin. Patient's symptoms were solved with Sumetrolim therapy. He was vaccinated with DaPT in his childhood.

# **Microbiological analysis of bronchoalveolar lavage from immunocompromised patients**

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**Introduction:** Bronchoscopy is one of the indispensable diagnostic and therapeutic procedures in pulmology. For diagnosing infections in immunocompromised patients we use a mini BAL technique consisting of three 20 mL aliquots of 0.9% saline solution (BAL I, II and III). Each sample is used for specific microbiological analysis: BAL I (most contaminated) for detection of *Pneumocystis jirovecii* and *Toxoplasma gondii*, BAL II for detection of viruses, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* and BAL III (least contaminated) for gram stain and bacterial/fungal cultures.

The aim of this study was to assess the diagnostic utility of this technique and the impact for previous antibiotic therapy on the yield.

**Methods:** In a retrospective study 91 samples from 79 patients (51 males and 28 females, average age 56.6 years) were analysed. They were divided into following groups: hematological patients (12 [13.2%]), patients after transplantation (bone marrow: 7 [7.7%], solid organs: 39 [42.9%] and lungs: 7 [7.7%]), patients receiving chemotherapy (11 [12.1%]), patients receiving systemic corticosteroids (10 [11.0%]) and patients with HIV (5 [5.5%]). The samples were obtained in a 3-year period (2012 – 2014).

**Results:** In total, there were 77 (84.6%) positive and 14 (15.4%) negative samples. In 11 (12.1%) cases obvious contamination was detected. In the group of patients who were receiving antibiotic treatment before sampling (67 samples, 73.6% of total) 58 (86.5%) were positive and in the group of patients who did not receive antibiotic treatment (24 samples, 26.4% of total) 19 (79.2%) were positive. There was no significant statistical difference in the yield of sampling between these two groups. BAL I was positive in 23 (25.3%), BAL II in 23 (25.3%) and BAL III was positive in 67 (73.6%) of cases. Number of negative samples was the highest in the group of patients after bone marrow transplantation (43%) and in the group of hematological patients (25%). The most common isolated pathogen was *Pneumocystis jirovecii*, except in groups of patients after bone marrow and lung transplantation where there were no *P. jirovecii* cases, possible due to strict prophylaxis use. *Pseudomonas aeruginosa* was isolated only in group of patients after organ transplantation, *Veillonella* sp. and fungi were isolated in all groups of patients. There was no difference between groups regarding other isolated bacteria or fungi.

**Conclusions:** The method of triple mini BAL was useful for detecting pathogens in the group of immunocompromised patients (yield 84.6%). Antibiotic treatment did not reduce the yield of examination. The results must be evaluated according to clinical picture as some pathogens (*Veillonella*, *C. albicans*) may represent contamination.

## **Glucocorticoid induced osteoporosis and adrenal insufficiency in 37 patients with interstitial pulmonary diseases**

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Osteoporosis is a common complication of glucocorticoid therapy. Awareness has grown in recent years, yet it remains under-diagnosed and under-treated. We retrospectively examined documentation of 37 patients treated for interstitial pulmonary diseases at Klinika Golnik from November 2013 onwards. Nearly all patients 97% (37/38) underwent a dual-energy X-ray absorptiometry (DXA) at the beginning of treatment with systemic glucocorticoids, yet in 21,6% (8/37) patients the read-out was inaccurate and underestimated the possibility of fracture. 65% (24/37) of patients were treated with active form of vitamin D and supplemental calcium. 19% were prescribed bisphosphonates and another 22% (8/36) should have been treated but were not due to underestimation of risk for glucocorticoid induced bone fracture or due to doctor oversight. Only 32% (9/28) of patients were re-evaluated with DXA 6-12 months after therapy with glucocorticoids was started. Nine patients were lost to follow-up or data was missing. Bone mineral density was significantly reduced at control in 22% (2/9), yet none of them were treated for osteoporosis. For 2 patients data is missing. In only 2 patients there is evidence of osteoporotic fractures, yet in 94% (31/33) of patients this crucial data is missing. 48% (14/29) of patients stopped treatment with glucocorticoids in the observed period of time, yet in only 3 (21%) Synacthen test was performed to assess for adrenal insufficiency (for 6 patients data is missing). In 66% the test was either inaccurately performed or the result was not interpreted properly. In conclusion, while awareness of glucocorticoid induced osteoporosis is high, identification and treatment of patients at risk and follow-up of these patients can still be improved. Assessment of adrenal insufficiency at termination of glucocorticoid treatment is rarely performed.

## **Aspiration of barium contrast**

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A man aged 47 years was hospitalized cause of dysphagia. 26 years earlier his esophagus had been removed and the jejunopharyngeal anastomosis had been made due to corrosive injury of the esophagus with hydrochloric acid. During hospitalization, the gastroscopy was not done because of the impossibility of passing the instrument at the level of the pharynx. X-ray passage of the esophagus with barium porridge was done. Due to the strong cough, the aspiration of the contrast appeared into the trachea and right bronchial hemisystem. Right bronchogram was strongly positive. Urgent therapeutic bronchoscopy examination has been done. Diffused small deposits of the contrast were seen in the right bronchial hemisystem, especially in region of the middle and low lobe. They had been aspirated and consequent hyperaemia of the epithelium has appeared.

Patients complained on productive cough and dyspnea, as well as mild pain on the right side of the chest. After three days chest X-ray showed infiltrate with a small amount of pleural effusion in the middle and lower lobe of the right lung. Antibiotics and corticosteroids were administrated during next 13 days. Control chest X-ray showed the regression of the infiltrate and effusion. Subjective and clinical recovery was observed.

## **Effect of enzyme replacement therapy on lung involvement and changes in peripheral immune cell subsets in Fabry disease**

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**Introduction:** Fabry disease is an X-linked lysosomal storage disorder, causing accumulation of globotriaosylceramid (GL-3) in different organs. Glycolipids are activators of different immune cell subset, the resulting inflammation is responsible for organ damage. Pulmonary involvement leads to airway inflammation; however data on severity, as well as the effect of enzyme replacement therapy (ERT) on lung involvement and changes in peripheral immune cell subsets are sparse.

**Methods:** Seven Fabry patients and 4 carriers were screened for pulmonary manifestations. Repetitive measurements were performed on 5 patients on ERT (average follow-up 5 years). Patients with Fabry disease (n=3, repetitive measurements) and control volunteers (n=33) were included into peripheral blood cell measurements.

**Results:** Lung involvement was present in all patients, symptoms suggestive for lung disease were mild, however obstructive ventilatory disorder, dominantly affecting small airways accompanied by hyperinflation was demonstrated in all patients as compared to carriers. ERT resulted in stabilization of lung function in all treated patients. Decreased ratio of myeloid DC, NK cells, invariant (i)NKT cells, Th17 cells while increase in T helper (Th)1 cells, and no change in Th2 and regulatory T (Treg) cells were detected in Fabry patients compared to controls.

**Conclusions:** Fabry disease results mainly in asymptomatic lung involvement, characterized by moderate non reversible obstructive ventilatory disorder. Stabilization of airway obstruction during follow-up was observed using ERT. Significant decrease in myeloid DC, NK, iNKT and Th17 and increase of Th1 cells in the peripheral blood might represent a GL-3 mediated inflammatory process of Fabry patients on ERT.

## **Female patient with CVID and pulmonary granulomatosis**

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Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency. Amongst patients with CVID, it often presents itself as granulomatous disease that can involve different organs. Some of them show clinical manifestation similar to sarcoidosis, with symptoms like dyspnea, persistent cough, artralgia. Non-caseous granulomatous lesions that affect CVID patients are histologically indistinguishable from those in diagnosis of CVID. There is often a delay in diagnosis of CVID.

A 57 year old female patient was diagnosed with sarcoidosis of the lungs with hypercalcemia in 2010. After treatment with systemic corticosteroid the patient improved. After a few months on an already low corticosteroid dose she developed serious infection and CVID was diagnosed. Upon therapy with immunoglobulins she clinically improved and her lung function remained stable.

## **Drug addict with respiratory insufficiency**

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We report here an 48 yrs old male patient, ex-drug addict on metadon supplemental therapy since 1998 with progressive dyspnea over last two years and marked respiratory insufficiency. He also has chronic hepatitis C infection with histologically confirmed moderate liver damage and inflammation grade 8/ stage 2, which was untreated due to bad psychiatric condition of the patient in the past. On admission, the patient was dyspneic on minimal exertion, with pO<sub>2</sub> at rest on air 5,8 kPa, pCO<sub>2</sub> 4,3 kPa, oxygen saturation level 80%, clear sign of platipnea and orthodeoxia with pO<sub>2</sub> 5,3 kPa in upright position and pO<sub>2</sub> 8,0 kPa in supine position. Pulmonary function test shows normal flow rates and nonspecifically lowered DLCO of 40%. Echocardiography was almost normal, but contrast enhanced echocardiography revealed right-to-left shunt on the level of pulmonary vessels. CT scan showed dilated peripheral pulmonary vessels and emphysema. There were dilated portal and lienal vein on abdominal ultrasound. According to triad of chronic liver disease, impaired oxygenation and right-to-left pulmonary shunt diagnosis of hepatopulmonary syndrome was made and long term supplemental oxygen therapy was initiated. Advisory council suggested treatment of hepatitis C with subsequent liver transplantation as the only successful treatment plan option for our patient, but unfortunately, both treatment options were refused by the patient, who is now at home on high flow supplemental oxygen therapy of 15L/min, on palliative care, uncapable of any exertion or being in upright position due to progression of the disease.

## **Farmer's lung with a high CD4/CC8 ratio lymphocytic alveolitis – a case report**

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**Background:** Farmer's lung is one of the most common forms of hypersensitivity pneumonitis. It is a granulomatous inflammatory disease of the pulmonary parenchyma caused by the immune response to inhalatory antigens, mostly actinomycetes or moulds. The diagnostics range from imaging techniques to bronchoalveolar lavage, which demonstrates a lymphocytic alveolitis with a low CD4/CD8 ratio, typical for hypersensitivity pneumonitis, in only one third of patients. It is hypothesised that a low CD4/CD8 ratio predicts a prosperous course of the disease, but a high CD4/CD8 ratio lymphocytic alveolitis has yet to be determined to announce a more severe clinical course.

**Case report:** This case report presents a patient with farmer's lung with an unusually high CD4/CD8 ratio lymphocytic alveolitis and the dynamics of her disease in relation to her environment and therapy. The diagnosis was based on the following criteria: history of exposure to moulds at home, typical clinical picture such as crackles on chest exam, weight loss, breathlessness and cough, high titres of specific IgG against moulds (serum precipitins), diffuse "ground glass" interstitial changes on HRCT, lung biopsy revealing partially developed noncaseating granulomas, yet BAL revealed lymphocytic alveolitis with a high CD4/CD8 ratio. During this diagnostic procedure in hospital, even with no therapy, there was clinical improvement. It was the same each time the patient moved away from the risk home environment, with a setback every time she returned back home. Thorough sanitation of her house was advised, but she managed to renovate it only partially, thus even with appropriate glucocorticoid therapy, disease gradually led to lung fibrosis with pulmonary hypertension.

**Conclusion:** Our case report does not only illustrate a clear etiological correlation between exposure to causative antigens and progression of farmer's lung, but also emphasises the necessity of early recognition and thorough sanitation of patients' living space. Furthermore, a high CD4/CD8 ratio lymphocytic alveolitis, which is not typical for hypersensitivity pneumonitis, might well be an indicator of a worse clinical course of the disease, despite appropriate therapy, and may also be a manifestation of a still unknown genetic disposition.

**Key words:** hypersensitivity pneumonitis, lymphocytic alveolitis, high CD4/CD8 ratio, disease dynamics, living environment, sanitation

## **Case report: Eosinophilic granulomatosis with polyangiitis associated with montelukast**

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**Background:** Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome) is an uncommon vasculitis of unknown etiology. Cases of EGPA appeared in asthmatic patients treated with leukotriene modifier-montelukast. Studies suggest that montelukast could be related to this syndrome by unmasking the underlying vasculitis and it is probably not the direct cause of the syndrome.

**Methods:** data from medical history was collected.

Case report: 23-year old female student with a history of asthma and nasal polyps, treated with ICS, SABA, antihistaminics and montelukast. Sometimes treated with glucocorticoids intravenously. Disease started few days before hospitalization with fever (39°C), dry cough and progressive shortness of breath. Applied medications for asthma exacerbation were not helpfull. Blood leukocytes were  $14 \times 10^9/L$ , segmented 54% non-segmented 2%, eosinophils 22%, lymphocytes 9%. Chest x-ray showed infiltrates in upper lobe and in the base of the left lung, also right subpleural. (image 1) Stool examination for parasites was done repeatedly and it was negative. Histopathological findings (transbronchial biopsy): densit eosinophilic infiltrates in lung parenchyma and also in blood vessel wall, it could match the diagnosis of EGPA. (image 2)

She was treated with glucocorticoids (0.6 mg/kg BW) for two weeks with dosage reduction over several days to the maintenance dose of 6 mg of metilprednisolone. Three-four days after the treatment with glucocorticoids started, she started feeling better. She did not have dry cough and breathlessness anymore. Chest x-ray returned to normal after ten days of treatment. She continued taking montelukast although she was advised otherwise.

She stopped taking corticosteroid (after two months) and montelukast because she became pregnant. Her condition became worse in the last month of pregnancy and she started taking montelukast again. She came to emergency department very often where she would be treated with oxygen and intravenous glucocorticoids.

Twenty days after giving birth, she came to pulmonologist because of extreme shortness of breath and chest pain. She was pale, subfebrile (37.4°C), tachypnoic (respiratory rate: 32/min) and tachicardic (pulse: 120/min). Lung sounds were decreased, no obstruction was heard. Her blood leukocytes were  $8.6 \times 10^9/L$  with 12% of eosinophils, liver function test were normal, D-dimers were 1.67 mg/L. Chest x-ray showed bilateral pleural effusions with no lung infiltrates, heart shadow could not be analysed. (image 3).

Pulmonary embolism was excluded with CT angiography but it showed not only pleural but also pericardial effusion. Left thoracentesis was done, exudate was obtained and citological analysis of pleural effusion showed increased eosinophil counts. Metilprednisolone was included but montelukast was excluded from therapy. She took corticosteroids for four months. After four-year follow-up, she had no relapse.

**Conclusion:** It seems like that montelukast acts as an external cause of eosinophilic granulomatosis with polyangiitis in patients with genetic predisposition for the syndrome. Although it is not the direct cause of the syndrome, it should be excluded from therapy.

## Patient with rheumatoid arthritis and obstruction in lung function testing

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We present a 53 years old female patient, non-smoker, who has had rheumatoid arthritis since 1996. So far she has been treated with methylprednisolone, gold, methotrexate and sulfasalazine. In 2003 she was diagnosed with asthma/COPD due to obstruction noted on lung function testing and some respiratory symptoms (cough, dyspnoea). Despite inhalation therapy there was no change in lung function testing and no improvement in symptoms and exercise capacity. In 2011 she was referred to our outpatient clinic for diagnostic work-up of possible interstitial lung disease associated with rheumatoid arthritis. There was no change in lung function as compared to 2003, on body plethysmography and HRCT scan there were signs of air trapping. We performed open lung biopsy which revealed constrictive bronchiolitis. She was treated with cyclophosphamide and steroids but treatment gave no results in regard to pulmonary function and symptoms. She also gave up all inhalation therapy with no deterioration of her respiratory symptoms. In patients who present with progressive deterioration in lung function, and, even more, as in this case, are non-smokers and have rheumatoid arthritis, other causes of bronchial obstruction beside most frequent ones (like asthma and COPD) should be sought.

## Cystic fibrosis and lung transplantation in Slovenia

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Lung transplantation has become an established treatment option for selected patients with terminal lung disease, including patient with cystic fibrosis (CF). According to ISHLT registry, CF is 3<sup>rd</sup> most frequent indication accounting for about 16% of all lung transplantations. Among all lung transplant patients, CF patient have the best prognosis with median survival 8.3 years. The recommended time for referral is when the predicted survival time is under 2 years and functional class is WHO III or IV.

Between 1997 and 2014, a total of 41 patients were sent to AKH Vienna for lung transplantation, 13 (32%) of them had CF (8 females, median age 24 years, range 13-52 years). CF was the most frequent indication for lung transplantation among Slovenian patients. One CF patient had re-transplantation due to rejection of allograft 2 years after primary transplantation. Only two patients died, both in the early post-operative period (due to primary graft failure and rejection). The survival of remaining population ranged from 3.7 to 15.6 years. Five (38%) patients experienced at least one acute rejection, 3 (23%) had BOS. The main co-morbidities of surviving patients were osteoporosis (73%), diabetes (46%) and chronic kidney failure (45% with stage III or higher). To summarize, Slovenian CF patients who received lung transplantation had good outcome, comparable to international data.

## **Successful transition of cystic fibrosis patient with low treatment compliance and frequent exacerbations of lung infections from pediatric to adult care – a case report**

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Transition to adult care is a major life event for young people with cystic fibrosis (CF). It is most difficult in poorly cooperating patients, who are depressed, with no hope and neglected all kinds of therapy. However in some cases transition might be positive despite of that, if it is well planned in cooperation from both pediatric and adult team. In addition, clinical psychologists are able in this period to help a patient coping with their fears and existential questions. All together can again motivate a patient and unexpectedly improve the course of the disease, what was the case in our situation with a 21 years old male with advanced CF, already colonized with MRSA, mucoid *Pseudomonas aeruginosa*, *Citrobacter freundii* and *Candida albicans*. He used to have frequent exacerbations (9 hospitalizations during last year before transition). Besides regular therapy, he already needed a non-invasive ventilation during nights. He had a negative attitude to all kinds of treatment including lung transplantation. He was depressed, anxious and with no hope for the future. Exacerbations were probably caused mainly due to bad adherence to treatment, while he was at home. However, with the well coordinated process of transition, we achieved again his motivation for treatment. Thus, up to now, during all four years after the transition, the disease has been only slowly progressed, with only one exacerbation of infection, which needed hospitalization.

## **Individual shared-care for a cystic fibrosis patient with frequent exacerbations of *Pseudomonas aeruginosa* infection – a case report**

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Pulmonary disease is the leading cause of morbidity and mortality in patients with cystic fibrosis (CF). The major driver is infection with mucoid *P.aeruginosa* combined with *S.aureus*. Treatment is multifaceted, involving besides antibiotics also chest and whole body physiotherapy, inhaled medications to promote secretion clearance, and nutrition. Improved use of antibiotics substantially increased survival. However treatment of frequent exacerbations with resistant strains of *P.aeruginosa* becomes challenging (especially for patients living far from specialized CF centers), due to prolonged in-hospital treatments with intravenous antibiotics. In such cases individual shared-care with local hospitals is excellent solution, when teams cooperate and regional hospitals organize all facilities needed for such a shared-care. We described a 25 years old female CF patient with advanced disease, chronic colonization with *S.aureus* and mucoid *P.aeruginosa* resistant to almost all antibiotics in whom an individual shared-care was excellently implemented between pre- and post-transplant CF center in University Medical Center Ljubljana and Hospital Topolšica. With our joint efforts facilities were organized in such a way, that patient got all needed treatment. Cooperation has been excellently lasted already for four years, since patient first presentation for evaluation of her eligibility for lung transplantation, which could be postponed up to now. However during these four years (as expected) disease progressed and she is now in the process of putting her on active list for transplantation.

## **Lymphangioleiomyomatosis- our center experience with sirolimus**

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Lymphangioleiomyomatosis (LAM) is rare progressive, cystic lung disease affecting women of child bearing age. It is best characterized as a low grade, destructive, metastasizing neoplasm. Pathogenesis of LAM is still unknown but we know that disease has genetic association with mutation of tuberous sclerosis complex genes (TSC) 1 and 2. LAM affects lungs in most of the patients. The most common extrapulmonary manifestations are: renal angiomyolipomas, lymphangioleiomyomas, chylous pleurale effusions and/or ascites. There is no standard treatment for this disease yet, but few recently published studies have revealed that treatment with sirolimus may stabilize lung function and improve quality of life in patients with LAM.

We present the clinical course of three premenopausal women suffering from LAM. At the initial presentation they had diffuse cystic lung disease, chylous effusions and abdominal lymphangioleiomyomas. The patients were treated with low-dose sirolimus (1-3 mg a day; sirolimus trough levels 2,9-8,5 µg/L). All the patients had a remarkable clinical response to sirolimus: resolution of effusions, improvement in lung function and shrinking of abdominal lymphangioleiomyomas.

## **Adult multi-organ Langerhans cell histiocytosis with fatal outcome**

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**Introduction.** Langerhans cell histiocytosis (LCH) is a rare disorder characterized by abnormal proliferation of cells with a Langerhans cell phenotype. It contains some of the elements of both a neoplastic process and a reactive immune disorder.

**Case report.** A 55-year-old female patient presented in March 2014 with diarrhea, fever, leg edema and skin lesions on the torso. She was an ex-smoker who had been treated for COPD since 2011 and suffered from dermatitis-like skin lesions for the previous 5 years. Thoracic MSCT revealed a pathological reticular lung pattern. Langerhans cells (S-100+, CD1a+) were found in biopsies of epidermis, intestinal mucosa and bone marrow, whereas non-specific macrophage collections (CD68+, CD1a-) were found in lung tissue. Treatment with methylprednisolone resulted in significant clinical improvement. In November 2014, she developed a spontaneous left pneumothorax. A month later, she was diagnosed with active M.tuberculosis infection. The patient died one week after starting triple ATL therapy, in January 2015.

**Conclusion.** LCH has various clinical manifestations which often lead to misdiagnosis or delayed diagnosis of this rare condition, especially in adults. Our patient had a multiple system disease with the involvement of "risk organs", predicting poor prognosis.

## An extraordinary thoracic tumour

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Castleman disease is an angiofollicular lymph nodes hyperplasia. It's member of a group of uncommon lymphoproliferative disorders that share common lymph node histological features that may be localized to a single lymph node (unicentric) or occur systemically (multicentric). In our case we would like to flash how important is the histological verification in case of the tardily advanced mediastinal tumours.

## Amiloidosis: case report

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Female patient, non smoker was presented with 6-mont lasted dry cough, which deteriorated in the evening. Physical finding: tightened airway tone on both side. Total and specific IgE, as well as the absolute number of eosinophils in the serum were increased. Spirometry testings: in the reference values (flow in the large airways easily reduced). Inhalatory corticosteroids resulted in subjective improvement. Three months later: shortness of breath, wheezing and recurrence of dry cough. Spirometry testings: moderate broncho-obstruction with negative bronchodilator test. Body plethysmographic test: high resistance. Chest X ray: normal finding. Computed tomography (CT) of the chest and CT angiography with 3D reconstruction: enlarged lymph nodes in mediastinum and less obstruction in both main bronchi with compression of the distal right side of the trachea, as well as dextrocardia. Bronchoscopy examination: minor pulsating extramural compression in the lower half of the trachea without significant reduction of tracheal lumen, as well as infiltration and partial obstruction in both main bronchi. Pathohistological finding of transbronchial needle biopsy of left main bronchus: amyloidosis.

Thoracic surgeon did not set indication for stent application, nor any other interventional technique at the very time.

Therapy: inhalatory corticosteroids with long-acting beta agonists; leukotrienes antagonist; selective beta blockers.

## Lung transplantation in severe idiopathic pulmonary arterial hypertension (iPAH): presentation of two similar cases with different outcome

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**Introduction:** Despite several novel medical options with targeting drugs for iPAH (inhibitors of endothelin-1 receptors, inhibitors of phosphodiesterase-5, stimulator of soluble guanylate cyclase and prostacyclines) disease progresses in several patients. In these patients lung transplantation is optimal life-saving solution, when they are suitable for procedure.

**Case presentation:** A 21 years old male patient with severe iPAH and a history of syncope's did not significantly improved after introduction of bosentan. Disease slowly progressed and sildenafil was added one year later after he had again syncope during 6MWT at 360m with desaturation and progression according to echocardiography and NT-proBNP increase. Also combination therapy was not importantly effective. He again experienced syncope during only mildly greater exercise as usually. RHC showed deterioration. Thus therapy with subcutaneous terprostinil was introduced and he was listed for lung transplantation, which was successfully performed one year later. Similar patient (a 21 years old female) with iPAH, who also suffered syncope's upon exertion and had progressive disease despite triple therapy with PH targeting drugs, died while on active list for lung transplantation, as reanimation after cardiac arrest (which had been started with syncope) was not successful.

**Conclusion:** These two cases provide insights regarding importance of up-front medical therapy in young patients with severe, progressing iPAH with syncope's and early decision for lung transplantation in those patients in whom medical therapy is not effective.

## Late detection of chronic thromboembolic pulmonary arterial hypertension (CTEPH): case presentation

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**Introduction:** CTEPH might be potentially curative with removal of organized emboli from pulmonary arteries by pulmonary endarterectomy. In the case of inoperable disease a new effective targeting vasodilating drug- a stimulator of soluble guanylate cyclase (riociguat), was developed. Thus early detection and early decision for treatment can improve quality of life and outcome.

**Case presentation:** A 60 years old, obese (BMI 36) female with hypothyreosis (Hashimoto thyroiditis) and hyperlipidemia, positive familial history of venous thromboembolisms (VTE), without history of acute VTE throughout her life was evaluated due to progressive fatigue, dyspnea and palpitation by cardiologist five years before severe CTEPH was diagnosed, when she was already in chronic respiratory insufficiency. Only partially successful pulmonary endarterectomy was possible and she remained on long-term-oxygen treatment. At the time of first presentation to cardiologist pulmonary hypertension (PH) was already detected on echocardiography (assessed pressure in RV 46mmHg), however only reduction of body weight and change of life style was suggested. Patient did not seek any medical evaluations for five years since she was convinced that all symptoms she had are due to obesity, "lack of fitness" and aging.

**Conclusion:** This case of patient who would have probably better outcome if CTEPH was detected at first presentation to cardiologist insights importance of early thorough evaluation of patients with PH detected by echocardiography for correct diagnosis and better outcome.

## Pulmonary venoocclusive disease: case presentation

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**Introduction:** Pulmonary-veno-occlusive-disease (PVOD) is a very rare (<0.05%) subgroup of pulmonary arterial hypertension (PAH). It is idiopathic or associated with some other diseases including hematopoietic stem cell transplantation (HSCT). Histological verification with lung biopsy is contraindicated due to a high risk. Noninvasive diagnostics including chest high-resolution CT are helpful. Pulmonary edema during RHC triggered by vasodilator test is also diagnostic. Despite that, caution use of targeting, vasodilating drugs can be helpful in some patients. Prognosis is poor except in patients suitable for lung transplantation.

**Case presentation:** In 63 years old man, two years after allogenic HSCT due to acute myeloid leukemia, with skin relapse severe PAH was detected after he had developed progressive dyspnea. Thorough investigations excluded all possible causes and PVOD was confirmed only after pulmonary edema developed during vasodilator test with nitric oxide. Lung transplantation was not possible due to relapse of leukemia and age. Supportive therapy was started and careful introduction of bosentan was planned according to second opinion from PH expert Prof. Nazzareno Galie. However after transient improvement the patient suddenly died, reanimation was not successful. Autopsy did not show any additional pathology thus the cause of death was probably due to some kind of fatal arrhythmia.

**Conclusion:** This case provides some insights regarding diagnostic pitfalls and poor prognosis of PVOD.

## Combined pulmonary fibrosis and emphysema with pulmonary hypertension: Case presentation

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**Background:** Availability of imaging techniques has improved our awareness of combined idiopathic pulmonary fibrosis with pulmonary emphysema (CPFE) - a syndrome with a characteristic presentation of upper lobe emphysema and lower lobe fibrosis. Associated severe precapillary hypertension, which is particularly frequent in this syndrome (estimates approaching 30% to 50%) worsens the prognosis of CPFE. Currently no targeting therapy for PAH is effective in CPFE. However, supportive therapy might be very beneficial.

**Case presentation:** A 70 year old male, long time smoker had implanted heart pacemaker for syncope due to bradycardic atrial fibrillation. Bronchial obstruction was also noted and echocardiography showed severe pulmonary hypertension at rest. Three months later the patient was again admitted due to congestive heart failure. Computed tomographic angiography ruled out chronic pulmonary thromboembolisms and confirmed CPFE. Optimization of diuretic therapy and bronchodilators resulted in significant reduction of pulmonary pressures (systolic from 80 to 40 mm Hg) and improvement of patient's physical performance.

**Conclusion:** This case shows the importance of supportive therapy for improving PH in CPFE although some case presentations reported that off-label use of novel PAH, targeting drugs might sometimes be also effective.

## **Pulmonary alveolar proteinosis - a case report**

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Pulmonary alveolar proteinosis (PAP) is a rare lung disease of unknown origin, where an amorphous lipoprotein material accumulates in the alveoli of the lungs. We describe a young male with a four month history of progressive dyspnea after pneumonia, low grade fever, hypoxemia, dyspnea and weight loss. He worked with industrial gases. Chest X-ray showed diffuse interstitial and alveolar infiltrates in both lungs. The diagnosis of PAP was confirmed with BAL and trans-bronchial lung biopsy. Because of a deteriorating clinical course a whole lung lavage was performed. Under general anesthesia, both lungs were lavaged with warm saline in two different sessions with good results. Two years later the patient is almost free of symptoms and lung function has markedly improved and he also changed the workplace.

## **Pulmonary Langerhans cell histiocytosis – presentation of two consecutive patients**

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Pulmonary Langerhans cell histiocytosis (PLCH) is a rare interstitial lung disease associated with cigarette smoking. It primarily affects young adults between ages of 20 to 30 years. The diagnosis is made in less than 5% of lung biopsies and has been seen in less than 2 % of the patients. In October 2013 young male smoker, 20 pack years (aged 40 years, positive family history of lung cancer) and in November 2013 young female smoker, 15 pack years (aged 31 years) were presented to our out-patient clinic due to chronic, dry cough. They are both otherwise healthy, with no known allergies and no symptoms of gastroesophageal reflux. Spirometry including metacholine test and DLCO was normal in both cases. Chest-X-ray of male was only slightly abnormal, as seen in long-time smokers, and in female some nodular opacities were seen in upper lobes. Computed tomography of chest showed in both patients interstitial changes suspicious of PLCH (showing a combination of nodules, and thick- and thin-walled cysts). BAL was suspicious of PLCH in both patients (macrophage alveolitis, increased percentage of langerin, CD1a and S100 positive cells). In male open lung biopsy confirmed diagnosis of PLCH. Female decided to go under procedure of open lung biopsy only in the case of deterioration. In last two years both patients are doing well. Dry cough disappeared in both patients after they completely stopped smoking, they are without any symptoms or signs of deterioration, chest-X-rays are without progression and spirometry stable.

## **Langerhans cell histiocytosis and multiple malignant tumors**

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Adult pulmonary Langerhans cell histiocytosis is a rare disorder of unknown aetiology occurring in young smokers.

The definite diagnosis of pulmonary Langerhans cell histiocytosis requires identification of Langerhans cell granulomas, which is usually achieved by surgical lung biopsy.

The occurrence of Langerhans cell histiocytosis was only 5% in surgical lung biopsies. Since 1983 on

increasing number of case studies have reported the manifestation of malignant lymphomas and lung tumors in patients with Langerhans cell histiocytosis.

During a 15- years follow-up of two Langerhans cell histiocytosis patients we observed development of multiple malignancies.

In addition to functional and radiological follow up, this patients require oncological vigilance as well.

## **Sporadic pulmonary lymphangioleiomyomatosis – a case report**

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Pulmonary lymphangioleiomyomatosis (LAM), a benign mesenchymal neoplasm with perivascular epithelioid cell differentiation, characterized pathologically by the appearance of interstitial collections of atypical smooth muscle cells and cyst formation in the lungs is a rare lung disease that afflicts young women of childbearing age. Pregnancy and the use of supplemental estrogen accelerate the disease process .The term sporadic LAM is used for patients with pulmonary LAM not associated with tuberous sclerosis complex. Clinically, radiographically, and physiologically LAM has more in common with pulmonary emphysema than with interstitial lung diseases. It is often misdiagnosed as asthma or chronic obstructive pulmonary disease because of significant airflow limitation. Spontaneous pneumothoraxes are a hallmark of the disease. If detected early, when cysts in the lungs are still very small, prognosis might be beneficial. In advanced disease however the only remained option is lung transplantation. We presented a case of 50 years old female, who had right sight surgical pleurodesis due to several spontaneous pneumothoraxes at age of 31, one year after first child-birth. Seven years later, when she was presented to pulmonologist due to prolonged dry cough after respiratory infection diagnosis of LAM was suspected on the basis of these clinical data. The HRCT findings of diffuse, small, thin-walled cysts scattered throughout both lung fields were characteristic of LAM and TBB showed positive HMB 45 cells. After ovariectomy (not recommended any more due to new medical options) and anti-estrogen therapy disease hasn't been progressed up to now. Thus we did not decided to give her new drugs from the group of mTOR inhibitors (sirolimus, everolimus), which might be associated also with severe side effects.

## **Primary ciliary dyskinesia – a case report**

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Primary ciliary dyskinesia (PCD, also called the immotile-cilia syndrome) is a rare disease, characterized by congenital impairment of mucociliary clearance due to a defect of cilia in the airways. Because the embryonic, nodal cilia are also defective, body asymmetry occurs randomly so that approximately 50 percent of the patients have situs inversus totalis. In absence of situs inversus PCD often remains under-recognized. The most common features of PCD are recurrent infections of the upper and lower respiratory tract. The major infecting bacteria are: *H. influenzae*, *S. pneumoniae*, *S. aureus*, *P. aeruginosa* or nontuberculous mycobacteria. Mucoid *P. aeruginosa* tends to appear after age 30, which is delayed compared with cystic fibrosis. We represent 30 years old female patient with PCD. In her childhood she has several exacerbations of infections in bronchiectasias, which had been treated frequently also with iv. antibiotics before lobectomy of lingula was performed at age of twelve. Although performance of lobectomies seems to be a poor prognostic factor for PCD in adulthood, she hasn't experienced any severe exacerbations so far after transition to adult care at her age of fifteen. While she had had several exacerbations of infections mainly with *H. influenzae* and in the last few years also with *P. aeruginosa*, she still hasn't have colonization with mucoid *P. aeruginosa*. Despite this rare genetic disease she has practically normal life and become the established young artist.

## **Coping strategies in patients with pulmonary hypertension**

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**Introduction:** Pulmonary hypertension (PH) is a chronic disease associated with lower quality of life (QoL) and prognosis. In addition to medical therapy coping strategies (CS) might be very important both for QoL and outcome. However, little is known about which CS developed PH patients and their relatives during the disease course. The aim of study was to examine CS of our PH patients and their family members.

**Methods:** Thirty-four PH patients, 11 relatives and 14 healthy controls were evaluated with Coping response inventory (CRI, Moss, 1993a and 1993b) which evaluated both approaching (logical analysis, positive reappraisal, seeking guidance and support, problem solving) and avoiding CS (cognitive avoidance, acceptance or resignation, seeking alternative rewards, smotional discharge). SPSS was used for statistical analyses.

**Results:** PH patients and relatives (independently of gender, education or employment) significantly more often used both approaching and avoiding CS compared to controls (all  $p < 0.05$ ). There were no significant differences in CS between patients and their relatives.

**Discussion and conclusions:** Intense development of both CS in PH patients and relatives showed that living with PH affects whole families, requiring psychological support especially when avoiding predominate over approaching CS. Psychological support might importantly improves the QoL and outcome, what has to be proved.

## **Children with cystic fibrosis – psychological problems and management pattern**

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Serious chronich diseases alter vital concepts and build new interpersonal relationships. The depression and suicidal idea in these cases are an expression of vulnerability and inability to cope with life. According to WHO more than 500 000 people yearly in the world have at least one suicide attempt or commit suicide in a period of depression.

Object of the present study were 36 patients with cystic fibrosis (CF) average on 12,4 years. The package used for psychological methods included: quality of life (QoL) questionnaire; scale of anxiety Spilberger; thematically apperception test (TAT) - Picture; "Enchanted Family" drawing; interview with the family.

Our results show that patients with CF define quality of life as poor; their level of anxiety and depression is abnormal, and in 1/3 of respondents manifest and suicidal thoughts and behavior. Often, a failure in the family leads to a dramatic experience of the disease in apparently good vital signs in the patient. Psychotherapy is the main and most difficult method in auto destructive psychosomatic patients, and those with severe physical diseases.

The collected material from psychological research give us reason to develop the following exemplary model of addressing the medical team at work with patients suffering from severe chronic diseases, namely:

1. Empathy of the return to reality after illness and death and stimulate the recovery;
2. Joint search of sources of support;
3. Allow and encourage free expression of feelings through:
  - New ways of communication with the sick child;
  - Abandonment of beliefs in " automatic traction" and giving the family their own space to grieve in their own unique way.

We established a recommendation for management pattern in such cases. Compliance with these recommendations leads to improvement the doctor-patient relationship, and thus optimizing the treatment and improving the quality of life of patients. "Life will never be the same, but it could be better ..."