Book of Abstracts

Slovenian Pneumology and Allergology Congress joined with Golnik Symposium and Balkan Pneumology Meeting

Personalised Medicine in Respiratory and Immunologic Diseases

Združenje pnevmologov Slovenije
Slovenian Respiratory Society

Bled, 6 - 8 October 2016

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6 - 8 October 2016

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UNIVERZITETNA KLINIKA ZA PLJUČNE BOLEZNI IN ALERGIJO
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Slovenian Pneumology Congress joined with Golnik Symposium and Balkan Pneumology Meeting:

Personalised Medicine in Respiratory and Immunologic Diseases

6 - 8 October 2016

Bled, Hotel Golf

Programme

THURSDAY, 6TH OCTOBER

13:15 **Opening the congress**

	SESSION 1:	
13:30-15:30	PERSONALISED MANAGEMENT OF INTERSTITIAL LUNG DISEASES Chairs: ***Katarina Osolnik, Duška Vidovič, Branislav Perin (Serbia)***	
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18:20	Satellite symposium ***(Novartis)***. Marc Miravitlles: Towards a new algorithm for the treatment of COPD
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FRIDAY, 7TH OCTOBER

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	SESSION 4:
10:30-12:00	BRONCHOSCOPY AND INTERVENTIONAL PNEUMOLOGY Chairs: ***Aleš Rozman, Marjeta Terčelj, Dženan Halilović (B&H)***

	SESSION 5:
12:00-12:30	HYPOVENTILATION DISORDERS Chairs: ***Irena Šarc***

12:30	Satellite symposium ***(Roche)***. Tanja Čufer: Novosti v tarčnem zdravljenju raka pljuč

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16:20	Satellite symposium ***(TEVA).*** Andrea Rossi: TBA	

	SESSION 7:	
17:00-19:00	WHAT IS NEW / HOT TOPICS Chairs: ***Mihaela Zidarn, Barbara Salobir, Miroslav Samaržija (Croatia)***	
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Skoro-Sayer Nika	Baloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension - a new hope for inoperable patients	
Mišo Šabović	What is new - pulmonary arterial wall in focus (MSD sponsored lecture)	
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19:30-20:00	***International round table:*** Post-doc residential and research fellowship in CEE countries; curriculum and network of education centers. Discussion moderators: Matjaž Fležar, Mitja Košnik, Branislava Milenkovič (Serbia), Miroslav Samaržija (Croatia), Neven Miculinić (Croatia), Branislav Perin (Serbia), Bakir Mehić (BiH), Biljana Ilievska-Poposka (Macedonia)	

SATURDAY, 8TH OCTOBER

	SESSION 8:	
8:30-10:30	MOLECULAR ALLERGOLOGY: A STEP TO PERSONALISED ALLERGY MANAGEMENT Chairs: ***Peter Korošec, Peter Kecelj, Asja Stipić Marković (Croatia)***	
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Spillner Edzard	Recombinant allergens as a major step in molecular allergology: scientific and methodological considerations	77

PERSONALISED MANAGEMENT OF INTERSTITIAL LUNG DISEASES

Chairs: Katarina Osolnik,
Duška Vidovič,
Branislav Perin (Serbia)

Xenobiotic-induced interstitial lung diseases

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Alveolar-capillary membrane is an extensively broad „meeting point“ where blood is in touch with the environment. Lung parenchyma has immunological and metabolic mechanism to protect organism from environmental toxic adverse effects, but sometimes it may result with injury and destruction of fine alveolar structure. An individual susceptibility to the impact of various xenobiotics also determines their adverse effects.

Xenobiotics can injure lung tissue by inhalation (organic and mineral dust, fumes, vapour, drugs, illicit drugs), aspiration (food, gastric acid, water), ingestion (drugs, food, accidentalor suicidal poisoning), intravenous route (drugs, illicit drugs), and radiation. Xenobiotic-induced histopathological pattern in lung tissue may mimic the whole pulmonary pathology. This group of pulmonary diseases is an example for detailed and personalized diagnostic approach. Recognition of causal xenobiotic and associated clinical pattern may explain pathogenesis of certain disorders previously known as idiopathic (ex. giant-cell pneumonia – GIP and hard metal pneumoconiosis).

Lung tissue is a fine structure reacting to numerous factors. We must be aware that introducing new technologies or compounds could cause new pulmonary diseases in future.

New treatment options for lymphangioleiomyomatosis: Our center experience

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BACKGROUND: Lymphangioleiomyomatosis is rare progressive, cystic lung disease predominantely affecting women of child bearing age and 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 and common extrapulmonary manifestations are: ranal angiomyolipomas, lymphangioleiomyomas, chylous ascites. In the last few years few studies were published which showed that treatment with sirolimus stabilize lung function decline and improve quality of life in patients with LAM.

METHODS: We treated three premenopausal women suffering from LAM manifesting as diffuse cystic lung disease, chylous effusions and lymhangioleioyomas with low dose sirolimus (1-3 mg a day; sirolimus trough levels 2,9-8,5 μg/L).

RESULTS: All three patients had a remarkable response to sirolimus, with resolution of effusions, improvement in lung function and shrinking of abdominal lymphangioleiomyomas. They did not have any side effects.

CONCLUSION: This three cases contribute to the fact that sirolimus is a safe and an effective treatment for LAM.

Lung transplantation in interstitial lung disease: Slovenian experience

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BACKGROUND: Lung transplantation has become an established therapy for carefully selected patients with end-stage lung disease. Interstitial lung disease (ILD), mainly idiopathic pulmonary fibrosis (IPF), is the second most common indication for lung transplantation in adult patients. According to ISHLT registry current expected median survival for this group of patients is about 6 years which is superior to natural disease course. We analyzed the data for Slovenian patients who had lung transplantation at AKH Vienna.

METHODS: Between July 1997 and August 2016 55 patients received lung transplantation. Data was collected continuously during this period. Data was analyzed using SPSS 15.0.

RESULTS: In the observed cohort there were 10 patients with ILD (18.2%) – 6 with IPF (11%), 1 with silicosis (1.8%), 1 with non-IPF pulmonary fibrosis (1.8%) and 2 with lymphangioleiomyomatosis (3.6%). This is less than world-wide average for this indication (in ISHLT registry 24% of indications was IPF). Three transplantations (30%) were "highly urgent" (1 patient intubated, 2 patients on ECMO). Due to small number of patients (majority recently transplanted) long term survival could not be estimated at this time. Two patients (both IPF) died in the early post-operative period, one (LAM) died 7.5 years after transplantation. One patient (silicosis) developed advanced bronchiolitis obliterans syndrome early after transplantation. Three patients with IPF on the waiting list died before the transplantation.

CONCLUSION: ILD is an increasingly recognized indication for lung transplantation in Slovenia but long term experience is still lacking.

Patients with IPF after 6 months of therapy with pirfenidone or nintedanib - our center experience

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INTRODUCTION: Idiopathic pulmonary fibrosis (IPF) is specific form of chronic, progressive, fibrosing disease. It is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). Pulmonary function tests typically demonstrate a restrictive pattern (eg, reduced forced vital capacity (FVC), but normal ratio of forced expiratory volume in one second (FEV1/FVC), a reduced diffusing capacity for carbon monoxide (DLCO), and, as the disease progresses, a decrease in the six-minute walk distance. No medication has been found to cure IPF, but two medications, nintedanib and pirfenidone, appear to slow disease progression.

METHODS: We were assessing 30 patients (F 8, M 22) with IPF treated for 6 months with nintedanib (15: F 3, M 12) or pirfenidone (15, F 5, M 10) at Golnik. We were testing FVC, FEV1/FVC, DLCO at the beginning of the treatment and after 6 months.

RESULTS: In group nintedanib average FVC was 84.8%, after 6 months 83.6% (0.2% decrease) average FEV/FVC was 80.933%, after 6 months 81.2% (0.267% increase) and average DLCO was 59%, after 6 months 56.933% (2.067% decrease).
In group pirfenidone average FVC was 70%, after 6 months 69.933 (0.067% decrease), average FEV/FVC was 80.467%, after 6 months 82.4% (1.933% increase) and average DLCO was 47.333%, after 6 months 47.067% (0.266% decrease).

CONCLUSIONS: Interpreting the results we have to take into account short observation time (6 months). Both groups of patients were of comparable age and sex. There is statistically significant difference of FVC between both groups (P=0.0174). According to insurance restrictions treatment with pirfenidone is available only for patients with FVC less than 80%.
In group with pirfenidone one patient had decrease in DLCO 9%, this patients disease has progressed and has been included in transplantation process.

Temporary decline of lung function in progressive systemic sclerosis with Reynaud phenomenon but without signs of pulmonary fibrosis (Case record)

Jusuf Mehić[1], Merima Unkić[1], Besim Prnjavorac[1], Rifat Sejdinović[1], Belkisa Hasanić[1], Edin Jusufović[1], Katarina Krajina[3]

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[2] Health Service Tuzla, BiH
[3] University Pittsburgh,PA, USA

BACKGROUND: Scleroderma is a progressive inflammatory disease of connective tissue with manifestation of pulmonary fibrosis, and loss of lung function, mostly as decline of FVC and DLco. Fibrosis is irreversibl, but some circumstances could cause reversible decline of lung function in patients, like this case record presented here.

CASE PRESENTATION: Female patient, 47 years old. The disease began in 2012 with body rash, primarily on the face, hands, more specifically dorsum of the hands. The hand rash was followed by stinging and periodic discoloration of the fingers (pale, bluish, red). The rash progressed onto the feet causing the legs to subsequently swell. She felt shortness of breath. As the outside temperature changed from warm to cold, hands become pale, then black and red. She was permanently tired, weak, feeling muscle pain, difficulty walking, with an occasionally cough. Her first hospitalization was at the Department of Rheumatology from November 2nd thru 28th of 2012. Complete diagnostic procedures were performed with a diagnose of progressive systemic sclerosis. Mild stage of pulmonary fibrosis was detected as well. The patient's therapy was: Methotrexate tablets; Folacin tablets; Aspirin tablets; and Pentoxifylline tbl. On two separate occasions she was hospitalized at the Pulmology Department of General Hospital Tešanj. During both hospitalizations, complete lungs functional diagnostic tests were performed. Her first stay was in October 2015. During this hospitalization, she was diagnosed with mild restrictive lung function disorder (FVC 75%, FEV1 73%, TLC 81%, Rtot 167, DLco 89,2%, VA: 81,7 %). Due to progression and exacerbation of the disease, she was admitted to Department of Pulmology again in January 2016. Both times she had similar symptoms: fatigue, shortness of breath, cough with poor sputum, and muscle cramps. During the second hospitalization, tests of lung function showed significant progression in restriction, with an initial reduction of lungs diffusion capacity (DLco) (FVC 55%, FEV1 54%, TLC 76%, Rtot 230, DLco 75,2%, VA 70,5%). A third controlled spirometry test was performed in July 2016. Significant recovery of lung function (reducing of restriction) with better DLco compared with the findings 6 months prior (FVC 70%, FEV1 67%, DLco 85,3%, VA 71,1%). Decline of lung function during hospitalization in February 2016 was caused by middle degree of respiratory infection.

CONCLUSION: Decline of lung function in patients with progressive systemic sclerosis could appear without signs of pulmonary fibrosis, mainly due to respiratory infections or diseases with general signs of inflammation.

Advanced COPD and IPF have highly comparable inflammation patterns in periferal lung tissue

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BACKGROUND: Lymphocytes T have been implicated in the pathogenesis of chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), but their role is not fully explained and remains controversial due to conflicting results of different studies. The aim of our study was to investigate subsets of lung tissue lymphocytes T in advanced COPD and IPF patients undergoing transplantation and compare them to healthy lung tissue from donors. To our knowledge this is the first study to directly compare lung tissue lymphocytes T in COPD and IPF.

METHODS: Periferal lung tissue was collected in Thoracic surgery department in University hospital Vienna; it was obtained from 9 patients with COPD and 9 patients with IPF as well as 7 donor patients. Tissue lymphocytes were analysed for expression of Th1, Th2, Th17, Treg surface markers, markers of activation and differentiation markers of CD8 cells using multi-colour flow cytometry. Expression of transcription factors was analyzed by quantitative PCR.

RESULTS: The most prominent finding was more than 20-fold difference of Th1 cells in COPD and IPF compared to healthy controls (median 6.8% (IQR 2.7-15.5) and 6.9% (4.2-10,2) respectively vs. 0.28% (0.12-1.06) of lymphocytes, p 0,001). Flow cytometric differences in Th1 response were confirmed with upregulation of TBET1 transcription factors. Furthermore, in COPD and IPF patients CD8+ T cells were increased as compared to controls (p=0.042) and were predominantly of fully differentiated cytotoxic phenotype CD27-CD28- (more than 98.7%). The proportions of this CD8+ phenotype were significantly increased in COPD and IPF (median 12.6% (8.9-22.6) and 15.2% (9.6-27.6) respectively vs. 2.3% (1.0-10.8) of lymphocytes, p=0.013). No differences was detected in the expression of activation markers between groups.

CONCLUSIONS: Our results indicate a highly comparable patterns of adaptive immunity inflammation in advanced COPD and IPF, which predominantly involves Th1 lymphocytes and CD8+ lymphocytes with the greatest cytotoxic potential.

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PERSONALISED MANAGEMENT OF ASTHMA AND COPD

Chairs: Sabina Škrgat,
NadjaTriller,
Bakir Mehić (B&H)

Personalised care of COPD

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Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory respiratory condition, characterized by progressive airflow limitation that is not fully reversible. The accelerated deterioration of pulmonary function may occur at any stage in the course of the disease. The associated episodes are called acute exacerbations of COPD. The World Health Organization projects that COPD will become the third leading cause of death worldwide by 2030 (1). The increasing COPD mortality might be associated with the aging population, tobacco use, air pollution, and infectious diseases. (2). In COPD patients, exacerbation has been linked to a mounting economic burden generated by frequent events that might require hospitalization and by chronic disability. Although there are different drugs for COPD there is still a need for new treatment strategies. i.e. personalized medicine. But there is no such thing as the *COPD biomarker* or different biomarkers and their panels. So, it will be needed to assess different components of this complex and heterogeneous disease.

THE CURRENT STATE OF COPD MANAGEMENT

Treatment of patients with COPD ahould be conducted by a multidisciplinary team in order to: prevent disease progression, elimination of symptoms, prevention of exacerbations, improvement of exercise tolerance and improve quality of life. It is recommended that an individualized therapeutic approach that includes non-pharmacological and pharmacological treatment measures (2).
Some patients have reccurent exacerbations that are associated with accelerated lung function deterioration, reduction of quality of life, and decreased survival in COPD. Some COPD patients are susceptible to exacerbations, requiring frequent hospital visits and hospitalizations. Frequent exacerbations hasten lung function decline affecting quality of life, exercise capacity and survival in patients with COPD (3). Thus, frequent exacerbation has been recognized as a major clinically relevant COPD phenotype. The identification of predictive markers for these episodic and recurrent worsening of symptoms could contribute to the better management of this chronic condition. Caucasian COPD patients are suggested to be more commonly frequent exacerbators if they have the *HYPD* haplotype of *MBL2* gene. Serum MBL level (≥75th percentile) at stable state seems to be associated with an increased survival rate in patients with COPD (4).

COPD BIOMARKERS

More biomarkers can be used for the diagnosis of COPD and evaluate the optimal treatment. However,

for now α1-antitrypsin is the only specific biomarker for COPD, or emphysema. The level of C-reactive protein (CRP) is negatively correlated with a decrease in FEV1, or the protein is not significantly sensitive to determine the etiology of exacerbations.
The most extensive analysis of potential biomarkers for COPD is performed in the ECLIPSE study ("Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints"), in which levels were determined: chemoattractants (CCL24, CXCL5, IL-8, CXCL10, CXCL11, CCL2, CCl4, CCL23 , CCL18, CXCL7), inflammatory mediators (CRP, IFN-γ, IL-1b, IL-1RA, IL-6, IL-10, IL-12p40, IL-15, IL-17, TNFα, sTNFRI, sTNFRII), indicators of tissue destruction and / or recovery and / or remodeling (BDNF MMP9, MMP8, TIMP1, TGFα), as well as other biomarkers (MPO, fibrinogen, ACRP30, leptin, β-defensin-2, prolactin). Also the authors analyzed the blood levels of CC-16 ("Clara Cell secretory protein-16" - CC-16), surfactant protein D (SP-D) and the level of MMP / TIMPs. However, the best marker of poor prognosis of COPD was the number of exacerbations of COPD in the past year, while biomarkers were not correlated with the severity of the disease (5).
Since the ideal biomarker for COPD has not yet found, further clinical trials are required in order to determine the most specific and the most sensitive markers of disease severity and prognosis.
Although exacerbations are key events in COPD progression there is scarce information about the mechanism by which exacerbations may contribute to airway remodeling and associated structural changes in lung tissue. In this respect it has been shown that chronic inflammation in COPD and exacerbations are associated with disturbances in the homeostasis of extracellular matrix (ECM) molecule (6,7). Upon tissue inflammation, MMP expression and proteolytic activity is upregulated, causing protein fragments to be released into the circulation, where they may serve as ECM specific biomarkers. Therefore, assessment of lung ECM protein fragments, also known as neoepitopes, may provide novel biomarkers for disease exacerbation, prognosis and activity (7). The detection of the individual proteins potentially enables the early, non-invasive identification of preponderant histopathological processes, i.e. destruction of alveolar walls, fibrosis of the small airways and/or clinical relevant subgroups of COPD patients, i.e. fast-deteriorators, emphysema preponderance, amenability to particular therapies. It is also tempting to speculate that further phenotyping by this means could facilitate the development of targeted anti-fibrotic or anti-proteolytic therapies (7).
Since the ideal biomarker for COPD has not yet found, further clinical trials are required in order to determine the most specific and the most sensitive markers of disease severity and prognosis.

COPD COMORBIDITIES

The natural course of COPD is complicated by the development of systemic consequences and co-morbidities. The structural abnormalities of airways and pulmonary parenchyma were associated with inflammatory reaction of the lung, which was followed with oxidative stress and extracellular matrix proteolysis (8). Recently, besides the typical pulmonary pathology of COPD, several effects occurring outside the lung and has been described as so-called systemic effects of COPD. The major systemic consequences/co-morbidities now recognized are: osteoporosis, skeletal muscle dysfunction, metabolic impact, anxiety and depression, cardiovascular disease (9,10).

COPD PHENOTYPES

COPD is a complex and heterogenous disease. The identification of clinically relevant phenotypes facilitates a better understanding of COPD pathobiology and the development of novel drugs (11). It also facilitates the progress toward more personalized and better treatment for patients with COPD. There are different COPD phenotypes and three of these phenotypes are related to COPD prognosis and therapeutic response:
a) *phenotype with frequent COPD exacerbations* – the patient with at least 2 exacerbations in previous year; there is positive response to inhaled corticosteroids added to the long acting bronchodilators;
b) *COPD and asthma overlap phenotype* – the patient has increased variability of the air flow through the airways and partly reversible bronchial obstruction; there is positive tretament response to inhaled corticosteroids added to the long acting bronchodilators;
c) *emphysema phenotype* - the patient has hyperinflation and poor therapeutic response to inhaled corticosteroids; the prescribed individualized treatment is based on long-acting bronchodilators and rehabilitation.

It is very important to know all COPD phenotypes, and to assess the each patient's phenotype because the optimal therapy will be planed and prescribed according to the phenotype .

PRECISION MEDICINE IN COPD

The concept of precision medicine includes prevention and treatment strategies that take individual variability into account. The prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (i.e. human genome sequence), powerful methods for characterizing patients i.e. proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data. There are some good results in personalized medicine in cancer and asthma patients. Unfortunately, there are no drugs prescribed for COPD patients because there is a need to develop creative new approaches for detecting, measuring, and analyzing a wide range of biomedical information (12). Such innovations will first need to be tested in pilot clinical studies. Most importantly, the detection of the individual proteins potentially enables the early, non-invasive identification of preponderant histopathological processes, i.e. destruction of alveolar walls, fibrosis of the small airways and/or clinical relevant subgroups of COPD patients, i.e. fast-deteriorators, emphysema preponderance, amenability to particular therapies. Further phenotyping by this means will facilitate the development of targeted anti-fibrotic or anti-proteolytic therapies (13).

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Tracheobronchomalacia in adults

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ABSTRACT
Tracheobronchomalacia (TBM) is a disease defined by an excessive collapse of the trachea and main bronchi. It is an under recognized cause of dyspnea, recurrent respiratory infections, cough, secretion retention, and even respiratory insufficiency.

Patients with severe, diffuse TBM usually present with a complete or near-complete collapse of the airway during expiration caused by excessive bulging of the airway's posterior membrane, diagnosed by bronchoscopy and/or dynamic CT.

Exact etiology of this acquired form of TBM is unknown, but is frequently associated with Chronic Obstructive Pulmonary Disease (COPD) and must be distinguished from TBM due to failure of the cartilaginous part of the airways.

The therapeutic management of TBM should be conservative and all concomitant respiratory diseases, such as asthma, COPD and extrinsic compression of the airways (i.e. due to thyroid goiter or a tumor) should be treated first.

Noninvasive ventilation can be considered in patients with increasing symptoms. Airway stenting is sometimes used as a palliative or temporary measure, but complications such as mucostasis, migration, and granulation often limit its durability.

Surgical stabilization of the airway by posterior splinting (tracheobronchoplasty) effectively and permanently corrects malacic airways. Patient selection can be facilitated by a short-term stent trial.
Other treatments such as endoscopic laser therapy is still experimental, and its efficacy remains to be determined. Tracheostomy to help clearing of the secretions by suctioning is usually used as a last resort.

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Clinical value of cytologic profile in induced sputum

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INTRODUCTION: Since 1990 induced sputum has been useful diagnostic tool particularly in obstructive lung diseases. Protocol of induction has been optimised and standardised in recent years. Induced sputum enables useful information in clinical context as a safe, noninvasive and repeatable procedure. It enables phenotyping of inflammation in airways and helps predict response to corticosteroid treatment. It is also diagnostic tool for eosinophilic bronchitis, occupational asthma, COPD, lung cancer, tuberculosis.

METHODS: In this retrospective study I have analysed 209 induced sputums between january 2013 and december 2015. All samples were done and analysed at University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia. Purpose of this study was to analyse indication, clinical outcome, quality and cytological profile of sample. Some results are presented here.

HYPOTHESIS:
1: smoking affects cytologic profile in induced sputum
2: sputum eosinophils correlates with eNO and FEV1

RESULTS: Quality evaluation of induced sputum (good, acceptable, bad, not representative, no evaluation) is based on visibility, presence of debris, presence of squamous cells and cell viability. 23,4 % of all samples were evaluated as good, 35,9 % as acceptable, 8,6 % as bad, 24,4 % as not representative, 7,7% as no evaluation.
There is limited data on the influence of active smoking on cytological profile in induced sputum. There was a significant difference in macrophages percentage between asthma smokers (n = 6) and asthma nonsmokers (n = 75) (p = 0.049). For other cells and cell viability there was no statistical significant difference between these two groups.

Results shows that NO in exhaled air poorly correlates with eosinophils in induced sputum. To prove eosinophilic inflammation in airways induced sputum has to be done. Measuring NO in exhaled air is not sufficient marker for eosinophilic airway inflammation.
Eosinophilic bronchitis and asthma are in terms of cytologic profile equivalent conditions.

Special thanks go to Sabina Škrgat, MD, PhD for mentoring and Izidor Kern, MD.

Implementing clinical guidelines for chronic obstructive pulmonary disease in Medical Centre Murska Sobota

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Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by progressive fixed airflow limitation. The goals of management of COPD patients are to reduce symptoms and improve quality of life. How to archive these goals are summarized in international and national guidelines. Several evidence-based guidelines are available including the GOLD guidelines. Slovenian guidelines (last version will be published this year) also try to help physicians to improve every day clinical practice. We know that publishing a guideline document is not a guarantee that it will be acted on. Implementation of guidelines requires that the medical professionals are willing to follow them and translate the best available evidence into clinical practice. Correct diagnosis and appropriate treatment have been the most common areas of deficiency. High percentages of primary care physicians still not use spirometry in the diagnosis of COPD. Knowledge of the appropriate treatment and possibilities of pulmonary rehabilitation are also low.

We try to implement guidelines for COPD into everyday clinical practice by organizing professional educational meetings between GPs and pulmonologists. Together with primary care services we encourage patients to attend smoking cessation program. Almost all newly diagnosed patients with COPD receive guideline-appropriate treatment and individual education how to use inhalers. We do our best to include more patients into outpatient rehabilitation program; those with COPD D are included into four weeks institutional rehabilitation program.

The future efforts should focus on implementing COPD guidelines into every clinical practice to ensure that all COPD patient will receive the best and appropriate care.

Depression-frequent comorbiditi in chronic obstructive pulmonary disease and asthma

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BACKGROUND: Chronic obstructive pulmonary disease (COPD) and asthma are the most common chronic respiratory diseases in the working-ability population and represents serious public health problem both in developed and developing countries. Both diseases are associated with numerous comorbidities, including depression which leads to frequent use of health services, increases duration of hospitalization and causes poorer control of COPD and asthma.
The aim of this study: was to determine the frequency and degree of depression in patients with COPD and asthma; to determine whether there is a correlation between the severity of COPD and the frequency and level of depression; to determine whether there is a correlation between the level of asthma control and the frequency and level of depression; to determine whether there is a difference in the frequency and level of depression among patients with COPD, patients with asthma and healthy population.

METHODS: The study included total of 500 individuals (200 with asthma and 200 with COPD) who were referred for control check-up and 100 healthy individuals who were in the control group.

RESULTS: In patients with asthma, depression is registered in 14.5 %. In patients with COPD, depression is registered in 23.5%. Patients with poorly controlled asthma are significantly more often depressed and have higher degree of depression than patients with controlled asthma ($p<0.001$). Patients with more severe level of COPD are significantly more frequently depressed and their level of depression is more severe than in patients with milder degree of COPD ($p<0.001$). Patients with COPD are significantly more likely to have depression, that is of higher level than in patients with asthma ($p<0.001$) or compared to healthy subjects ($p<0.001$). Patients with asthma are significantly more likely to have depression, which is of more serious level than in the healthy subjects ($p=0.002$). Multivariate logistic regression was associated with each factor weight value and calculated the statistical significance of the impact of each factor on the occurrence of depression.

CONCLUSION: Independent predictors of depression in a group of patients with asthma were: age, smoking habits and uncontrolled asthma. An independent predictors of depression in a group of patients with COPD are the total number of hospitalizations and dyspnea degree higher than one.

Systemic and airways oxidative stress and Th2/Th1 immunological shift in competitive swimmers training in indoor chlorinated swimming pools

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OBJECTIVE: To characterise systemic and airway oxidative stress and inflammation in competitive swimmers training in indoor chlorinated swimming pools.

STUDY DESIGN: A prospective study.

SUBJECTS: We included 41 competitive swimmers. There were 23 (56.1 %) females and 18 (43.9 %) males. Median age was 16 years (IQR 4 years).

INTERVENTION: All subjects were followed during two months: in the period of high intensity training (at the beginning of national championship, February 2015) and after training has been stopped for one month (September 2015). Concentration of chlorine in the swimming pools was in recommended range (free chlorine 0,5-0,6 mg/L).

OUTCOME MEASURES: The outcome measurements were pulmonary function test FEV1 (forced expiratory volume in first second), concentrations of 8-isoprostanes as marker of oxidative stress, and TNF and interleukin 5 (IL-5) as markers of Th1 and/or Th2 type of immune response. Markers were determined in serum and induced sputum in high intensity training period and in nontraining period. 8-isoprostane was measured with competitive ELISA. IL-5 and TNF were measured with FACS Cytometric Bead Arrays. The normality of the distribution of the data was checked with Shapiro-Wilk test. Since the data were not normally distributed, the paired samples were compared to each other with Wilcoxon signed rank test.

RESULTS: Swimmers in high training period have significantly higher concentrations of isoprostanes in plasma (median 52,5 pg/ml) and in induced sputum (median 923,8 pg/ml) comparing to swimmers in the nontraining period (plasma 11,6 pg/ml; ($p<0,001$), induced sputum 81,8 pg/ml; ($p<0,001$)). Serum TNF concentrations are higher in high intensity training (median 28,0 pg/ml), comparing to nontraining period (median 17,9 pg/ml; $p=0,023$).

There is a trend toward higher concentrations of IL-5 in plasma in high training period (median 1,1 pg/ml), comparing to nontraining period (0,9 pg/ml), but the difference did not reach a statistical significance ($p=0,154$). There was no difference in pulmonary function test FEV1 and concentrations of IL-5 and TNF in induced sputum between training and nontraining period.

CONCLUSIONS: High intensity training in competitive swimmers results in marked oxidative stress at the airway and systemic level. We find a moderate increase in inflammation at systemic level, but not at the level of the airways and no difference in pulmonary function.

3

LUNG INFECTIONS

Chairs: Viktorija Tomič,
Matjaž Turel,
Biljana Ilievska-Poposka (Macedonia)

Multidrug- resistant tuberculosis - state of the art

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Tuberculosis (TB) is curable, but inappropriate treatment can lead to multidrug-resistant TB (MDR-TB), which is resistant to at least isoniazid and rifampicin, the two most effective anti-TB drugs. Based on figures from 2014, the latest year for which data are available, WHO estimates that 5% of TB cases are multidrug-resistant. This translates into 480 000 estimated cases and 190 000 deaths each year. Extensively drug-resistant TB (XDR-TB) is a form of MDR-TB that is also resistant to any fluoroquinolone and any of the second–line anti-TB injectable agents. On average, an estimated 9.7% of people with MDR-TB have XDR-TB. More than half of these cases were in India, the People's Republic of China and the Russian Federation. Globally, an estimated 3, 3% of new TB cases and 20% of previously treated cases have MDR-TB, a level that has changed little in recent years. In 2013, of the estimated 480,000 individuals with MDR-TB, only 136,000 were properly diagnosed, 97,000 were started on therapy, and 47,000 were successfully treated. Factors that lead to MDR-TB are related to: Patients, Healthcare providers and Healthcare system. Examples include when patients do not complete their full course of treatment; when health-care providers prescribe the wrong treatment, the wrong dose or length of time for taking the drugs; when the supply of drugs is not always available; or when the drugs are of poor quality and when airborne transmission of bacteria in public places is present. Drug resistance can be detected using special laboratory tests which test the bacteria for sensitivity to the drugs or detect resistance patterns. These tests can be molecular in type (eg, Xpert MTB/RIF) or else culture-based. Molecular techniques can provide results within hours and have been successfully implemented even in low resource settings. Patients with MDR-TB are treated with a different combination of second-line drugs, usually for 18 months or more. Attempts to reduce the length of conventional MDR-TB regimens and to use a combination of drugs which is tolerable have been ongoing for several years through various studies. Based on data from these studies, WHO updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation on the use of the shorter MDR-TB regimen under specific conditions : 4-6 Km-Mfx-Pto-Cfz-Z-Hhigh-dose-E/5 Mfx-Cfz-Z-E (Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide; Cfz=Clofazimine; Z=Pyrazinamide; Hhigh-dose= high-dose Isoniazid; E=Ethambutol. WHO encourages ongoing and future randomized controlled clinical trials to strengthen the evidence base for shorter and more effective regimens.

Atypical mycobacterial infections

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Atypical mycobacteria or non-tuberculous mycobacteria (NTM) are microorganisms ubiquitous in the nature and can be found in water and soil. For this reason some call them environmental mycobacteria. NTM belong to the same genus as *M. tuberculosis complex* and *M. leprae*. Currently more than 150 species of NTM are known that may cause infections in humans and animals. NTM are of low pathogenicity for humans and primarily cause infection in persons with underlying lung disease (e.g. patients with COPD, bronchiectasies, cystic fibrosis, after treatment for TB) or immunocompromised persons (e.g. HIV infected persons). Person-to-person NTM infection transmission is extremly rare.
Prevalence of infections caused by NTM varies between different parts of the world. Incidence of clinically important NTM infections is rising especially in industrialised countries where the estimated incidence of NTM caused diseases is 1-1.8 cases/100 000 population. Prevalence of specific NTM in different parts of the world varies as well. In some patients NTM infections can become chronic and need prolonged, continuous treatment which influances the quality of life.
More frequently isolated human pathogenic NTM are *Mycobacterium avium, Mycobacterium intracelullare, Mycobacterium scrofulaceum, Mycobacterium kansasii, Mycobacterium xenopi, Mycobacterium malmoense, Mycobacterium fortuitum, Mycobacterium chelonae* and *Mycobacterium marinum*. Species with less clinical importance are *Mycobacterium gordonae, Mycobacterium gastri, Mycobacterium terra, Mycobacterium triviale, Mycobacterium nonchronogenicum,* and *Mycobacterium flavescens*.

CLINICAL MANIFESTATIONS

NTM may cause asymptomatic infection or symptomatic illness. NTM disease (mycobacteriosis) can clinically manifest itself as lung, lymph nodes, skin and soft tissue involvement or disseminated disease.

Lung mycobacteriosis may present as cavernous or nodular disease, only rarely as hypersensitive pneumonitis. The most common causative agents of lung mycobacteriosis are *M. kansasii, M. avium intracellulare complex (MAC), M. malmoense* and *M. xenopi*.

Cavernous lung mycobacteriosis is more often detected in older males with underlying pulmonary disease (emphysema, bronchiectasies, pneumoconiosis or chronic bronchitis). It may have an acute or subacute course with productive cough, dyspnea, tiredness, weight loss, increased body temperature, and even blood-tinged sputum. On chest x-ray the abnormalities are seen predominantly in upper lobes and in 60-70 % cavernous forms are present.

Nodular lung mycobacteriosis is more often detected in astenic, older women without preexisting lung disease but with frequent chest wall deformities (e.g. pectus excavatum, scoliosis of the spine). Produc-

tive cough is the most prominent symptom. On chest x-ray abnormalities are seen in the right middle lobe and lingula.

Hypersensitive pneumonitis can occur in persons exposed to MAC. Improvement of symptoms follows after exposure cessation and in most cases treatment with corticosteroids and antimicrobials is not needed.

Mycobacteriosis of the lymph nodes commonly develops in children up to 5 years of age and is uncommon in adults, except in HIV infected persons. In most cases only one lymph node is affected and appears enlarged, possibly painful, inflammed but patient has no systemic signs of the disease. Mycobacteriosis of the lymph nodes is usually caused by M. malmoense and MAC. Treatment success is usually achieved by surgical removal of the diseased lymph node.

Disseminated mycobacteriosis affects mainly HIV infected persons and is presented with malaise, sweating, fever, weight loss, diarrhoea, lymphadenopathy, skin ulcers, hepatosplenomegaly. On chest x-ray mediastinal lymphadenopathy and nodules are usually seen. Disseminated mycobacteriosis is most often caused by MAC.

Skin and soft tissue involvement – abscesses and fistulas are present in skin and soft tissue. Skin and soft tissue involvement may develop as surgical or chronic wound infection. Most common causative agents are M. chelonae, M. fortuitum, M. ulcerans and M. marinum (swiming pool granuloma).

DIAGNOSTIC PROCEDURE

NTM infection can be suspected based on patient history, clinical presentation, and medical imaging. The diagnosis is confirmed by microbiological detection of NTM in clinical samples.

Diagnosis of pulmonary atypical mycobateriosis is based on clinical and microbiological criteria.

Clinical criteria are:

1. Pulmonary symptoms, nodular or cavernous abnormalities on chest x-ray or bronchiectasies with numerous small nodules on HRCT
2. Exclusion of other diseases

Microbiological criteria are:

1. positive culture from at least 2 separate sputum samples or
2. positive culture from at least one bronchial washing or BAL or
3. TBB or BB with histological criteria (granulomatous inflammation) and/or acid fast bacilli and positive culture from biopsy sample

TREATMENT

Treatment is not always indicated when NTM are isolated since the microbiological finding can also mean colonisation with NTM. Treatment is warranted for clinically important mycobacteriosis. Treatment course is prolonged (several months) with a combination of two or more antimicrobial agents. In some cases additional surgical treatment is needed. The choice of appropriate antimicrobial combination and treatment duration depend on the NTM species which is causing the disease. Resistant strains of NTM have already been detected around the world causing serious NTM disease especially in immunocompromised patients. Thus appropriate and regular administration of antimicrobial drugs is imperative.
The disease may reoccur despite the appropriate choice of antimicrobial agents and prolonged treatment. Mortality due to NMT disease is very low.

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Brief Report from EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) and the role of inhaled antibiotics and macrolides in non CF bronciectasis

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1. BRIEF REPORT FROM EMBARC, DATA FROM SLOVENIA (1)

BACKGROUND: Despite bronchiectasis not being a rare disease, it seems to be a neglected pathology within pneumonology. There have been few clinical trials conducted and therefore management of bronchiectasis is largely based on expert opinions and knowledge, which is extrapolated into the field of bronchiectasis from other fields of obstructive diseases or cystic fibrosis. Project EMBARC (European Multicentre Audit and Research Collaboration), founded by European Respiratory Society, deals with clinical, microbiological, radiologic and functional data about patients with bronchiectasis (patients with cystic fibrosis excluded) with the goal of encouraging research and international scientific collaboration in this field. Slovene segment of the EMBARC register is based at the University Clinic Golnik (2,3).

AIM: The aim of our study was to present clinical, radiographic and microbiological characteristics of adult patients with non-cf bronchiectasis in Slovenia based on the data we collected. This is the first time this data has been organized and presented.
We hypothesized that our patients with bronchiectasis will present with airflow obstruction and lower FEV1 results will be associated with more symptoms and increased sputum production. We also anticipated that the presence of *P. aeruginosa* would correlate with decreased lung function and higher frequency of hospitalizations, the presence of S. aureus with more episodes of haemoptysis.

METHODS: This retrospective study was conducted on a sample of 152 patients with non-cf bronchiectasis, which were examined between 27.5.2014 and 29.7.2015 at University Clinic Golnik. The data included medical history, clinical, microbiological, laboratory and radiographic data, which was entered into the EMBARC register and statistically analysed. We focused especially on clinical characteristics and microbiological analysis of sputum and their correlation.

RESULTS: The median age of patients was 67 years. The median of patients produced 5 ml of sputum daily. Patients had a median FEV1 of 1,805 L (74%) and FVC 3,317 L (102%). We saw statistically significant correlation ($p < 0,001$) between FEV1 and dyspnoea. The analysis of correlation between FEV1 and sputum volume ($p = 0,7$) and dyspnoea and sputum volume ($p = 0,56$) was not statistically significant. Lung function of patients colonized with *P. aeruginosa* was lower with median FEV1 57 % ($p = 0,012$) and median FVC 91,7 % ($p = 0,019$) compared to non colonised patients. The median of hospitalizations

in P. aeruginosa colonized patients in one year was 1 compared to non colonised patients with 0 (p = 0,276). Patients with S. aureus did not report haemoptysis episodes.

We have analysed 204 sputum samples. Most frequently (25%) normal bacterial flora was isolated from sputum. *H. influenzae* was isolated in 13,2%, followed by *P. aeruginosa* (8,8%), *S. aureus* (7,8%), *S. pneumoniae* (6,4%) and *M. catharalis* (3,4%). *H. influenzae* was resistant to amoxicilin and clavulanic acid in 3,7%, to azitromicin in 3,7% and cefuroxim in 3,7%. *P.aeruginosa* was resistant to ceftazidime in 5,6%. *S. aureus* was resistant to klinindamicin in 6,3%, eritromicin in 18,8% and penicilin to 93,8%. *S. pneumoniae* was resistant to klinidamicin in 23,1% and eritromicin 23,1%.

CONCLUSIONS: Subjects with the median age of 67 years produced 5 ml of sputum daily (median). Lung function showed mild obstruction. Lower FEV1 significantly correlated with increased levels of dyspnoea, however not with increasing volume of sputum. We proved significantly worse lung function in patients colonised with P. aeruginosa compared to non colonised patients, but not that they were statistically significantly more frequently hospitalized. We did not find a higher incidence of haemoptysis in patients with *S. aureus. H. influenzae, P. aeruginosa* and *S. pneumoniae* were the most common bacteria in patient s sputum. The grade of resistance to antibiotics was acceptable.

2. THE ROLE OF INHALED ANTIBIOTICS AND MACROLIDES IN NON CF BRONCHIECTASIS

Antibiotics are used in the following scenarios (4):

- in an attempt to eradicate Pseudomonas
- to supress the burden of chronic bacterial colonisation
- to treat exacerbations

The goal of suppressive antibiotic therapy is to reduce the bacterial burden. There is a direct relationship between bacterial load and levels of airway and systemic inflammation. A study of Chalmers in stable non CF bronchiectasis showed a direct relationship between sputum bacterial load and increased levels of airway and systemic inflammation (5). This evidence supports and effort to reduce sputum bacterial load in patients with non CF bronchiectasis. Inhaled antibiotics are safe and effective in reducing sputum bacterial load over the long term because they deliver a high concentration of drug to the airway with reduced systemic absorption. Tobramicyn, gentamicin ,colistin and aztreonam are prescribed in non CF bronchiectasis population. Use of inhalational antibiotics is »off label« because most supporting data come from CF population (4,6-10).

Macrolides exert immunomodulatory effects on host inflammatory response without suppression of the immune system. These effects include modifying mucus production, inhibition of biofilm production, suppression of inflammatory mediators, moderating leukocyte recruitment and function. Reduced frequency of respiratory exacerbations, decreased 24 hour sputum volume and improved well being are among outcomes seen in studies that employed low dose azithromycin (250 mg three time weekly or 500 mg twice weekly (11,12). The problem is the potential development of resistant bacterial strains. There are reports of statistical greater percentage of macrolide-resistant pathogens in the azithromycin group (13,14). Chronic use of macrolides also has the potential for fostering the growth of macrolide resistant strains in of NTM (nontuberculous mycobacteria). Because of the significant increase in macrolide resistance associated with monotherapy, experts recommend vigilance in ruling out chronic infection with NTM before initiating chronic macrolide therapy in patients with bronchiectasis (5).

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Antimicrobial stewardship

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INTRODUCTION

Antimicrobial resistance has been recognized as an important health threat for at least two decades (1). In spite of awareness of a part of professionals and sometimes also lay public and politicians, the problem is growing faster than expected. Dry pipelines especially for antibacterials further complicate the situation. In a recent report on the problems antimicrobial resistance globally, the authors stated that by 2050 several hundred thousand deaths will be attributed to antimicrobial resistance on yearly basis in Europe. The figures will be far greater in several other parts of the world (2).
In addition to poor infection control, sanitation and the use of antimicrobials in animals, human use of antimicrobials is recognized as a mayor driver of antimicrobial resistance, which is recognized as an adverse effect of antimicrobial therapy. Antimicrobial resistance cannot be avoided by not using antimicrobials at all, but inappropriate use and unnecessary use should be controlled. The goal of prudent antimicrobial prescribing is to optimize the treatment in an individual patient with the use of therapy which is maximally effective with the least possible adverse effects including antimicrobial resistance. Antimicrobials, especially antibiotics are prescribed by virtually all physicians which makes the efforts for improvement very difficult. Antimicrobial stewardship has been developed as a bundle of interventions aimed to improve antimicrobial prescribing (3).

ANTIMICROBIAL STEWARDSHIP IN HOSPITALS

Two Cochrane reviews have demonstrated the effect of antimicrobial stewardship interventions in hospitals which supports their use in practice (4,5). Recently a systematic review of antimicrobial stewardship in hospitals which were proven to be successful in at least one goal (outcome, safety, cost, antimicrobial resistance) highlighted adherence to guidelines, de-escalation, therapeutic drug monitoring, switch to oral, bedside consultation, list of restricted antibiotics as most successful interventions (6).
Antimicrobial stewardship guidelines were published for the first time in 2007 by Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). This year a new edition of the same guidelines were published with slightly different recommendations based on the results of newly published studies (3). German and Austrian guidelines for antimicrobial stewardship were published for the first time two years ago, English version of the text was published this year. They are more structurally oriented and aim to provide a backbone for introduction of an antimicrobial stewardship programme in the hospital (7). The strongest recommendations from both guidelines are presented in table 1.

Table 1: Strongly recommended antimicrobial stewardship interventions in IDSA/SHEA and German and Austrian guidelines (3,7)

IDSA/SHEA guidelines 2016	German and Austrian guidelines 2016
pre-authorisation and/or prospective audit and feedback	REQUIREMENTS
reduced use of antibiotics associated with the highest risk for *Clostridium difficile*	• antimicrobial stewardship team
pharmacokinetic monitoring and adjustment programmes for aminoglycosides	• the availability of surveillance data for antimicrobial resistance and consumption
appropriate initial use of oral antibiotics and timely switch from intravenous to oral antibiotics	CORE STRATEGIES
guidelines and strategies to reduce antibiotic therapy to the shortest effective duration	l• ocal guidelines, anti-infective formularies, formulary restriction and approval requirements
	• design and implementation of education, training and information
	• conducting pro-active audits of anti-infective prescribing
	• quality indicators

ANTIMICROBIAL STEWARDSHIP IN OUTPATIENTS

Antimicrobial stewardship interventions have been addressed in a Cochrane review in 2005. At that time the authors concluded that the effectiveness of an intervention on antibiotic prescribing depends on the particular prescribing behaviour and the barriers to change in the particular community. Multi-faceted educational interventions may be successfully applied to communities after addressing local barriers to change (8). These were the only interventions with effect sizes of sufficient magnitude to potentially reduce antimicrobial resistance. Many interventions were investigated as potentially effective in the last ten years. Recently, the antimicrobial stewardship interventions were analysed in two reviews. In the systematic review by Drekonja, they included 50 studies. The programmes incorporating communication skills and laboratory testing were found to be more successful in reducing antimicrobial use than other types of interventions. No study reported microbiological outcome (9). In the narrative review the authors concluded that the interventions are successful when they include behavioural change and/or a change in health-care system (10). The types of interventions and other factors known to influence antimicrobial prescribing analysed in the review are listed in table 2.

Table 2: Interventions and factors influencing antimicrobial prescribing in outpatients (10)

Prescriber level interventions	System level interventions
Education incl. academic detailing and training in communication skills	Limitation of the over-the-counter prescribing
Guidelines and clinical decision support	Limitation of the number of brand names available and pricing
Delayed prescribing	Unit dispensing
Patient materials: dedicated forms to prescribe antibiotics, non-prescription pads and patient information leaflets	Prescribing and dispensing
Public commitment	Prescriber remuneration system
Point-of-care tests	Pay for performance
Selective susceptibility reporting	Public reporting of health-care performance
Quality indicators	Sickness leave regulation
Audit and feedback	Pharmaceutical advertising
Restrictive antibiotic prescribing	
Limitation of the over-the-counter prescribing	

Limitation of the number of brand names available and pricing	
Unit dispensing	
Prescribing and dispensing	
Prescriber remuneration system	
Pay for performance	
Public reporting of health-care performance	
Sickness leave regulation	
Pharmaceutical advertising	

ANTIMICROBIAL STEWARDSHIP AND BEHAVIOURAL CHANGE

The main objective of antimicrobial stewardship is to improve antimicrobial prescribing and increase adherence to guidelines. Long has been known that adherence to guidelines is related to the knowledge and attitudes which finally affect physician's behaviour. Better antimicrobial prescribing requires behavioural change which is often forgotten in the design of the interventions. In a recent systematic review addressing the behavioural change in antimicrobial stewardship interventions only 17 out of 123 interventions applied behavioural change techniques (11). Several studies addressed knowledge in antibiotic prescribing in students and young doctors, the results reveal that the situation is far from ideal (12). Another important finding in recent years is the correlation of antimicrobial prescribing and sociocultural environment. The societies with high power-distance index, masculinity, and uncertainty avoidance tend to prescribe more antibiotics than the others (13).

INTERNATIONAL PERSPECTIVE OF ANTIMICROBIAL STEWARDSHIP

There are several international political and professional initiatives aimed to improve antimicrobial prescribing and reduce the burden of resistance world-wide. In Europe, the political support began with the Copenhagen declaration in 1998, which was followed by various recommendations and conclusion. The last EU Council conclusion related to the combat against antimicrobial resistance were adopted in June 2016. The conclusions highlight the importance of one-health approach which includes parallel activities in human and veterinarian medicine. The EU Council calls the EU Commission and the Member states to prepare national and supranational action plans by the mid-2017. The EU guidelines for prudent use of antimicrobials in humans are under review and are expected to be adopted in the fall this year. The Conclusions intend to strengthen the requirements for the Members states and also for the health-care providers (14).

World Health Organisation (WHO) adopted the Global Action Plan on antimicrobial resistance which includes five objectives: awareness, knowledge, infection prevention, prudent use of antimicrobials, and investments related to antimicrobial resistance (15).

CONCLUSIONS

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Nontuberculous mycobacteria in Slovenia – before and after stopping mandatory BCG vaccination

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BACKGROUND: Nontuberculous mycobacteria (NTM) are ubiquitous bacteria capable of infecting and causing disease in both immunocompetent and immunocompromised hosts. The frequency of nontuberculous mycobacterial diseases (mycobacteriosis) differs with regard to different geographical regions of the world. In general, cases of mycobacteriosis are on the rise in the last years. Slovenia had a rapid decrease of tuberculosis in the last years (the notification rate 19.1 in 2000 and 6.3 in 2015) and therefore mandatory BCG vaccination of the newborns was stopped in March 2005. The aim of our study was to analyze laboratory diagnostics of NTM and mycobacteriosis in the last sixteen years (2000-2015) and to detect any changes in distribution of NTM in Slovenia.

METHODS: Between 2000 and 2015, there were between 6 and 2 laboratories in Slovenia that were performing laboratory diagnostics of tuberculosis and NTM in humans. In the majority of laboratories in the past and in both labs the last years, cultures were grown on/in at least one solid and one liquid media. All clinical isolates of mycobacteria were sent to the National Reference Laboratory for Mycobacteria Golnik for identification. GenoType Mycobaterium CM/AS assays (Hain Lifescience, Nehren, Germany), colony morphology of NTM on transparent medium and/or in the first years AccuProbe tests (GenProbe, San Diego, USA), or classical biochemical tests were used for identification of mycobacteria.

RESULTS: A total of 4080 isolates of NTM were isolated from different clinical specimens in Slovenia in the period 2000-2015. *Mycobacterium (M.) xenopi* (27.06%) was the most frequently isolated species followed by *M. gordonae* (18.36%), *M. avium* (15.12%), *M. kansasii* (7.52%), *M. fortuitum* (7.26%) and *M. intacellulare* (6.74%) on the sixth place. In contrast, *M. kansasii* and *M. avium* complex were found to be the most common disease-causing mycobacteria in our country in the last 16 years. Mycobacteriosis has been observed in at least 256 persons in the same period. Thirty-three of them were children (20 girls and 13 boys) aged between 1.5 and 6 years and all of them had lymphadenitis caused by NTM mycobacteria. *M. avium* caused lymphadenitis in 24 (72.72%), *M. intacellulare* in 5 (12.12%) children, and *M. kansasii*, *M. celatum*, *M. interjectum* and *M. lentiflavum* only in one (3.03%) kids each species.

CONCLUSIONS: Mycobacteriosis are being detected more often in the last years in Slovenia, but are still relatively low. NTM lymphadenitis in children, “an expected novelty”, appeared first time in 2006, a year and a half after non-selective mandatory BCG vaccination was stopped in our country. Since this year we have between 1-6 cases of children lymphadenitis per year. *M. xenopi* was the most frequently isolated NTM and *M. avium* the most common disease-causing mycobacteria in our country in the last 16 years.

Analysis of cases of the extra pulmonary tuberculosis

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BACKGROUND: Extra pulmonary tuberculosis (TB) is a therapeutic challenge. For the follow up, after the therapy for TB, there are no precise parameters to properly assess the efficiency of the treatment. According to literature, 10-25% out of all TB cases are extra pulmonary ones. Diagnose of extra pulmonary TB is relatively challenging. The most common sites of EPTB are pleura, lymph node, bone - mostly spine, joints, genitourinary, meninges, peritoneum, larynx etc. Some cases remained unclassified. Aim of this study is to examine the frequency of EPTB in all TB pathology.

METHODS: A retrospective study of TB patients was performed, in the Department of Lung Disease, during an 18-month period spanning from January 2015 to June 2016. Analysis included clinical, radiological, patohystological, and laboratory examination of TB patients. Analysis of age, gender, as well as the length TB treatment was also reviewed.

Localisation	Number of patients	BK positivity	Quantiferon test positivity	Histopatological confirmed	MRI confirmed	CT confirmed	RTG confirmed
Lymph nodes	9	1 (11%)	4 (44%)	4 (44%)	-	7 (77%)	1 (11%)
Pleural	8	2 (25%)	1 (12.5%)	1 (12.5%)	-	4 (50%)	4 (50%)
Vertebral	8	-	2 (25%)	-	8 (100%)	-	-
Genitourinary	1	1 (100%)	-	-		-	1 (100%)
Peritoneal	1	-	-	1 (100%)	-	1 (100%)	-
Laryngeal	1	1 (100%)	1 (100%)	1 (100%)	-	1 (100%)	-

Table 1: Results of diagnostic procedures.

RESULTS: In the 18-month period 209 TB patients were treated. Out of them, 28 (13.3%) were cases of EPTB. The mean age was 55.21±17.64 years (range 19 to 83). Among the 28 EPTB patients, 15 (53%) were female and 13 (47%) male. All patients were treated according to DOTS (Directly Observed Chemotherapy, Short Course), recommended by WHO. A six month treatment regiment was performed for 27 patients. One patient was treated with a prolonged, individualised treatment plan (eight months).

According to DOTS, strategy diagnostic of TB should be confirmed by direct BK smear microscopy, BK positive in couture, or pathohystology. Out of the 28 patients with EPTB, up to 30 % could be treated without these confirmations.

CONCLUSION. Diagnostic confirmation of the EPTB is difficult, mostly due to the difficulties of obtain tissue specimens. Consequently, other diagnostic procedures should be performed, to help decide on TB treatment.

Trend of tuberculosis incidence in Slovenian statistical regions in the last decade

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BACKGROUND: Health service availability, traffic flows, economical situation, social and geographical conditions are some of the important factors, which influence the control of infectious diseases in a given region. The same also refers to tuberculosis (TB), which is a rare infectious disease in Slovenia. For several years annual incidence for TB has been less than 10 cases / 100000 inhabitants. Furthermore, the trend of rapid decline of TB incidence has also been detected in last years.
In this study we were interested in TB incidence (occurrence of TB) in different regions in Slovenia and in the trends of TB incidence for the individual statistical regions in period from 2006 – 2015.

METHODS: We performed a retrograde analysis of the data from TB patients registered in Registry of Tuberculosis in the period 2006 – 2015. Patients were classified in twelve statistical regions according to their permanent or temporary address in Slovenia. For each statistical region we calculated the annual TB incidence and determined the trend of TB incidence in the period from 2006 to 2015. Moreover the trend of TB incidence in each region was compared with declining trend of TB incidence for the entire country.

RESULTS: In the period from 2006 to 2015 a rapid decline of TB incidence is seen in Slovenia. From all twelve statistical regions eleven of them had a declining trend of TB incidence. These regions are Osrednjeslovenska, Notranjsko-kraška, Podravska, Gorenjska, Pomurska, Zasavska, Koroška, Spodnje-posavska, Savinjska, Obalno-kraška regija and Jugovzhodna Slovenija. The steepest decline of TB incidence was seen in Pomurska region. During this period an increasing TB incidence was seen in only one statistical region (Goriška).

CONSLUSIONS: In recent decade Slovenia became a country with low TB incidence and also with declining trend of TB incidence. A declining trend was seen in majority of statistical regions, with only one exception (Goriška region), where TB incidence is increasing.
According to analysed data, we can assume that Slovenia is a country with good control of TB. However in region with noticeable increase in TB incidence, an additional control over the management of the disease is required.
It is important to know, that TB is not the problem of one single region or one country, but a global problem, especially nowadays due to increased migrant flows. For that reason it is necessary to seek cooperation between regions and between neighbouring countries. These actions yield great results in lowering TB incidence.

Percentage of persons with risk factors for developing tuberculosis in Slovenia in the last decade

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BACKGROUND: Slovenia belongs to the group of countries with low incidence of tuberculosis (TB). Key feature of these countries is that TB mainly emerges in persons predisposed to infection such as homeless persons, elderly, immigrants or refugees from countries with high incidence of TB, prisoners, people with congenital or acquired immunodeficiency, healthcare or laboratory workers exposed to MT bacilli, patients treated with immunosuppressive drugs, persons addicted to alcohol, intravenous drug users and patients with malignant or other chronic diseases.
We were interested in percentage of TB patients with age and gender distribution in each risk group in the period 2006 - 2015.

METHODS: We have performed a retrograde analysis of data from TB patients registered in Registry of Tuberculosis in the period 2006 – 2015. They were sorted by gender, age, birth country and risk factors that qualify patients into risk groups. Every risk factor of TB patient was considered for the analysis.

RESULTS: TB was diagnosed in 1738 persons in the period 2006 – 2015 (male 59 %, 41 % female) with an average age of 56 years (52 years male, 60 years female). In the same period 37 % of all TB patients were older than 65 years (57 % of them were female), 27 % were immigrants (73 % of them were male). Furthermore, 15 % of all TB patients were unemployed (64 % of them were male), 13 % were addicted to alcohol (92 % of them were male) and 4 % were in contact with other TB patient. Other risk groups contributed small percentage of all TB patients in the period 2006 – 2015.

CONCLUSIONS: Elderly, immigrants, unemployed, persons addicted to alcohol and contacts were the most common risk groups among TB patients in Slovenia in the period 2006 – 2015. Male TB patients were more frequently immigrants, addicted to alcohol, unemployed or in contact with other TB patient. Female TB patients were more frequently elderly. Contrary to the majority of countries with low TB incidence Slovenian TB patients most commonly do not abuse drugs, are not homeless, prisoners or infected with HIV. Cause of this is relatively low population density in bigger Slovenian cities, good health-care accessibility, relatively low HIV infection rate, less homeless persons and less illegal immigrants.

4

BRONCHOSCOPY AND INTERVENTIONAL PNEUMOLOGY

Chairs: Aleš Rozman,
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Central airway obstruction

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Central airway obstruction (CAO) is a life threatening condition with an imminent suffocation threat. In many cases clinical picture is dramatic, presenting in 54% of cases in respiratory distress. It can be due to malignant diseases, mainly lung cancer, or it can be caused by non-malignant diseases. For that reason we divide tracheal stenosis in malignant and non-malignant. They cannot really be called benign for their course can be very dramatic and malignant. The incidence of central airway stenosis is not known, but it seems to be on the rise. Firstly, since the incidence of lung cancer is increasing malignant central airway stenosis are encountered more often. And also with the advance of modern medicine an incremental number of patients is treated in intensive care units where they are being intubated and kept on mechanical ventilation for varying lenghts of time. This leads to growth in incidence of benign tracheal stenosis.

Malignant tracheal stenoses are mostly caused by lung cancer invading trachea and main bronchi, followed by invasion by oesophageal and thyroid cancer. Primary tracheal malignancies are less common and comprise squamous carcinoma and adenoid cystic carcinoma, while distal of carina carcinoid is more frequent. Endotracheal metastases are a less frequent cause of airway obstruction, but often complicated by bleeding and haemoptysis (1,2).
Non-malignant airway obstructions occur most often due to endotracheal intubation and tracheostomy. It develops after 10-19% of intubation, yet clinically relevant becomes only after 1%. The earliest it presents after 2 days, but in some it can be even 3 months before it becomes symptomatic (mean 10 days). Development of stenosis is triggered by mucosal injury and ischemia leading to fibrosis. Sometimes it complicates by chondritis and cartilage destruction causing airway wall instability. Less frequently the cause of obstruction can be trauma to the trachea, either mechanical, thermal (combustion) or chemical. Several inflammatory diseases (tuberculosis, Wegener granulomatosis) can also trigger stenosis formation. Those are all progressive, fibrotic and fixed stenosis, yet tracheobronchomalatia causes dynamic stenosis present only during expiration.

Symptoms of CAO usually present late in the disease course. First symptoms are non-specific, mainly breathlessness on exertion and cough. Thus it is often mistaken for obstructive lung diseases or heart failure. Breathing problems most often progress leading to dyspnea even at rest. Due to the fluid dynamics the flow of the air over stenosis is not affected until the stenosis becomes critical. For that reason patients stay asymptomatic for long time, but then worsening is quick. It is not until diameter of airway

gets down to 8 mm that dyspnea on exertion starts, but already at diameter of 5 mm it is present even at rest. At that point diagnostics should be prompt and intervention imminent (3,4).
As always evaluation of a patient with CAO should start with medical history and detection of the cause for obstruction, followed by physical examination. In advanced cases of obstruction wheezing or stridor might be present. Functional test should be performed when possible and in advanced stage of obstruction blunting of flow-volume loop can be seen. Standard X-ray is rarely diagnostic, but CT scan, if possible to perform can give us very useful information. It can detect the position and length of stenosis, as well as diameter of the remaining lumen. Secondly analysis of adjacent cartilages and surrounding tissue is important for the decision on the type of intervention. Still, the most important is to perform a bronchoscopy and evaluate the stenosis. At this point both interventional bronchoscopist and thoracic surgeon should be present in order to decide the best approach.

According to CT scan and bronchoscopy results benign tracheal stenosis can be divided it three types. First is weblike, presenting as a circular, usually thin membrane, without affection of cartilage and tracheal wall. Second is complex, extending over longer stretch of airway, sometimes with destruction of cartilaginous rings. And the third is pseudoglotic, resembling of the vocal cords. Type, location and the extent of stenosis are important for the decision of treatment.

Surgical approach comprises resection of the stenotic segment and TT anastomosis. The length of resected segment could be 4-5 cm, maximal length being 7 cm if mobilisation of trachea is performed. Postoperative mortality is up to 5% and restenosis occurs in 15% of cases. In some cases granulations formed on sutures are removed then by interventional bronchoscopy (5).
Interventional bronchoscopy technics used are balloon and core dilatation, Nd:YAG laser and electrocautery incision and stent placement. Usually in weblike stenosis incision is performed first, followed by dilatation. In case of restenosis the procedure can be repeated once more, but after that it is recommended to perform a surgical resection. In complex and pseudoglotic stenosis, if surgery is not the option, dilatation and stent placement is recommended. Dilatations and stent placement can complicate with granulation formation necessitating repeated interventions (6,7).

There is no need for prophylactic antibiotic treatment, unless putrid inflammation is present. Yet inhalations with saline might be useful, especially after stent placement. Control bronchoscopies are usually performed, although some authors claim that they are needed only in case of new symptoms. There are still dilemmas on the length of stent stay. It should be kept in place at least six months, as it seems, although some reports claim it can be taken out sooner if the stenosis was treated with mitomycin C.
In our institution from beginning of 2014 till July 2016 we performed 389 interventional bronchoscopies in 277 patients. Out of these, 31 patients had non-malignant central airway stenosis. Causes of stenosis was postintubational stenosis in 19 (61.2%) patients, tuberculosis in 2 (6.5%) and Mb. Wegener in 1 (3.2%) patients. In 2 (6.5%) patients the cause of stenosis was unknown, so we assume it was idiopathic, while 5 (16.1%) had granulations and 1 patient (3.2%) had tracheobronchial papillomatosis. There were 26 male and 5 female patients and average age was 49.6±19.0, statistically younger than the other treated patients (p=0.001). In 31 non-malignant stenosis patient were 72 interventions performed, ranging from 1 to 10 interventions per patient.
Most of the interventions were performed under general anesthesia (52, 72.2%), while 16 (22.2%) were performed under local anesthesia and 4 (5.6%) under concious sedation. In accord to this most procedures were done on hospitalised patients (56, 77.8%) and only 16 (22.2%) were done in outpatient conditions.
Procedures done during interventions were core dilatation in 32 (44.4%) cases, photocoagulation by Nd:YAG laser in 31 (43.1%), balloon dilatation in 21 (29.2%), electrocautery snooze also in 21 (29.2%) cases, electrocautery incision in 20 (27.8%). Core resection, criorecanalisation, forceps and argon-plasma coagulation were used in less than 10 cases. In 7 patient stent was placed (22.5%).
Surgical resection with TT anastomosis was performed in 8 (25.8%) patients. In 5 (16.1%) patients surgery was the first option, while in 3 (9.7%) it was performed for restenosis after interventional bronchoscopy. Patients who first underwent surgical resection all needed some sort of interventional bron-

choscopy intervention from 2 to 10 times, while the ones who were resected after prior interventional bronchoscopy had 1 to 4 interventions later.
Our results are in accordance with other groups and confirm the importance of team work between an interventional bronchoscopist and thoracic surgeon. The decision how to approach a patient with non-malignant tracheal stenosis is difficult and the decision is not always straight forward. Some patient obviously are more prone to restenosis or to granulation formation that acquires repeated interventions. Yet all our patients were succesfully treated.

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Diagnostic of peripheral lung lesions

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Peripheral pulmonary lesion (PPL) is defined as lesion surrounded by normal lung parenchyma without any CT evidence of endobronchial abnormalities, or as a intraparenchymal lung lesion less than 3cm in diameter, and is not associated with atelectasis or adenopathy .(1) Those lesions are common incidental findings. CT studies in the general population reports a prevalence of incidental nodules at 31 percent (1,13).
This rising incidence is in correlation with increasing use of computed tomography (CT) - and the majority of these nodules are not malignant.
Lesions smaller then 3 cm are diagnostic problem. Pathological findings of those lesions my be a malignant tumors, benign tumors and some are rheumatoid nodules, tuberculoma etc. Clinicians have a task to provide the safe and minimally invasive method of obtaining accurate tissue diagnostics for the pulmonary nodule.

INDICATION -patient selection — While the optimal approach to managing patients with a peripheral pulmonary lesion (PPL) is unknown.
Following rules are accepted:
- Some of PPL require only further diagnostic evaluation (patients with small or stable PPLs do not need to be biopsied)(2).
- Surgical biopsy is preferred in patients with PPLs who are at high risk of malignancy.

Image-guided biopsy techniques may be considered as one option
- nonsurgical biopsy is preferred in those with PPLs who have an intermediate risk for malignancy,
- those who have a high risk of malignancy who are not surgical candidates,
- patients with benign disease resistant to therapy (eg, mycobacterial disease),
- for therapeutic interventions to inoperable patients (ENB and EBUS controlled brachytherapy).

DIAGNOSTICS TECHNIQUES
Diferent techniques can be used for diagnostics which depends on: tumor size, location, patients comorbidites (esp.emphysematous lung), respiratory function.
General management strategies are to use:

1. Imaging techniques
Use of CT and CT/PET for detection PPL. CT/PET has a great role in lung cancer diagnosis but it lacks the sensitivity and specificity to definitely establish a diagnosis on its own. Although CT/ PET is more sensitive than CT in identifying lung lesions it could often give false positive results. Tissue diagnosis has a key role and is a standard in diagnosis.

2. TTNA (transthoracic needle aspiration)
-TTNA under fluoroscopic control - CT guided TTNA- (which is highly sensitive for malignancy in 90%, but this technique also has a false negative rate in 20-30%.(3)

3. Bronchoscopy
Flexibile bronchoscopy is the standard in the diagnosis of lung lesions. Although the FB is least invasive procedure for sampling, it is limited by its inability to reach lesion in the peripheral segments of the lung especially when the lesion are smaller than 30mm and in cases when is PPL are radiologically invisible. Other new bronchoscopic procedures (EBUS, electromagnetic navigation, etc..) are also used.

4. Surgery
Surgical methods are the most invasive technique with almost 100% sensitivity, using video assisted thoracoscopic surgery (VATS) or thoracotomy.

BRONCHOSCOPY IN DIAGNOSIS OF PPL
Standard flexibile bronchoscopy (FB) under fluoroscopic guidance.
PPL the diagnostics is usually performed as transbronchial lung biopsy (TBB), brush, needle and suction catheter biopsy under fluoroscopic guidance. This standard technique has a low sensitivity.
It is known that TBB under fluoroscopy is limited in evaluating small pulmonary nodules. In lesions smaller than 3 cm reported sensitivity varies from 20 percent to 84 percent in malignant lesions and from 35 percent to 56 percent in benign cases. (4).

New metods in diagnostics are:
Image-guided bronchoscopy (IGB) techniques which include the following:
- Virtual bronchoscopy (VB)
- Navigation bronchoscopy (NB)
- Virtual bronchoscopic navigation (VBN)
- Electromagnetic navigation bronchoskopy (ENB)
- RP-EBUS(radial endobronchial ultrasound probe) and
- other techniques including CT bronchoscopy and ultrathin bronchoscopy.

The diagnostic yield of IGB techniques ranges from 44 to 88 percent, typically varying with lesion size, location, and equipment used as well as other factors including the presence of a bronchus sign and biopsy technique.

Virtual bronchoscopy (VB) is a noninvasive form of bronchoscopy that reconstructs the airways in a three-dimensional manner producing images that appear similar to those visualized during invasive bronchoscopy. VB cannot biopsy lesions per se.but can be used to navigate (VBN) conventional bronchoscopes and other biopsy equipment to the target PPLs.

Navigation bronchoscopy (NB) — Navigation bronchoscopy (NB) uses a navigational system to guide ins truments (eg, flexible or ultrathin bronchoscope) through the airways to a target lesion for biopsy.

Virtual bronchoscopic navigation (VBN) is a technique that utilizes VB computer tomographic (CT) imaging to guide the bronchoscope to a peripheral target lesion in the lung. This **Technique** consists of :

- **Planning phase** – First, CT scan images used to create a virtual bronchoscopic pathway to the target lesion
- **Guidance phase** – During the guidance phase, the virtual images of the airway pathway are displayed and synchronized with real-time images from the bronchoscope
- **Biopsy phase** – Depending on the procedure chosen to biopsy the lesion, a PPL can be sampled: by flexible or ultrathin instruments.-(Radial endobronchial ultrasound probes (RP-EBUS) can be placed with a guide sheath through the working channel of a flexible bronchoscope so that the target nodule can be visualized and its location confirmed.)

Efficacy — The diagnostic yield from VBN has only been reported from centers with expertise and ranges from 67 to 80 percent

-A large meta-analysis of 39 studies, many of which used VBN in conjunction with other image-guided bronchoscopic (IGB) techniques reported a diagnostic yield of 72 percent [10].
-Two randomized clinical trials of VBN- versus non-VBN-assisted techniques for PPLs showed mixed results with one reporting increased diagnostic yield (80 versus 67 percent) and the other showing no difference (67 versus 60 percent) (11, 12)
-The diagnostic yield for small peripheral pulmonary lesions is increased when VBN is combined with EBUS. Virtual bronchoscopy(VB) with EBUS RP vs. EBUS RP alone --the diagnostic yield was significantly higher in the VB- EBUS RP group (80,8% vs 67,4% p=0,032) for lesions < = 2cm.(9).

Electromagnetic navigacion bronchoskopy (ENB)

• Electromagnetic navigation bronchoscopy (ENB) is the most common IGB technique. It incorporates VB imaging with an electromagnetic field, an additional navigational tool, to guide biopsy equipment (eg, forceps, brush, guide sheath) to the target lesion.
ENB is relatively new technology that provides electromagnetic navigation to localize and sample PPLs. The system consists of four components
- virtual bronchoscope planning software that converts CT scans into multiplanar images with three-dimensional virtual bronchoscopy reconstruction
- “location board” which emits low fr.electromagnetic waves
-extended working chanel (like guide sheat), an eight way catheter to enable selective cannulation of bronch and
- “locatable guide” containing sensors that allow precise tracking of both position and orientation throughout the electromagnetic field.(8).
This system enables navigation guidance within the lungs to endobrochially invisible targets, but it is based on a virtual environment and when used by itself, did not provide assurances that the intended lesion has indeed been reached.
ENB can be used alone or in combination with radial probe endobronchial ultrasonography (RP-EBUS) to biopsy PPLs The diagnostic yield for ENB alone is highly variable and ranges between 59% to 77,3 %. No guidelines are currently available for ENB.

Radial endobronchial ultrasound (RP-EBUS)

is an adjunctive imaging tool used to visualize the target lesion prior to biopsy. It can be used together with conventional bronchoscopy as well as with navigational tools (virtual or electromagnetic), to facilitate biopsy of PPLs. Neither RP-EBUS nor ENB provide actual real-time biopsy visualization as the ultrasound or navigation probes must be removed in order to pass the biopsy instruments.
Radial probe-endobronchial ultrasound (RP-EBUS), first reported in 1990 in diagnostic bronchial wall integrity and mediastinal limphadenopathy. This metod now is used in diagnostic evaluation of peripheral pulmonary nodules (PPN). This method uses ultrasoud to visualise periferal lesions of the lung tisue as one hypoehoic lesion. Solid tumor appear darker and more homegenous (well differentieted against lung tissue). Inflamatory tissue or atelectasis have an inhomogenous distribution. This form of endobronchial ultrasound (EBUS) utilizes a 20-MHz miniaturized ultrasound probe (UM-S20- 17S, Olympus, Tokyo, Japan) with radial side scanning properties, producing a 360-degree ultrasound image of the surrounding lung parenchyma. Herth et al. (in 2002), who reported a diagnostic yield of 80% in 50 lesions not using disposable guide sheaths (DGS). Other diagnostic studies reported success rate 58% to 82% success rate using the RP-EBUS with DGS (disposable guide sheaths). (5, 6)
The Steinfort et all in 2011, reported significant difference in obtaining a diagnosis of lesions smaller than < 20mm and larger than >20mm (56,3% vs 77,7%). (7)

Other bronchoscopic procedures are:

- H-EBUS (hybrid endobronchial ultrasound)
H- EBUS scope offers a higher degree of flexon, 10 degree oblique viewing field and allowed for visualization of significantly more airway segments.
- THIN- EBUS
Using the VBN and an ultrathin bronchoscope (2,8 mm, more than 50 percent of the lesions were di-

rectly visualized and diagnostic yield was 80%.(15)
- Bronchoscopic trans-parenchymal nodule access (BTPNA)

CONCLUSION

Diferent techniques can be used for diagnostic PPL.
Image guided bronchoscopic techniques and systems are designed to provide direct visualization of lesions before biopsy. Combination of these techniques (VB/EBUS, ENB/EBUS) increases diagnostic sensitivity.

Multimodality diagnosis with the combined use of EBUS /ENB has pushed diagnostic yield of flexible bronchoscopic procedures closer to the sensitivity obtanibale through either transtoracic CT –guided (92%) or surgical biopsies(100%).
These techniques may provide a means for therapeutic interventions to inoperable patients (ENB and EBUS controlled brachytherapy).(14)
If we know that lesions smaller than 15 mm are harder to reach with the EBUS system, that about 11 to 24 percent of solitary pulmonary nodules could not be localized by EBUS - problem in diagnostic of this lesions become bigger than we thought.

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New developments in EBUS-TBNA

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INTRODUCTION

Endobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA) is probably the most important innovation in bronchology since the introduction of the flexible bronchoscopy. It was introduced in praxis in 2004 for lymph node (LN) staging in patients with lung carcinoma. The addition of linear ultrasound probe to the bronchoscope enables first the ultrasound image evaluation of mediastinal and hilar LN or lesions adjacent to the airways and second, the needle biopsy under real-time ultrasound (US) guidance (figure 1). The later has importantly influenced the diagnostic yield. Another advantage of the technique is it's minimally invasiveness and safety with low complication rate. Despite its minimal invasiveness, it can provide adequate samples including cell block preparation which enables immuno-cytologic and molecular testing for accurate diagnosing of the cancer. EBUS-TBNA has been adopted quickly throughout the world and its use has been expanded also to benign and infectious diseases. Introducing EBUS bronchoscope into the esophagus enables sampling of the lesions and LN around esophagus and thus additionally enlarges the scope of reach (EUS(B)-FNA).

New developments are focused on one side on introducing novel imaging modalities that could distinguish between malignant or benign LN with high reliability. In the sampling field, there are efforts to increase the size of the sample (needle developments), the sampling area (thin EBUS scope for intrapulmonary LN), and adequacy of sampling (additional guidance - EM navigation, image techniques). In future, it might also be a therapeutic technique (targeted cytotoxic drug injection - EBUS-TBNI, cyst evacuation).

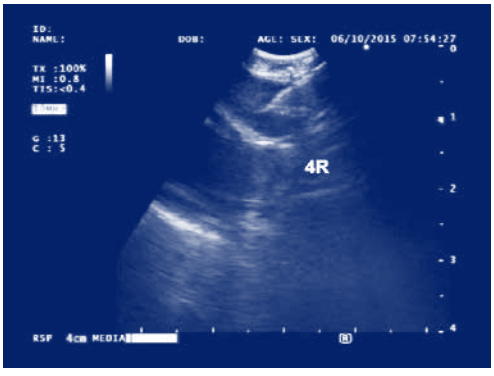

Figure 1: *EBUS-TBNA image of needle puncturing LN in right lower paratracheal region (4R)*

LUNG CANCER STAGING AND DIAGNOSING OF INTRAPULMONARY TUMOURS

The most known indication for EBUS-TBNA is mediastinal and hilar LN staging in potentially operable patients with lung carcinoma. A combination of EBUS-TBNA and EUS(B)-FNA provides sampling of majority of mediastinal LN stations and increases a detection of N2 disease (figure 2). Meta-analyses have shown that sensitivity and NPV of combined EBUS-EUS(B)-FNA are at least comparable to surgical methods (table 1). In European and American guidelines (2014 ESTS, 2013 ACCP guidelines) EBUS-TBNA and EUS-FNA are regarded as the best first test over surgical staging for LN that are suspicious by radiology and are accessible by an endoscopic approach. However, in the case of negative EBUS/EUS finding and high probability of metastatic disease surgical staging is necessary prior to operation.
Because of its small invasiveness EBUS-TBNA is also useful with some limitations for restaging after initial treatment.

Table 1: Sensitivity, specifity and negative predictive value for LN metastasis of different non-invasive and invasive methods (Chest 2013, 1).

Method	n	Sensitivity (%)	Specificity (%)	NPV (%)	Prevalence (%)
CT	7368	55	81	83	30
PET-CT	2014	62	90	90	22
MES	10648	81	100	91	34
EUS/EBUS	881	91	100	96	33

MES - mediastinoscopy

Few imaging methods have been developed for the purpose of better distinguishing between metastatic and non-metastatic LN (CEUS, elastography, 3D US). They have a potential to provide a better information of which node should be sampled and where, but none of them can replace cytology investigations so far.
EBUS-TBNA and EUS-FNA are highly successful in diagnosing metastatic LN from extra-pulmonary tumours and lung tumours adjacent to the larger airways or esophagus (of malignant or benign ethyology). Through the esophagus we can safely puncture left adrenal gland in case of metastasis suspicion. Endosonographic evaluation of mediastinal structures invasion by the tumour is possible and could add important information for the treatment decision, but the investigator needs a lot of experiences to properly evaluate the invasion.
The development of thin EBUS scope might expand the area of tumour and LN sampling further to smaller airways.

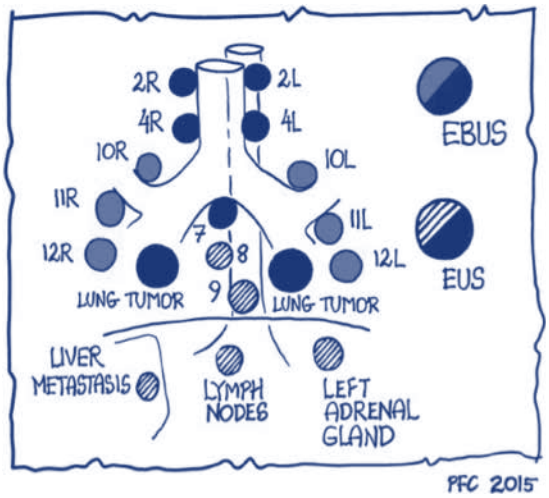

Figure 2: *Schematic representation of LN stations, lung tumours and extra-thoracic lesions that can be reached by EBUS/EUS-FNA (figure from Bonta PI et al, 2)*

LYMPHOMA

Endosonography has the potential to be effective in lymphoma diagnosis, but so far its limitation is that accurate subtyping (which is crucial for treatment choice) in small cytology or histology samples is often difficult or impossible. In an attempt to overcome this limitation bigger 19 gauge histology needles have been developed, the trials are still going on. EBUS-TBNA can be very useful for the detection of recurrent lymphoma.

ENDOSONOGRAPHY IN BENIGN DISEASES

EBUS/EUS(B) – FNA is highly sensitive in diagnosing sarcoidosis. Randomized trials have shown its superiority compared to conventional bronchoscopy methods. Where available, it should be qualified as a first step in diagnosing sarcoidosis stage I or II when there is an indication for tissue confirmation. In other cases, it is recommended to be combined with trans-bronchial lung biopsy (TBLB).
In cases of tuberculosis lymphadenitis EBUS-TBNA can be a sensitive and safe diagnostic tool.
Mediastinal cysts are of different origin (bronchogenic, pericardial, infectious, malignant). EBUS can be a valuable tool in confirming a cystic nature of the lesion with its typical sonographic appearance. Needle aspiration is seldom required and controversial because of risk of infection. Safe endoscopic therapeutic cyst drainage is one of the future challenges.

EBUS IMAGE ANALYSES OF LN

In an attempt to improve inadequate non-invasive distinction between metastatic and non-metastatic LN different image techniques and classifications have been developed. The first report was on B mode image classification of mediastinal and hilar LN. The classification uses six indicators: size, shape, margin, echogenity, central hilar structure and central necrosis sign. The four predictors of round shape, distinct margin, heterogeneous echogenicity and central coagulation-necrosis sign were independent but limited predictors of LN metastasis. Recent advances in imaging include 3-dimensional US, contrast enhanced US (CEUS), 3-D CEUS, real time elastography (RTE). Briefly, CEUS enables detailed visualization of the vascularity of LN, while elastography is based on the visualization of relative elasticity differences. Both image techniques can be helpful in identifying malignant areas within LN and are useful for the guidance of fine needle aspiration. The sensitivity and specificity for detection of metastatic LN are improved by using new imaging techniques, but they still can't replace cytology (figure 3).

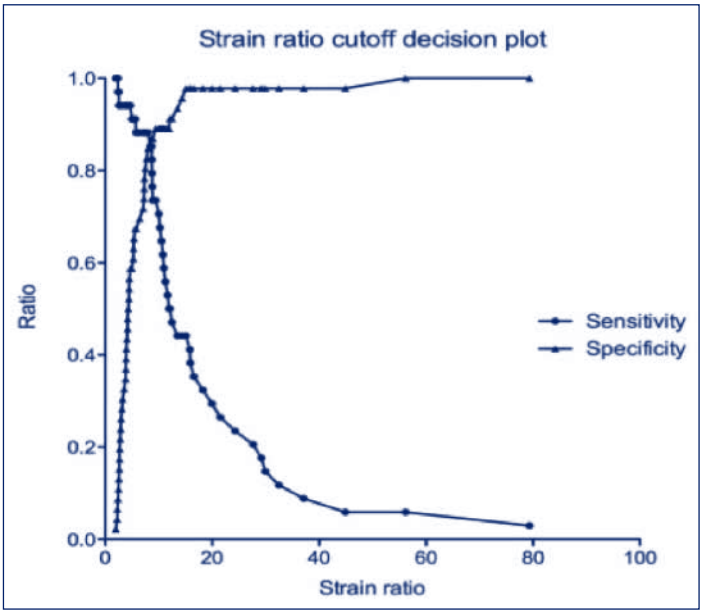

Figure 3: *Elastography - sensitivity and specificity decision plot to determine the optimal cutoff for strain ratio. Curves cross at strain ratio value 8 (Rozman A. et al,5)*

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Unexpandable lung

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ABSTRACT
Unexpandable lung is described as mechanical complication, resulting in the inability of the lung to expand sufficiently to achieve normal visceral and parietal pleural apposition. The causes are: endobronchial obstruction, severe lung fibrosis and restriction of visceral pleura, which is further subdivided in trapped lung and lung entrapment. Trapped lungs are considered as a consequence of remote, yet inactive pleural inflammation, which is characterised by chronic, stable pleural effusion. On the other hand is the lung entrapment a consequence of active, ongoing inflammatory process or pleural malignancy. The distinction between these two conditions is important because of different therapeutic approach. Diagnosis is established on the basis of pleural manometry and histological examination of pleural disorder.

INTRODUCTION
Pleural effusion is a common clinical condition, and one of the first procedures in the diagnostic / therapeutic work-up is thoracenthesis with partial or complete removal of pleural fluid. Although evacuation of the pleural fluid is often beneficial for a patient and results in symptomatic relief, sometimes causes chest pain, worsening of dyspnoea, pneumothorax or reexpansion pulmonary edema. Extensive changes in pleural pressures, provoked by rapid removal of pleural fluid are often responsible for such complications. In the centre of pleural pressures is the elasticity of pleural space, primarily lungs. Unexpandable lung is well known phenomena, recognized already in the first half of 20th century, in the era of collapse therapy. A proportion of patients developed parenchymal lung fibrosis or visceral pleural fibrosis with permanent pneumothorax, which was later replaced by ex vacuo pleural effusion.

Unexpandable lung is described as mechanical complication, resulting in the inability of the lung to expand sufficiently to achieve normal visceral and parietal pleural apposition. The term “trapped lung” is often used in daily practice to describe this condition, but its use is incorrect, since trapped lung represent only a proportion of patients with unexpandable lung.

UNEXPANDABLE LUNG
There are several reasons that lead to the phenomenon of unexpandable lungs. Pathologic mechanisms include:

1. endobronchial obstruction (tumour, foreign body, deformation),
2. advanced pulmonary fibrosis,
3. visceral pleural restriction.

Visceral pleural restriction is further subdivided into two categories:

1. trapped lung,
2. lung entrapment.

This last subdivision is very important from the clinical point of view and represents the rational basis for further therapeutic strategies. Trapped lung is considered a unique clinical diagnosis which characteristic is stability and chronicity over time. The diagnosis requires exclusion of any ongoing inflammatory or malignant process. The cause is remote but resolved inflammatory process that caused fibrosis of visceral pleura. Such conditions are often associated with empyema (or complicated parapneumonic effusion), pleural tuberculosis, rheumatoid pleurisy, hemothorax, cardiac syndrome or coronary bypass grafts and uremic pleuritis. Pleural fluid is the consequence of pure mechanical imbalances, which result in negative hydrostatic pressure. Although many authors hypothesize, that pleural fluid is typically transudate it often reveals elevated protein and LDH levels. Alternative explanation may relate to parietal pleura, which was affected by the same inflammatory process. Thickened in fibrosed parietal pleura is a common co-founding and its reduced functionality at the level of affected Wang's pores may result in reduced protein uptake.

Lung entrapment on the other hand is a mechanical complication of an active pleural disease. It occurs, when the above-mentioned pathological processes are still active or in the setting of malignancy. It is not a disease per se, but rather a complication of these conditions and is therefore treatable. The active disease is most often the leading cause of patient's symptoms and the lung entrapment becomes evident only at the attempt of complete pleural fluid evacuation.

DIAGNOSTIC PROCEDURES

One of the initial diagnostic procedures is the **chest X-ray**, which already provides a great deal of information. Central tumour, atelectasis, suspected foreign body (together with patient's history) or lung fibrosis can be suspected. Trapped lung usually have moderate amount of effusion in the absence of contralateral mediastinal shift. Affected hemithorax is usually smaller in size than the healthy side. In entrapped lung we observe variable amount of pleural fluid: from moderate to extreme with or without contralateral mediastinal shift.

In most cases **chest CT scan** is performed to exclude central obstruction, malignancy and lung fibrosis (localized or diffuse). Air contrast in the pleural space may reveal abnormal visceral pleural thickening, but cannot differentiate between trapped lung and lung entrapment. Lung CT is best performed after the attempt of pleural fluid removal since patency of bronchi is better assessable in this way.

Pleural fluid analysis can reveal low protein and LDH concentrations, which favours the diagnosis of trapped lung over lung entrapment, but the finding is not specific.

Pleural manometry is the method of choice for diagnosis of unexpandable lung. A simple water column manometer (similar to CVP measuring device) or more sophisticated electronic system with hemodynamic transducers can be used. The procedure is performed in a patient in the sitting position with the thoracenthesis catheter inserted in the most dependent portion of pleural effusion. The insertion spot is safely determined by chest ultrasound. Measurement of pleural pressure is performed initially and for every selected quantity of removed pleural fluid (for example every 100 ml). Measured values are recorded in the table and pressure/ volume plot can be created with calculations of pleural space compliance (elastance). Pleural fluid can be safely removed until one of the following conditions ensues:

1. complete removal of pleural fluid,
2. drop of pleural pressure below -20 cmH2O,
3. patient reports symptoms (chest pain, cough).

On pressure/volume plot three distinctive curves are typically recognized:

1. monophasic curve with normal elastance in patients without unexpandable lung,
2. monophasic curve with high elastance in patients with trapped lung,
3. biphasic curve with normal initial elastance, inflection point and subsequently high elastance in the terminal portion in patients with lung entrapment.

Thoracoscopy with pleural biopsy is the final diagnostic procedure in patients with undiagnosed pleural effusion. Majority of patients with trapped lung require histologic examination of parietal pleura since the exclusion of any active process is required. Visual examination reveals uniform pleural changes with thickened visceral and in many cases also parietal pleura in the absence of histologically active inflammation or malignancy.

IMPLICATIONS FOR THE CLINIC

Unexpandable lung is pretty heterogenic group of disorders with pleural effusion which requires different therapeutic strategies.

Endobronchial obstruction is managed by removing of the foreign body or re-establishing the patency of the airway in lung tumours whenever possible.

When significant lung parenchyma fibrosis is present and pleural pressure is initially low, the repeated removals of pleural fluid don't bring meaningful improvement.

Pleural effusion in patients with trapped lung is often asymptomatic, but may result in dyspnea. The later is most often present in patients with comorbidities, which usually contribute to its severity. Pleural fluid removal is meaningless, because of the risk of complications and quick recurrence of effusion. Observation is the method of choice in treatment of asymptomatic patients, while surgical decortication is considered in the rest.

Lung entrapment is characterized by active pathological pleural process, which can be treated in order to prevent late sequellae. Parapneumonic effusion and empyema should be drainaged with the attempt to complete lung reexpansion in stepwise fashion when the patient develops symptoms or if pleural pressure falls to low during pleural fluid evacuation. In the cases of pleural malignancy the complete reexpansion of the lung and pleurodesis should be done early in the course of the disease whenever possible. Systemic therapy only occasionally influences pleural effusion, but delay may cause incomplete reexpansion of the lungs and the window of opportunity for pleurodesis is lost. Indwelling pleural catheters may be used for palliation this condition.

CONCLUSIONS

Unexpandable lung is important clinical condition in patients with pleural effusion, which requires specific therapeutic strategies. Exclusion of airway obstruction and parenchymal fibrosis is important diagnostic step. Pleural manometry should be used to distinguish patients with trapped lung and lung entrapment. It should be used also in patients with malignant pleural effusion to better select patients for pleurodesis and for indwelling catheters. Patients with trapped lungs are usually less symptomatic and don't require specific therapy.

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5

HYPOVENTILATION DISORDERS

Chairs: Irena Šarc

Survival and gender differences on long-term oxygen therapy: comparison according to underlying disease

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BACKGROUND: Long term oxygen therapy (LTOT) is used in treatment of chronic respiratory failure (CRF) for over three decades, jet positive effect on survival is proven only in CRF resulting from severe chronic pulmonary obstructive disease (COPD). Aim of study was to compare the survival of patients on LTOT, according to the cause of CRF and investigate gender-related survival.

METHODS: A total of 1565 patients (65% male), who started LTOT between October 1982 and November 2003, were included, data were collected from National register for LTOT. Haemoglobin value, arterial blood gases, pulmonary function tests were recorded before starting LTOT. Vital status was obtained from Central Population Registry, data were censured in August 2014.

RESULTS: Five groups of CRF due to pulmonary diseases were identified; COPD (1193 patients, 70% male), interstitial lung diseases (140 patients, 55% male), sequelae after tuberculosis (72 patients, 58% male), kyphoscoliosis (46 patients, 30% male) and pulmonary vascular disease (49 patients, 39% male). All but 50 (3,2%) patients died in the study period. Median survival time after starting LTOT in patients with COPD was 922 (IQR 367-1910) days. Median survival of patients with interstitial lung disease was 411 (IQR 94-1015) days. Patients with sequelae after tuberculosis had a median survival of 1507 (512-2570) days and median survival for patients with kyphoscoliosis was 1568 (IQR 358-2666) days. Median survival time of patients with pulmonary vascular disease was 602 (IQR 206-1805) days. Differences in survival between groups were statistically significant (p<0,001). After adjusting for age, gender, haemoglobin values, arterial blood gases and pulmonary function survival did not differ over time. In multivariant Cox models adjusted for age, gender, haemoglobin values, arterial blood gases, pulmonary function and smoking status the mortality was lower for women than for men in COPD, hazard ratio (HR) 0.81 (95% confidence interval (CI), 0.69–0.94; P 0.007) and pulmonary vascular disease HR 0.28 (CI 0,085-0,93; P 0.038); in other groups gender was not independently associated with survival of patients.

CONCLUSION: Survival of patients on LTOT differed according to underlying disease, with shortest survival in patients with interstitial lung disease and pulmonary vascular disease and longest survival in groups of restrictive disorders - sequelae after tuberculosis and kyphoscoliosis. Female gender was associated with better survival in COPD and pulmonary vascular disease.

Women with obesity hypoventilation syndrome are less adherent to domiciliary noninvasive ventilation

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BACKGROUND: Domiciliary noninvasive ventilation is a standard of care for patients with obesity hypoventilation syndrome (OHS). Women with OHS differ from men in age and comorbidities, but there is little data on differences in usage of NIV therapy between men and women.

METHODS: In this retrospective study we have collected data on consecutive OHS patients seen in an outpatient follow-up NIV clinic between Dec 2014 and Feb 2016 from institutional NIV registry and medical records. Data on adherence was obtained from NIV machines software.

RESULTS: 94 patients with OHS were included in the study, 31 (33%) women, age 64.3 ± 10.5 years, body mass index (BMI) 42.3 ± 7.8 kg/m2, initial apnea-hypopnea index (AHI) 36/h ± 29/h. NIV was initiated in acute setting in 37% of patients and a mean follow-up was 2.0 ± 1.4 years. Women had higher BMI (44.9 ± 9.9 vs. 41.1 ± 28.0, p= 0.028), more often had comorbid obstructive sleep apnea (93% vs. 81%, p=0.018) and diabetes (64% vs. 35%, p=0.008), required higher IPAP (19.2 ±8.0 vs.15.4 ± 10.6, p=0.001), and had lower average NIV usage (4.7h ±2.05 vs. 6.3h ± 3.08, p= 0.028). Only 48% of women used NIV therapy for more than 4 hours on more than 70% nights, compared to 76% of men, p= 0.015. There was no significant difference in the age at NIV initiation, pCO2 at initiation, pCO2 at follow-up, EPAP or frequency of NIV initiation in acute setting, and mask problems.

CONCLUSION: One third of our patients were women. They were more obese, had more often comorbid obstructive sleep apnea and diabetes, required higher IPAP pressures. Adherence to NIV therapy was good, but women were significantly less adherent to NIV therapy than men.

Impact of patient knowledge about obstructive sleep apnea on CPAP adherence

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BACKGROUND: Patients with obstructive sleep apnea syndrome (OSAS) are most often treated with continuous positive airway pressure therapy (CPAP). To avoid complications of untreated OSAS good adherence to CPAP is crucial. The aim of this study was to assess whether knowledge about OSAS predicts CPAP adherence.

METHODS: Patients on CPAP therapy were prospectively recruited in our outpatient follow-up CPAP clinic at their first visit after 6 months of CPAP usage. They completed a questionnaire evaluating demographic data, level of education, Epworth sleepiness scale (ESS), and 11-item knowledge test about OSAS. Initial apnea hypopnea index (AHI) and initial ESS was obtained from medical records. Data on adherence was retrieved from CPAP machines software. Patients were divided in two groups: adherent (use of CPAP for at least 4 hours per night on more than 70% of nights), and non-adherent group.

RESULTS: Altogether 150 patients were recruited, 41 % women, age 56.7 ± 10.7 years, body mass index (BMI) 30.3 ± 4.4 kg/m2, initial AHI was 54.3/h ± 17.3/h, initial ESS 14.3 ± 4.5. 66% of patients were adherent and mean CPAP usage was 5.5h ± 1.9h. Adherent group had higher level of education (5.2 ± 1.3 vs. 4.7 ± 1.1, p = 0.008), better knowledge about OSAS (73% vs. 44% correct answers, p< 0.0001), lower AHI on CPAP (4.0 ± 3.5 vs. 5.9 ± 5.3, p=0.03), and lower ESS after CPAP treatment (4.4 ± 3.4 vs. 6.3 ± 4.1, p=0.005). In multivariate regression analysis adjusted for sex, age, BMI, level of education, initial AHI, AHI on CPAP, initial ESS, ESS on CPAP, good knowledge about OSAS (> 50% correct answers), initial AHI (OR 1.02, CI 1.00-1.05), AHI on CPAP (OR 0.9, CI 0.82-0.99), and good knowledge about OSAS (OR 8.15, CI 3.10-21.44), predicted good adherence.

CONCLUSIONS: In this cohort of patients, adherence to CPAP therapy was fairly good. Adherent patients had higher level of education, better knowledge about OSAS, lower AHI and ESS on CPAP therapy. Predictors of good adherence were higher initial AHI, lower AHI on CPAP, and especially good knowledge about OSAS.

6

PERSONALISED MANAGEMENT OF LUNG CANCER

Chairs: Katja Mohorčič,
Ilonka Osrajnik,
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Personalized systemic therapy for advanced non-small cell lung cancer

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Systemic therapy represents the mainstay therapy for patients with advanced non-small cell lung cancer (NSCLC). In the last decade major advances in the treatment of advanced NSCLC have been made through tailoring chemotherapy according to tumor histology and/or response to the first four cycles of chemotherapy (maintenance strategy) and through better understanding of the molecular biology of NSCLC, followed by the introduction of novel, targeted therapies in the treatment. At present, there are at least ten known oncogene alterations that drive NSCLC progression and represent targets for targeted therapy. Testing for EGFR mutations, ALK and ROS 1 rearrangements followed by targeted therapy with EGFR TKIs (afatinib, erlotinib, gefitinib) or ALK/ROS1 targeting TKI (crizotinib) became a standard practice in patients with advanced non-squamous-cell carcinoma (NSCC). Not surprisingly, the introduction of those highly individualized targeted therapies resulted in major improvements in response rates and progression-free survival rates compared to standard chemotherapy in advanced NSCLC; with impressive median survival rates of up to 35 months never seen before. Despite marked initial responses to first-line EGFR and ALK TKIs, patients inevitably experience disease progression while on therapy, mostly in 1-2 years. Of note, at that time a large majority of cancers are still driven by EGFR or ALK gene alterations (i.e. T790M and various ALK mutations) and respond well to second-line therapy with mutant-selective EGFR TKI (osimeritinib) or novel ALK TKIs (ceritnib , alectinib). A new technology of circulating tumor cells DNA (ctDNA) genomic analysis allows us for a continuous monitoring of action-able gene alterations during the course of therapy and treatment tailoring in each individual patient, thus welcoming era of "precision medicine " in NSCLC . In the recent years a number of additional oncogenic drivers, such BRAF, HER2, DDR2 and PI3KCA mutations, RET rearrangements and MET amplifications emerged as novel molecular targets; with already available encouraging results of targeted therapies in NSCLC patients harboring those alterations. The introduction of oncogene-directed therapies, with agents targeting FGFR1, such as brivanib, and DDR2 mutations, such as dasatinib, will hopefully stir the oncogene-directed therapy in the field of squamous NSCLC as well. Harnessing the immune system is yet another promising treatment strategy in lung cancer. In the field of cancer immunotherapy, intensive research is in progress to identify immune biomarkers for a better selection of patients that benefit from treatment with checkpoint inhibitors, thus allowing for individualization of immunotherapy, as well.

Immunotherapy in lung cancer

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Currently, the standard of care for management of newly diagnosed patients without targetable oncogenic driver mutations (eg, EGFR, ALK) is platinum-based doublet chemotherapy, which is generally associated with a median progression free survival (PFS) of 4 to 6 months and median OS of 8 to 10 months.[1] More recently, maintenance pemetrexed and the addition of monoclonal antibodies directed against vascular endothelial growth factor and epidermal growth factor receptor have resulted in additional, modest improvements in OS,[2-4] yet long-term outcomes remain poor underscoring the need for alternative therapeutic approaches.

Based on the need for more effective treatment options for refractory NSCLC, the suspected high immunogenicity of these tumors with their abundant genetic mutations, and the proven efficacy of immune checkpoint inhibitors in melanoma, clinical trials were designed to evaluate the efficacy of PD-1 and PD-L1 inhibitors in lung cancer.

Immune checkpoint inhibitors mechanism of acting is by altering the tumor microenvironment and blocking the immune system evasion that allows cancers to grow and proliferate.The most studied checkpoint at the present time is PD-1, a negative regulator of the T-cell immune response that signals upon binding its ligands, PD-L1 and PD-L2, which are often highly expressed in solid tumors and their tumor microenvironments.5 The result is that these immune checkpoint inhibitors, monoclonal antibodies targeting the programmed death-1 (PD-1)/PD ligand 1 (PD-L1) pathway, have dramatically reshaped landscape of non–small-cell lung cancer (NSCLC).

Anti–PD-1/PD-L1 has shown to have substantial clinical activity in advanced-stage non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with an overall response rate (ORR) of 15%–20%.6 This demonstrates that lung cancer is an immunotherapeutically responsive disease, and this strategy can have a major impact on OS and can influence the tail of the survival curve. The responses are frequently rapid and durable, increase median overall survival (OS) compared with chemotherapy, and produce long-term survivors. Despite these very significant results, many patients do not benefit from anti–PD-1/PD-L1. In fact, the majority of patients treated with PD-1 checkpoint blockade demonstrate no objective clinical response. One likely reason for this is that many patients' tumors lack sufficient infiltration of tumor-reactive TILs to be unmasked by checkpoint blockade. Tumors have also great potential to act on various immunosuppressive mechanisms other than aberrant expression of PD-L1.

In phase I studies, these agents demonstrated promising antitumor activity and durable clinical responses in a subset of patients with NSCLC.[5,7,8] Thus in a phase I expansion trial of nivolumab, 129 patients with advanced NSCLC who were heavily pretreated were treated with three different doses of nivolumab (1,

3, or 10 mg/kg) every 2 weeks. Median OS was 9.9 months, and patients receiving the dose of 3 mg/kg (the eventual FDA-approved dose) had impressive OS rates of 56%, 42%, and 27% at 1, 2, and 3 years, respectively. Treatment was well tolerated, with 14% of patients experiencing grade 3/4 adverse events, but also three deaths from presumed treatment-related pneumonitis occurred. Responses were seen in patients with both squamous and non-squamous histology.[9]

On the basis of these early efficacy findings, a series of randomized phase II and III studies were launched to evaluate the activity of PD-1/PD-L1 inhibitors in the second-line setting and beyond in NSCLC.[10-13]

Two subsequent phase III trials confirmed the benefit of the PD-1 inhibitor nivolumab over docetaxel as second-line treatment in patients with advanced NSCLC: in the CheckMate 017 and 057 studies, nivolumab produced significant improvements in overall survival (OS) compared with docetaxel in patients with previously treated, squamous and nonsquamous NSCLC, respectively.[10,11] In the CheckMate 017 trial of 272 patients with squamous NSCLC, median OS was 9.2 months with nivolumab versus 6.0 months with docetaxel.[10] Hazard ratio (HR) for death was 0.59 with nivolumab ($p < 0.001$), and the 1-year OS rate was 42% with nivolumab versus 24% with docetaxel. Similarly, the CheckMate 057 trial evaluated nivolumab versus docetaxel in patients with advanced non-squamous NSCLC.[11] Median OS was 12.2 in patients treated with nivolumab versus 9.4 months in patients treated with docetaxel. HR for death was 0.73 with nivolumab ($p = 0.002$), and 1-year OS rate was 51% with nivolumab versus 39% with docetaxel. Subgroup analysis from this trial showed higher efficacy for all endpoints in patients with PD-L1–positive tumors.

Similarly, the other PD-1 inhibitor pembrolizumab improved OS compared with docetaxel among patients with previously treated NSCLC whose tumors expressed PD-L1.[12]

The KEYNOTE-010 trial evaluated the role of pembrolizumab in patients with previously treated advanced NSCLC,[11] and patients enrolled on this trial had at least 1% of tumor cells with PD-L1 expression. A total of 1,034 patients received either pembrolizumab 2 mg/kg or 10 mg/kg versus docetaxel 75 mg/m2 every 3 weeks. With pembrolizumab, median OS was 10.4 months at the 2 mg/kg dose and 12.7 months on 10 mg/kg versus 8.5 months with docetaxel. OS was improved with both the doses of pembrolizumab compared with docetaxel. In patients with at least 50% of tumor cells expressing PD-L1, OS was 14.9 months with pembrolizumab 2 mg/kg and 17.3 months with pembrolizumab 10 mg/kg versus 8.2 months with docetaxel.[12]

These studies together enabled to establish PD-1 pathway blockade as a new standard of care for patients with advanced NSCLC who have progression on or after platinum-based chemotherapy.

Based on these trials, the FDA has approved both nivolumab and pembrolizumab as single agents for the second-line therapy of patients with advanced NSCLC. Nivolumab use does not require testing for PD-L1 expression while pembrolizumab does and is currently approved for treatment of patients with PD-L1 overexpression.

Toxicities of both of these antibodies can include immune-related adverse side effects, with 10% to 14% of patients having grade 3 or higher side effects. The most common side effects with PD-1 antibodies are rash and pruritus. Grade 3/4 diarrhea or colitis is seen in about 1% of patients, and grade 3/4 pneumonitis in about 2% of patients. Other less common immune-mediated side effects include transaminitis, nephritis, thyroiditis, hypophysitis, iritis, uveitis or conjunctivitis, and pericarditis.

Recently, the activity and improved tolerability of PD-1/PD-L1 inhibitors in NSCLC have gained a growing interest in giving them in the front-line setting. Data from two separate cohorts of the multiarm, phase IB CheckMate 012 study, each explores a different approach to PD-1 inhibition in patients with treatment-naive NSCLC.

Gettinger et al[13] report findings from 52 patients with advanced NSCLC treated with first-line nivolumab monotherapy. Confirmed responses were observed in 23% of patients, including complete responses in four patients (8%). Median PFS on nivolumab was 3.6 months, but the median duration of response was not reached (range, 4.2 to 25.81 months). Thus, as other studies of PD-1/ PD-L1 inhibitors, this one also indicate durable clinical responses - the median OS in this patient population was noteworthy at 19.4 months. Although the results by Gettinger et al[13] are intriguing, still the response rate to first-line nivolumab was similar to those observed in CheckMate 017 and 057.[10,11] Thus, this degree of activity can not be sufficient to beat platinum-based chemotherapy in randomized trials.

By contrast to second-line studies (CheckMate 017 and 057) comparing immunotherapy with docetaxel that has ORR of only 7%[14], in the first-line setting PD-1/PD-L1 inhibitors will need to overtake plati-

num-based doublet chemotherapy, which has much higher ORRs (25% to 35%).[1]
For PD-1/PD-L1 inhibitors to succeed in this setting, a biomarker enrichment strategy may be necessary. To date, such efforts have centered on assessments of PD-L1 expression. For instance, in the KEYNOTE 001 study,[7] pembrolizumab was associated with an ORR of 24.8% among treatment-naive patients, but the response rate increased to 50% among treatment-naive patients who were PD-L1 positive (proportion score ≥50). In part on the basis of these observations, two randomized phase III studies, CheckMate 026 and KEYNOTE 024, have been launched in PD-L1–positive patients comparing platinum-based chemotherapy versus nivolumab or pembrolizumab, respectively. Both studies have completed accrual, but results are not yet available.
Rizvi et al[15] report a separate first-line cohort from CheckMate 012 that consisted of 56 treatment-naive patients with NSCLC who were treated with nivolumab in combination with three different platinum-based chemotherapy doublets, a dose de-escalation design. In contrast to the currently approved nivolumab dosing regimen (3 mg/kg every 2 weeks), nivolumab was administered once every 3 weeks in this study (5 to 10 mg/kg based on cohort). After completing four cycles of therapy, patients received maintenance nivolumab once every 3 weeks. Overall, no dose-limiting toxicities were observed across study arms, but 14% of patients required discontinuation as a result of treatment-related grade 3 or 4 adverse events, which included pneumonitis (5%) and acute renal failure (5%). Additionally, hypersensitivity and infusion reactions were surprisingly common (23%) and were seen regardless of regimen, although infusion-related reactions had been rare (1% to 3%) in other studies of nivolumab.[10,11] In this study[15], confirmed responses were seen in 33% to 47% of patients across all chemotherapy arms. Nevertheless, these response rates were not substantially different from those expected with platinum-based doublet chemotherapy alone, but 2-year OS rates pointed to additional activity, particularly in the nivolumab (5 mg/kg) plus carboplatin-paclitaxel arm. Despite intriguing findings in certain subsets of CheckMate 012, this was a nonrandomized study conducted at high-volume referral centers in which treatment-naive patients were enrolled onto a phase I study and thus, likely to be highly select patient populations. On the other side, the degree of benefit in both studies was modest.
In addition to CheckMate 012, two other studies have explored PD-1/PD-L1 inhibitors in combination with chemotherapy in NSCLC and reported more encouraging preliminary results.[16,17] In a phase I/II study reported by Papadimitrakopoulou et al,[16] pembrolizumab in combination with carboplatin-pemetrexed was associated with a high ORR (58%; n 524), with more modest activity (ORR, 28%; n525) observed with pembrolizumab plus carboplatin-paclitaxel.
Liu et al17 reported in the same period preliminary safety and efficacy data on atezolizumab in combination with three different platinum-based doublet chemotherapy regimens. Although efficacy outcomes were reported in only 30 patients, atezolizumab based chemotherapy combinations seemed promising (ORR, 67%). It should be emphasized that the sample sizes in all of these studies were small, but still these studies suggest that immunotherapy plus chemotherapy combinations should be explored further.
Of importance is that despite very significant results, many patients do not benefit from anti–PD-1/PD-L1, i.e. the majority of patients treated with PD-1 checkpoint blockade demonstrate no objective clinical response. Reason for this might be that many patients' tumors lack sufficient infiltration of tumor-reactive TILs to be unmasked by checkpoint blockade. Tumors have also great potential to act on various immunosuppressive mechanisms other than aberrant expression of PD-L1. In some cases, there is likely a failure to generate sufficient functional tumor antigen-specific T cells, while in others, sufficiently generated tumor antigen–specific T cells fail to enter into the tumor parenchyma, or a large number of other immunosuppressive mechanisms - within the tumor microenvironment are expressed: other than PD-1 and CTLA-4 surface membrane immune checkpoint proteins, soluble factors and metabolic alterations interleukin (IL)-10, transforming growth factor (TGF)-β, adenosine, IDO, and arginase; inhibitory cells, cancer-associated fibroblasts (CAFs), regulatory T cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages. Thus, various different strategies are being investigated nowadays, some to generate more tumor-reactive T cells for patients: anti–CTLA-4, therapeutic tumor vaccination, and adoptive cellular therapy, with T cells redirected to tumor antigens using T-cell receptor (TCR) or chimeric antigen receptor (CAR) gene modification, or those to disable tumor microenvironment immunosuppressive mechanisms.
Combining adoptive transfer of engineered tumor-reactive T cells with checkpoint blockade may be an example to successfully applying immunotherapy to lung cancer. Preclinical studies have already demon-

strated the ability to augment TCR and CAR human T-cell control of lung cancer tumors by combining them with PD-1 blockade.[18]

What will be imperative is to incorporate blood and tissue analyses into future trials of PD-1/PD-L1 inhibitors to ensure insight into predictive biomarkers of response and resistance, particularly relevant in the front-line setting because such patients generally have a number of other therapeutic options. Despite an emphasis on PD-L1 testing in ongoing trials, it is obvious that PD-L1 expression alone is an imperfect biomarker with a number of pitfalls (eg, heterogeneity of expression, differences in PD-L1 assays, and the lack of a gold standard for PD-L1 positivity).[19]

Development of better predictive biomarkers may allow clinicians to identify particular subsets that are most likely to benefit from PD-1 pathway blockade, either alone or in combination with chemotherapy or other agents.

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Personalised treatment in real life – University Clinic Golnik lung cancer registry

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In the era of precision medicine and targeted therapy which is developing really fast in the last decade the value of registries is becoming more and more important. Trough data analysis they enable us to learn about diagnostic and treatment outcomes in routinely treated groups of patients (pts) with "rare diseases" like pts with molecular targets. University Clinic Golnik Lung Cancer Registry (UC Golnik LC Registry) was settled in 2010 and includes information about all pts diagnosed and treated for LC at UC Golnik since 2010 and also treatment outcomes for pts treated in our hospital (surgery, systemic treatment).

Molecular targets in NSCLC: Targets have been known and targeted therapy developed for lung adenocarcinomas and NOS NSCLC subgroup of pts (non- squamous NSCLC). For other types (squamous or small cell lung cancer (SCLC)) targeted therapy is still under investigations.
Our pts with non-squamous NSCLC are routinely tested sequentially for the presence of molecular targets: EGFR mutations since 2010, KRAS mutations since 2012, ALK rearrangements since 2013 and ROS1 mutation since 2015. Presence of those 4 most frequent molecular alterations was found in around 60% of pts with non-squamous NSCLC in pts diagnosed in 2015 (KRAS in 40.3%, EGFR in 14.2%, ALK in 4.4% and ROS1 in 0.8%), which is comparable to the published data for Caucasians.

Personalized treatment in advanced NSCLC has begun by tailoring chemotherapy according to tumor histology – by using pemetrexed since 2010 for advanced non-squamous NSCLC and by using maintenance approach with pemetrexed. Data from our registry show improvement in median overall survival (mOS) for 3.3 months after introduction of pemetrexed for non-squamous type of NSCLC pts.
All patients with advanced EGFR, ALK or ROS1 mutated tumors eligible to receive therapy have received targeted agents after they became available and reimbursed (anti EGFR since 2010: erlotinib, gefitinib, afatinib; anti ALK since 2014 crizotinib, ceritinib; anti ROS1 since 2015: crizotinib). Osimeritinib is the targeted drug against resistant EGFR mutation T790M. The drug can be used, when T790M mutation is confirmed in liquid or tissue biopsy at the time of progression on 1st line EGFR TKis. Since October 2015 our pts are treated with osimeritinib in the frame of compassionate use programe.
Immunotherapy treatment is a novel approach for advanced NSCLC patients, at our hospital currently only available in the frame of compassionate use programe with nivolumab for advanced NSCLC pts after progression on platinum based chemotherapy.

Survival of pts using personalized approach: Using personalized approach with targeted therapy with anti EGFR/ALK/ROS1 directed agents for mutated pts leads to improved mOS of advanced NSCLC pts. This progress in survival is also seen in routinely treated pts from 2010-2015 and is shown in Figure 1.

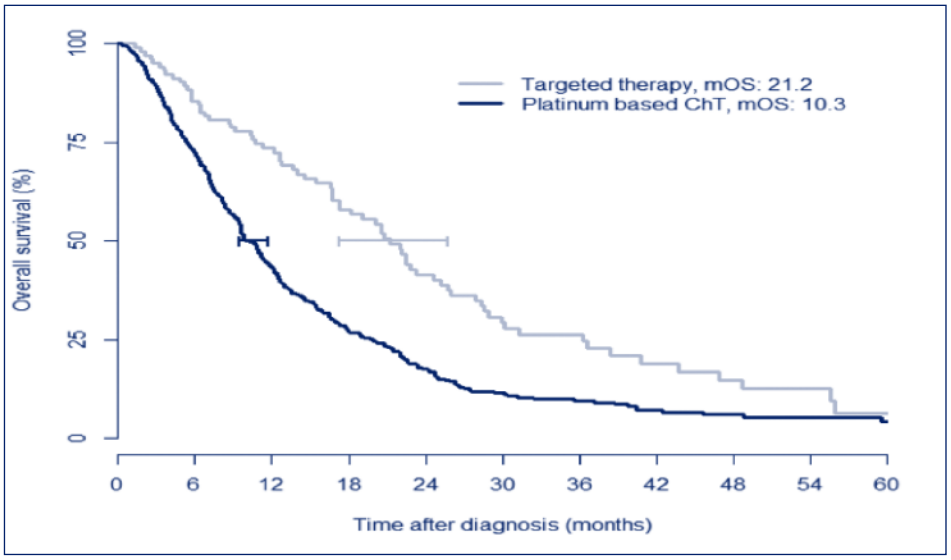

Figure1: Median overall survival of advanced NSCLC pts treated in a routine clinical practice at UC Golnik from 2010-2015; Pts with molecular targets (EGFR, ALK, ROS1 positive pts) treated with targeted agents have improved mOS comparing to NSCLC pts without targets treated with platinum based chemotherapy. mOS - median overall survival in months.

Future plans are to expand our hospital LC Registry project also to other 2 centers who diagnose and treat LC in Slovenia (Institution of Oncology Ljubljana and University Medical Centre Maribor). Having so many data about all LC Slovenian patients would be priceless, but in the era of personalized treatment also urgently needed for evaluating epidemiology and treatment outcomes for patients with rare diseases as those with molecular targets.

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Treatment of a patient with EGFR Positive Lung Adenocarcinoma: Case Report

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60-year old male patient was first admitted to our department in November 2013.

He had his first chest X-ray taken in December 2011, where tumor in the left upper lobe was spotted. CT scan of the lungs confirmed 4x3 cm large tumor in left lung and enlarged lymph nodes in aorto-pulmonary window, T2aN2 tumor. Patient declined any further investigation of the tumor.

In April 2013 he was admitted to hospital due to a bleeding mass in the left temporal region of the head which was surgically removed. Histologically it was subcutaneous metastasis of adenocarcinoma.

In October 2013 patient had severe headaches. CT scan of the head confirmed two metastases in the brain with profound cerebral edema. Metastases were surgically removed, after that he received WBRT. Brain metastases were also analyzed for determination of EGFR, KRAS and ALK status and deletions in exon 19 were confirmed.

Multidisciplinary board decided that patient should be enrolled in ITAC 2 study, where he was treated intermittently with systemic chemotherapy and TKI.

After 2 cycles of treatment with cisplatin and gemcitabine intermittently with erlotinib patient became extremely confused and somnolent. CT scan and MRI of the brain were performed to check for possible recurrence of brain metastases. There was newly developed lesion in the brain, surrouded by fluid, that could represent new metastasis with haemorrhage.

During the surgery neurosurgeon found purulent content and destruction of artificial dura, most probably due to radionecrosis after brain irradiation.

Patient was treated with antibiotics, he continued treatment with erlotinib as well. Systemic chemotherapy was discontinued.

After 8 months of treatment with TKI patient experienced severe paronychia and the dose of erlotinib had to be reduced.

In March 2016 there was clinical and radiological progression of the tumor. Bronchoscopy was performed again and hystological specimen of the tumor recovered, where T790M mutations were confirmed.

Patient was enrolled in compassionate use programme and since June 2016 he is treated with osimertinib. After only 2 weeks of treatment there was clinical and radiological responce, he continues the treatment with no side effects.

7

WHAT IS NEW / HOT TOPICS

Chairs: Mihaela Zidarn,
Barbara Salobir,
Miroslav Samaržija (Croatia)

Next Generation sequencing in pulmonology and allergology

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INTRODUCTION

Over the past years we are witnessing a revolution in the field of genetic and genomic research, which was achieved with the advent of next generation sequencing (NGS). Next generation sequencing, which is also called massively parallel DNA sequencing, by parallelizing the sequencing process allow high-throughput sequencing thus increasing the speed and reducing the costs of sequencing tremendously in comparison to standard sequencing methods. To illustrate the enormity of this breakthrough, take into consideration that the initial sequencing of the human genome using standard sequencing technologies took more than ten years and the estimated final costs were around $70 million per genome. On the other hand, using the today's NGS technology we are approaching the cost of $1000 per human genome, while the sequencing time has been reduced to a few days (1-3).

NGS TECHNOLOGY AND APPLICATIONS

The NGS technologies enable a wide variety of different applications and are increasingly used in medical research as well as in clinical practice (3,4,5). The most commonly used clinical NGS applications in pulmonology and immunology are sequencing (whole-genome, whole-exome or targeted sequencing) for identification of genes and mutations responsible for diseases. NGS applications are increasingly used also in cancer molecular diagnosis and prognosis, as well as in microbiology for the molecular detection of infectious diseases (3,4,5).

Other clinical applications include non-invasive prenatal testing for the detection of most common aneuploidies (trisomies), detection of biomarkers for the identification of the most suitable therapeutic interventions (pharmacogenomics) and recently also transcriptome sequencing for high-throughput expression analysis (3-6).

Novel methods are evolving at a very high speed and several other applications are expected to be moving from the research field into everyday clinical practice, such us metagenomics, ribosome profiling, methylation analysis, protein-DNA and protein-RNA interactions (ChIP sequencing) and others (1-5). Here our focus will be mainly on the use of NGS technology for the identification of genes responsible for diseases and on transcriptome analysis.

IDENTIFICATION OF DISEASE CAUSAL VARIANTS

Advances in NGS technology led to rapid increase in understanding of the basis of monogenic disorders (Mendelian diseases), applying whole-genome, whole exome or targeted sequencing. Using the standard sequencing methods, such as the Sanger or dideoxy sequencing, the identification of causal

variant responsible for the disease is time and price consuming. This is especially the case in sequencing of large genes and in monogenic disorders where several genes might be responsible for a specific phenotype (3,4,5,7,8).

There are several sequencing strategies used for genome analysis. In whole-genome sequencing the entire human genome, including promoters, regulatory and other non-coding regions, is re-sequenced. In whole exome sequencing only coding regions, i.e. all exons of all known genes, are re-sequenced, while in targeted sequencing only target regions, e.g. only a limited number of genes of interest, are re-sequenced, mapped and analysed. The advantages of whole-genome sequencing in comparison to whole-exome and targeted sequencing is the coverage of the entire genome, while the advantages of a more focused NGS sequencing methods (such as targeted sequencing) is significant reduction in costs and time (1,2,3). NGS sequencing has been used for the identification of genes associated with several monogenic conditions, including cancer, immunologic disorders, immunodeficiencies, bronchiectasis, fibrosis, and others. Especially targeted sequencing, where gene panels of different sizes are used, is successfully implemented in routine clinical practice in several centres (4,5,7,8). University Clinic of Respiratory and Allergic Diseases also implemented NGS technology in clinical practice for help in solving difficult diagnostic cases, where currently targeted sequencing of over 4800 clinically relevant genes is used for identification of causal mutations in genes responsible for different genetic disorders.

TRANSCRIPTOME SEQUENCING

Transcriptome sequencing is increasingly used in biomedical research, and is also finding its way into the diagnostics. In transcriptome sequencing (RNA-Seq) entire set of transcripts, including mRNA, miRNAs and other non-protein-coding RNAs, is quantitatively and qualitatively profiled, resulting in not only the determination of RNA expression levels but also of splicing profile (rearrangement of DNA sequences before transcription). Transcriptome sequencing helps us to better understand the disease mechanisms, and have been increasingly utilized for studying complex diseases, since the applications are extremely sensitive and allow us to accurately analyse also low abundant transcripts. Furthermore, using transcriptome sequencing we are able to detect allele-specific expression, post-transcriptional modifications, gene fusion, together with analysis of non-coding RNAs (1,2,9,10). Currently we are using NGS based transcriptome sequencing in analysis of global transcriptional changes in peripheral blood during anaphylactic reaction, where we have detected several alterations of gene expression during anaphylactic reaction, leading into better understanding of the mechanisms of anaphylaxis. Since our finding suggests that distinct immune cells are involved, and complex signalling changes, which reflect cellular movement and interaction are taking place during anaphylaxis (11).

CONCLUDING REMARKS

Taken together, NGS technologies has revolutionized biomedical genomic research, since it allows the generation of fast, cost-effective and accurate sequencing data. Therefore, different NGS applications are being used not only in research but also in clinical settings. Our understanding of disease mechanisms has improved considerably, and NGS technologies are a big step towards personalized medicine, since they will allow us not only to diagnose diseases but also to predict the disease outcomes for individual patients. Even though the present and future of genomics is in the NGS, there are still some challenges and opened questions to be considered. One of the challenges is the analysis and interpretation of huge amounts of data, followed by the need for method standardisation, and ethical issues.

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8

MOLECULAR ALLERGOLOGY: A STEP TO PERSONALISED ALLERGY MANAGEMENT

Chairs: Peter Korošec,
Peter Kecelj,
Asja Stipić Marković (Croatia)

Recombinant allergens as a major step in molecular allergology: scientific and methodological considerations

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BACKGROUND:
Recombinant allergens and their use in molecular diagnostics and therapeutic intervention represent an impressing success story. The availability and application are doubtlessly key to future immunological research and understanding of disease.
This increasing relevance is a result of several developments: First of all, in the last 25 years there has been a tremendously increasing body of knowledge about the identity and biochemical characteristics of natural allergens including primary structure and DNA sequence. In parallel biotechnical approaches including recombinant technologies for protein production have gained significant importance and are nowadays indispensable in all kinds of health-related diagnostic technologies. Last but not least these two points have backfired our understanding of the immunological basis for allergic reactions on a molecular level, insights into cross-reactivity and allergenic potency.
The rise of recombinant allergens started with the molecular analyses of allergen in the early 90s. One of the early examples is the major birch pollen allergen Bet v 1 which was successfully cloned and recombinantly expressed in bacteria. It is also the first allergen the structure of which was elucidated by X-ray crystallography.
Here the recombinant concept is definitely convincing and hampered by very few issues only. One important finding is the presence of several isoforms of some allergens, one of which is Bet v 1. The selective use of one isoform only might result in a biased analysis without reflecting the entire picture of sensitization.
The recombinant concept for Bet v 1 also translates into therapeutic applications with wild type allergens, mutated and hypoallergenic variants, mosaic proteins and chimeras, folding variants and much more.
The recombinant approach moreover allows to adjusting critical properties of allergens. Most latex allergens used in diagnostics still are recombinantly produced as fusion proteins with the maltose binding protein.
However, a variety of allergens represent a clear challenge for recombinant technologies that has to be addressed adequately. This challenge mainly refers to proper folding, activation of enzymatic activity and posttranslational modifications. Especially the glycosylation of allergens represents a difficult to address problem. Glycan structures of glyco-proteins are mostly beneficial for the quality of the recombinant protein but also provide the potential to provoke unwanted IgE reactivities.
It is well-known, that apart from a genuine sensitization to multiple sources, cross-reactivities can result in difficult to explain test results and confusing sensitization pattern. This phenomenon may be based on

common protein epitopes of homologous allergens broadly known and sometimes clinically relevant. Alternatively cross-reactivities can be attributed to IgE antibodies directed against so-called cross-reactive glyco-epitopes of the allergens (cross-reactive carbohydrate determinants, CCD) [1-3] ***(Fig. 1).***

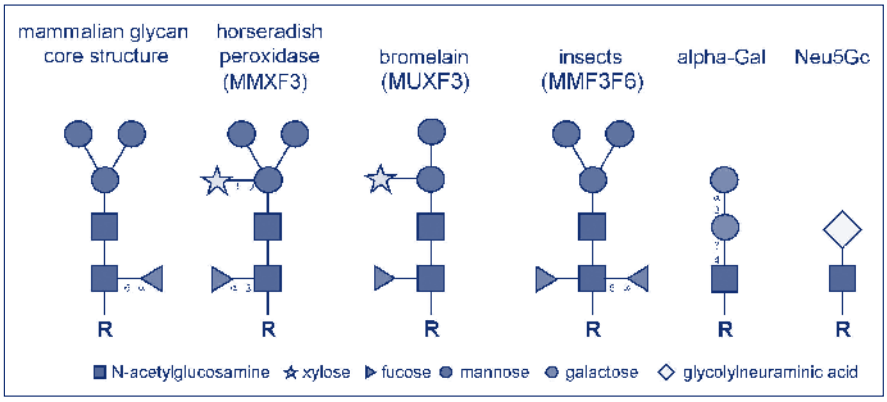

Fig. 1: Selected carbohydrate structures found on different glycosylated allergens

Causative for the phenomenon of cross-reactivity are IgE antibodies that are directed against an alpha1,3-linked fucose residue of the N-glycan core established by insects and plants. A beta1,2-xylose residue at the core glycan to which IgE also can be directed is found in plants, but not in insects.
A novel CCD with increasing relevance is the well-known alpha-Gal epitope representing a xenobiotic carbohydrate modification in most mammals. Relevant epitopes are found in red meat, other animal-derived products and also biologicals produced in mammalian cell lines that have no human background. All these xenobiotic modifications represent highly immunogenic epitopes which can induce specific immunoglobulin-G (IgG) as well as IgE antibodies [4]. CCD-specific IgE antibodies against the fucose-based epitope have been reported to be responsible for the majority of double sensitizations honeybee and yellow jacket venom [2],
Anti-CCD IgE represent an undoubted pitfall of in vitro allergy diagnostics, since they cause multiple reactivities with any glycosylated plant (food, pollen) or insect venom allergen and thereby interfere with the detection of clinically relevant sensitization to protein epitopes and complicate the choice of the appropriate therapeutic intervention.
An interesting example for the relevance of glycosylation is the grass pollen allergen Phl p 4. Phl p 4 is a group 4 major allergen and has two occupied glycosylation sites. Although it is known for its glycosylation, it is available as native protein only due to difficulties in recombinant production. Recently the importance of the glycosylation of Phl p 4 by comparative assessment of natural and recombinant forms [5].
Against the background of these considerations some questions remain it remains to be discussed if:

- Is IgE reactivity against all epitopes on an allergen a measure for allergy?
- Has the recombinant allergen of interest to be a mimic of nature?
- What impact has the production system on the allergen?

These questions will be further addressed against the background of insect venom allergy.

INSECT VENOM ALLERGY AND ALLERGENS

Insect venom allergies belong to the classical immunoglobulin-E-(IgE)-mediated allergies and is often manifest as severe anaphylactic reaction that even can be lethal. Systemic allergic reaction to Hymenoptera stings affect 0.3 – 3.5 % of the adult population.[6, 7] Venom immunotherapy (VIT) protects allergic patients from systemic reactions to subsequent stings.[7, 8] Effectiveness of VIT depends on a number of variables such as treatment duration, venom dose during maintenance therapy, and type of venom (HBV vs YJV) used for immunotherapy.[9-11]
Our knowledge about the composition of different hymenoptera venoms has increased significantly in the last years ***(Table 1).***

The majority of the allergens that has been described so far are enzymes, heavily glycosylated, of higher molecular weight and lower abundance.

Table 1: Insect venom allergens in honeybee and yellow jacket

Allergen A.mellifera	Common name/function	MW	% dw	N-glycos.	Bacterial expression	Eukaryotic expression	sIgE	BAT
Api m 1	Phospholipase A2	17 kDa	12	1	+	+	+	+
Api m 2	Hyaluronidase	45 kDa	2	2	+	+	+	+
Api m 4	Melittin	3 kDa	50	-		+	+	
Api m 3	Acid phosphatase	49 kDa	1-2	2-3		+	+	+
Api m 5	DPPIV	100 kDa	<1	5-7		+	+	+
Api m 6	Protease inhibitor	8 kDa	1-2	-		+	+	
Api m 7	CUB protease	39 kDa		2-4		+	+	
Api m 8	Carboxyesterase	70 kDa		4		+	+	
Api m 9	Carboxypeptidase	60 kDa		4-5		+	+	
Api m 10	Ikarapin	55 kDa	<1	4	+	+	+	+
Api m 11a	MRJP8	45 kDa		6		+	+	
Api m 11b	MRJP9	45 kDa		3		+	+	
Api m 12	Vitellogenin	200 kDa		3		+	+	
	PVF			?		+	+	
	C1q-like protein			?		+	+	
V. vulgaris								
Ves v 1	Phospholipase A1	35 kDa	6-14	-		+	+	+
Ves v 2a	Hyaluronidase	45 kDa	1-3	2-3	+	+	+	
Ves v 2b	Hyaluronidase	47 kDa		2		+	+	
Ves v 3	DPPIV	100 kDa		3-6		+	+	+
Ves v 4	CUB protease	35 kDa		?		+	+	
Ves v 5	Antigen 5	25 kDa	5-10	-	+	+	+	+
Ves v 6	Vitellogenin	200 kDa		4		+	+	

Inherent problems and general considerations apply for venom components. The venom and some proteins in the venom are toxic and mostly enzymes with degrading activity. A purification of native proteins from venom is a suitable approach for higher abundance allergens only. For a long time, native purified Api m 1 has been used for diagnostic testing. Hence, until recently only a very limited number of venom allergens was available for CRD such as Api m 1 and Ves v 5 either as native or recombinant proteins [12, 13].

MOLECULAR ASPECTS OF RECOMBINANT VENOM ALLERGENS

Applying recombinant technologies the problem of contaminating residual allergens does not exist, but difficulties rather lie in the establishment of an adequate and efficient production system.

For the first recombinant expressions of insect venom allergens the bacterial system was employed which definitely is suited to obtain easily and quickly large amounts of protein. Apart from efficient production however authentic fold and immunoreactivity of the allergens have to be guaranteed. Their toxic nature and enzymatic activities may also have an impact on efficacy of production and the characteristics of the resulting recombinant proteins. Selected insect venom allergens nevertheless could be produced in functional form in bacteria, primarily for structural analyses. The efficiency of the prokaryotic approach is often compromized by the need of extensive refolding steps limiting its use to structurally relatively simple and small molecules.

Eukaryotic cells grow more slowly and provide reduced yields of recombinant proteins, but result in proteins with invariant alterations in form of posttranslational modifications. In contrast to Escherichia coli eukaryotic cells such as yeasts as well as insect cells and mammalian cells add oligosaccharides that have a similar core structure mimicking the glycan of the native glycosylated allergen and influence both folding and immunoreactivity [14].

The majority of IgE epitopes appear to be conformational and demand an intact surface. Hence the eukaryotic approach for expression of allergens is superior as for the formation of correct three-dimensional structures of many eukaryotic proteins the secretory pathwas including folding control and post-translational modifications is essential.

In the last few years expression in insect cells was established as appropriate system for insect venom allergens. The functionality of proteins, the epitope authenticity, and the correct folding of resulting proteins could be demonstrated for a large number of allergens) [14-16]. Api m 1 serves as additional example for the potential of recombinant approaches. It has a single glycosylation site that can be occupied with a oligomannosidic N-glycan. In addition Api m 1 carries an alpha1,3-linked fucose on the N-glycan core structure and thus is reactive with IgE directed against CCDs. Hence Api m 1 exists in nature in different glycoforms. Expression of Api m 1 in E. coli results in a homogenous protein without glycan. Expression in eukaryotic systems yields a heterogenous set of glycoforms also present in the natural form that also could be produced on demand [17]. A mutation of the glycosylation site again results in a homogenous protein. Different variants of recombinant forms of Api m 1 are commercially available.
The use of glycosylated, species-specific allergens such as Api m 1 is only an inferior option and the deletion of glycosylation sites – as realized in a commercial product – de facto is not feasible for proteins with multiple glycans, e.g. Api m 3 and Api m 5.
We and others could show that the use of Sf9 insect cells from Spodoptera frugiperda as expression system results in allergens with functional glycosylation, proper folding, and complete epitope spectrum but not showing any immunologically detectable CCD-reactivity. This phenomenon is obviously based on the specific absence of alpha1,3-core fucosylation [16]. Notably, we also were able to show that Drosophila S2 cells exhibit the same CCD phenotype as Sf9 cells. In contrast, other insect cells however such as those from Trichoplusia ni, are able to establish the authentic phenotype including the CCD reactivity.
The potential of this approach can be realized in the future by additional species-specific as well as cross-reactive, but CCD-free allergens.
These approaches recently allowed a first systematic analysis of IgE reactivities to several individual allergens from honeybee venom [18]. We could show that much more venom proteins represent major allergens than anticipated. Moreover patients exhibited highly individual and complex reactivity profiles that often include sIgE antibodies to components that are only occasionally present in extracts [19].
A detailed analysis of the IgE and IgG response to selected critical allergens in therapeutic extracts further identified predominant sensitization to Api m 10, a component underrepresented in some therapeutic venom extracts, as risk factor for VIT failure [20] ***(Fig. 2).***
There is no doubt that getting rid of unwanted CCD reactivity by recombinant technologies enables a proper component resolved diagnostic approach that improves diagnostic sensitivity and can provide deep insights into individual patient profiles.

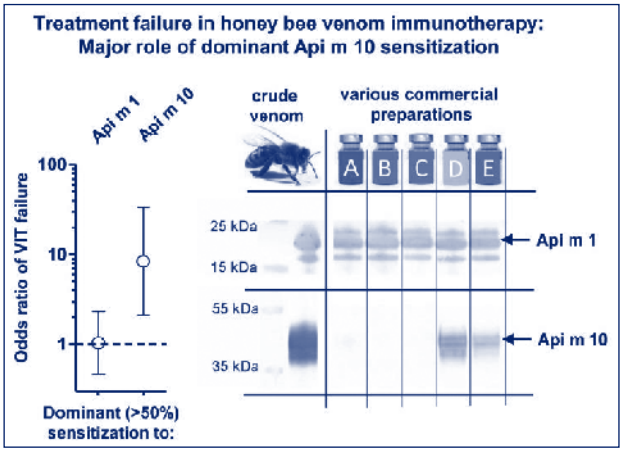

Fig. 2: Identification of predominant Api m 10 sensitization as risk factor for treatment failure [20]

ARE CARBOHYDRATE EPITOPES OF ALLERGENS RELEVANT?

Nowadays we are able to improve allergens according to our needs for specific applications by using recombinant technologies. In the case of the CCDs it remains however unclear if anti-CCD antibodies represent an important facette of the patients IgE response or not.

In order to analyse the structure function relationship of CCD-specific antibodies, we recently generated monoclonal antibodies by combinatorial technologies. These were converted into IgE antibodies and used for structural and functional analyses. From in vitro analyses, X-ray crystallography of antibody/antigen complexes and NMR experiments it is obvious that the interaction of antibodies with CCD is highly specific for well-defined carbohydrate epitopes and of high affinity. Notably, cellular activation tests using the CCD-specific IgE antibodies demonstrated a clear biological function. These data clearly support the hypothesis that IgE against carbohydrate modifications can form a functional part of the IgE response and their presence should be critically reconsidered.

CONCLUSIONS

Recombinant allergens still keep some secrets but their use is or is on the way to become state of the art in diagnostics as well as therapeutic interventions. Their use provides basic knowledge about mechanisms of sensitization and allergic reactions and is urgently needed to assess clinical relevance of components even beyond IgE reactivity.

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Clinical use of recombinant allergens in personalised allergy diagnosis and management

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Molecular diagnosis of allergy and microarray technology have opened a completely new avenue of insight into sensitization profiles from both the clinical and epidemiological point of view. Molecular diagnosis of food allergy brought a completely new approach based on sensitization to different molecules in frame of one food determining the grade of risk of severe anaphylaxis to the respective food. Nonetheless the usefulness of molecular diagnosis of inhalant allergens and respiratory allergy is also very high. Immediate hypersensitivity to one or more aeroallergens is a risk factor for asthma and allergic rhinitis. Sensitization to these allergens may play a role also in atopic dermatitis. The major sources of allergens in the outdoor air include pollens and fungi, in the indoor air house dust mite and fungi, as well as dander derived from domestic animals and rodents. Sensitization to distinct molecules may represent higher risk for asthma or atopic dermatitis (1-5) and several studies suggest that sensitization to multiple molecules ("molecular spreading") may be associated with higher probability of more severe symptoms of allergy (3-10).
While the diagnosis of IgE mediated inhalant allergy is primarily based on clinical history and sensitization demonstrated through an allergen extract prick test and/or measurement of serum specific IgE, this methodology has its limitations. This in vitro and in vivo allergy testing is based on sometimes insufficiently standardized allergen extracts that, owing to the natural variability of the allergen source or manufacturing procedure, can differ in terms of their allergenic content. This issue was already confirmed for grass pollen (11-13), mite (14-16), cat (17), dog (18) and mould (19-22) allergens. An even more important disadvantage of allergenic extracts is that they are incapable of differentiating between primary sensitization and immunological cross-reactivity. Multiple positivities are observed in many patients, but determining whether the sensitization is species-specific or a result of cross-reactivity to proteins with similar protein structures (e.g. profilins, polcalcins, tropomyosins, serum albumins and partially lipocalins) was formerly frequently impossible. Identification of sensitizations and co-sensitizations to species-specific and cross-reacting allergen components may be especially important in decisions concerning specific immunotherapy.

POLLEN

Grasses (Poaceae) are the most common cause of hay fever in Europe, and it has been estimated that more than 40% of allergic patients are sensitized to their pollens. In our study the rate was substantially higher – sensitization to at least one grass-pollen-specific component was observed in about three quarters of patients showing any positivity in the ImmunoCAP ISAC microarray (23).
Grass-pollen sensitized patients in our study were usually co-sensitized to several grass-specific com-

ponents; monosensitization was markedly less frequent. Phl p 1 (beta-expansin) and Phl p 5 (ribonuclease) are generally assumed to be the specific components most commonly involved in grass-pollen allergy, Phl p 1 sensitization being present in cca 90% of all grass-pollen allergic patients. We confirmed general findings that the most frequent targets for IgE binding are Phl p 1, Phl p 4, and Phl p 5 molecules; Phl p 5 sensitization without Phl p 1 sensitization was very exceptional.
In this context, it is necessary to stress again the importance of the allergen content in grass-pollen extracts used for diagnostic and therapeutic purposes. Several studies have focused on this issue and analyzed the composition of some commercially available preparations with respect to their qualitative and quantitative allergen composition. The spectrum of analyzed molecules was limited - one study analyzed only Phl p 5 content (12), other studies involved a wider spectrum of molecules including Phl p 1 and Phl p 4 (11, 13) and considerable heterogeneity of the content of these major allergens was found.
The most frequent sensitization to Betulaceae-derived components was, as expected, to Bet v 1. The sensitization rates to Aln g 1 and Cor a 1.0101 were also rather high, but the vast majority of patients with these latter sensitivities cross-reacted to Bet v 1. Cross-reactivity with plant-food-derived PR-10 proteins was also quite high in these same patients, presenting a pattern already generally known and described. Cross-reacting components ("panallergens") generally do not seem to represent very important pollen sensitization components in Middle Europe, somewhat in contrast to southern countries where the observed sensitization frequency is often higher and the clinical relevance of this sensitization may also be more important. High cross-reactivity of these molecules was described in several studies. In contrast to these findings our group of patients showed certain relationship between sensitization to species-specific molecules and the respective panallergen and cross-reactivity in frame of groups of profilins, polcalcins and LTPs was not complete.
Sensitization to other components from the same pollen source usually precede sensitization to profilins and/or polcalcins (10) and it has been proposed that, at least for grass pollen allergy, panallergens are typically being recognized at the late stage of molecular spreading. Such an assumption is in concordance with our observations of very low rates of mono-sensitizations to profilins and polcalcins.

HOUSE DUST MITES (HDM)

According to several studies, HDM sensitization and allergy is considered to be generally the most frequent among inhalant allergies. In our conditions it holds the fourth position behind grass pollen, birch pollen and cat allergens. Sensitization rate to the most frequent perennial inhalant derived component Fel d 1 and the second most frequent Der f 2 was 1.9x and 2.4x resp. less frequent than sensitization rate to the most frequent pollen derived component Phl p 1 (23), differing from data coming from other regions. This discrepancy may be caused by geographical differences or may be due to the population selected (predominant adult patients, predominant respiratory allergy).
It is known that patients sensitized to mites are not always sensitized to the molecules of group 1 and/or 2, but the number of patients sensitized only to other molecules is generally very low. Mite sensitized patients in our group were usually co-sensitized to several mite specific components; monosensitization was markedly less frequent.
As mentioned before, several studies have analyzed the composition of commercially available HDM preparations with respect to their qualitative and quantitative allergen composition and considerable differences in the allergen content were found (14-16). Group 2 allergens are highly cross-reactive, but as group 1 sensitization could be species specific in some patients and its prevalence is higher in children, an adequate balance of major mite species allergens must be considered in the design of mite allergy vaccines. It is necessary to point out the importance of quantifying at least three major mite components Der f 1, Der p 1 and Der f 2 (or Der p 2). Such information is crucial for effective diagnosis and treatment. Besides these molecules, Der p 23, a new, major house dust mite allergen must be considered to be an important component for allergen specific immunotherapy. The importance of eventual further allergens (so called "mid-tier" allergens – e.g. Der p 5) in this context has yet to be elucidated.

FURRY ANIMALS

Although some previous studies showed that the prevalence of cat allergy is not as high as dust mite allergy, we showed approximately the same global sensitization rate for these both allergen sources.

The explanation for this finding may be that the climate for mites is not optimal in Middle Europe and so the sensitization rate is lower than in other regions. More, the accumulation of cat and dog allergens in workplaces, schools and homes (without an animal), which occurs by passive transfer is a reflection of the overall prevalence of pet ownership in the community which is rather high in our conditions.
The major cat-derived allergen is Fel d 1 (secretoglobin). It is produced in the skin and also in the salivary glands of cats and becomes airborne. The role of Fel d 1 in cat allergy is very dominant, as it has been shown that up to 95% of all cat allergic patients react to Fel d 1what corresponds to our data.
Lipocalin Fel d 4 has received little attention, because of the dominant role of Fel d 1 in cat allergy. Nevertheless, the importance of Fel d 4 has recently been demonstrated by its cross-reactivity and cross-sensitization with dog, horse, mouse and rat lipocalins. Although a relatively high sensitization rate to Fel d 4 in cat allergic patients was described in other studies, we could not confirm this fact in our patients where the sensitization rate to Fel d 4 was substantially lower and co-sensitization with Fel d 1 was present in the majority of cases.
Althouhg Fel d 1 is most prevalent, co-sensitization with Fel d 4 seems to be more associated with asthma (5). This suggests that sensitization to Fel d 1 may represent original sensitization to cat, and sensitization to Fel d 4 a further evolved immune response with a higher probability of allergic disease. This hypothesis is based on the concept of „molecular spreading“ described for grass-pollen components (10).

Dog lipocalin Can f 1 is secreted from canine sebaceous and salivary glands is found in dog hair, dander, and saliva. It is estimated that 50 – 90% dog allergic patients are sensitized to Can f 1. Despite being a major allergen, Can f 1 alone is not sufficient for diagnosis of dog allergy. Sensitization to Can f 1 is more related to dog symptoms than Can f 5 and Can f 1 is the most important prognostic marker of dog allergy and superior to measurement of IgE levels to dog allergen extract (9). 20 - 33% of dog-sensitized subjects have IgE antibodies to another lipocalin Can f 2, but sensitization to Can f 2 without sensitization to Can f 1 was not observed. We showed that such cases exist but they are very rare.
Expression of the dog prostatic kallikrein Can f 5 is mainly restricted to male animals and the protein is secreted in the urine. Can f 5 has been reported as a major allergen, mainly in a Spanish population where 70% of the subjects were sensitized. It was identified as the major component for dog sensitization in Swedish children as well (5), although only only about one tenth of children mono-sensitized to Can f 5 reported symptoms to dog and Can f 5 showed generally a weaker association to dog allergy (9). Can f 5 was the most frequently observed dog-derived molecule sensitization also in our patients. It is necessary to remember that cross-reactivity between Can f 5 and human prostate-specific antigen has been described and that allergy to human seminal plasma, although rare, may be linked to dog allergy via Can f 5 sensitization.
Immunotherapy for dog allergy does not appear as efficacious as immunotherapy in cat allergy. The reason might be associated with the fact, that dog sensitization is complex and involves more molecules in comparison to Fel d 1 clearly dominating in cat allergy. The observed variability of currently available commercial dog extracts regarding their allergen contents likely has a negative influence on both diagnosis and therapy of dog allergy (18).

Severe asthma in children is associated with more frequent sensitization to lipocalins (Can f 2, Fel d 4, Equ c 1) and prostatic kallikrein (Can f 5) (7). This may be at least partially due to molecular polysensitization (“molecular spreading”) in more severe patients (10) and our data concerning the frequent co-sensitization to different lipocalins may support this idea.
Serum albumins are minor allergens, and around 15–35% of cat and dog allergic patients are sensitized to Fel d 2 and Can f 3, and around 15–20% of horse allergic patients appear to be sensitized to Equ c 3. Although a high sequence identity reaching above 50% is present, the cross-reactivity between different albumins is variable, which indicates that a significant proportion of albumin-specific IgE is directed towards species-specific epitopes.
Co-sensitization to more animal dander extracts, which is commonly observed, is in our population not explained by cross-reactive serum albumins which are minor sensitizers with a low prevalence compared to other studies. Similarly low frequencies of sensitization to serum albumins as in our study were observed in Swedish children (5).

MOULDS

Major geographic and age variations in the frequency of sensitization to moulds are seen in different studies and general lack of concordance between positive SPT responses and serum sIgE testing to moulds was described.

The most important allergenic fungi belong to the genera Alternaria, Aspergillus and Cladosporium and Alternaria is the most important fungal genus causing respiratory allergies (19). Several studies have also found an association between Alternaria sensitization and asthma severity. Alternaria belongs to the fungi with both indoor and outdoor occurrence, the latter one showing important seasonal variations in our climate. Alt a 1 is the main allergenic component of Alternaria alternata, sensitizing the great majority of patients allergic to Alternaria and it is the most important primary sensitizer in mould allergy patients in our region.

The knowledge concerning possible cross-sensitizations among moulds is controversial. Some sources describe that the majority of mould-sensitized patients reacts only to one species, but monosensitizations to other mould species assessed by means of extracts are observed not as frequently what may suggest a cross-reactive potential of these species.

On the other hand it is necessary to bear in mind that fungal extracts consist of a complex mixture of proteins, glycoproteins, polysaccharides, and other substances; these extracts show a considerable variability as a reset of interstrain genomic differences, different culture conditions, and variable extraction procedures so that quality of commercial fungal extracts is variable (19-22). The reactivity of such extracts might be even non-specific. Further, different other substances are present in various fungal species and may cause potential cross-reactivity. The sensitization rates to all these potentially cross-reactive molecules (Alt a 6 (enolase), Asp f 1 (ribonuclease), Asp f 3 (peroxisomal protein), Asp f 6 (Mn-SOD) and Cla h 8 (mannitol dehydrogenase) were rather low in our patients to explain the mentioned frequent cross-reactivity detected by extracts.

In our patients, we saw much more frequently mono-sensitizations in frame of mould molecules, the most frequent being mono-sensitization to species specific molecule Alt a 1. The relatively low sensitization rates of Aspergillus derived molecules (first of all Asp f 6) compared to Alternaria derived molecules does not necessarily reflect a lower sensitization rate to Aspergillus because the sensitization rate to Aspergillus extract was shown to be considerably higher than the sum of sensitizations to the used molecules. On the other hand, several studies showed considerably lower frequency of sensitization to Aspergillus and Cladosporium in comparison to Alternaria (19) what is in concordance with our findings. The absence of commercially available high quality fungal extracts (22) is a big diagnostic and therapeutic problem in the practice of clinical allergy. It is necessary to incite companies to work on production of such extracts, first of all Alternaria extract with defined content of Alt a 1.

CONCLUSION

Molecular diagnosis of allergy gives a more precise and reliable evaluation for an IgE-based allergy than does an extract-based approach. The geographical differences in sensitization patterns may reflect different ways of sensitization to the same allergen. The sensitization frequency to distinct components may be important in considering specific immunotherapy for allergy to this allergen and for optimizing the composition of therapeutic allergen vaccines used in the respective region.

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Effector cells as an important part of molecular allergology: scientific and methodological considerations

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INTRODUCTION

Mast cells and basophils play a central role in allergy since they are the prime sources of histamine and other inflammatory mediators that are responsible for the main symptoms of acute allergic responses. Both cell types originate from CD34+ stem cells but, although they share common functional properties (e.g. the ability to rapidly release histamine upon allergen binding), basophils develop in the bone marrow and are then released into the circulation whereas mast cells develop within their final tissue locations. While it has long been recognized that mast cells significantly contribute to immediate hypersensitivity reactions there is growing evidence to suggest that basophils, though fewer in number than mast cells, play an essential role in both acute allergic reactions as well as in late-phase responses (reviewed in 1). Furthermore, unlike their human mast cells counterparts, basophils readily produce IL-4 and IL-13, key cytokines that initiate and perpetuate Th2-type allergic immunity.

MAST CELL AND BASOPHIL HETEROGENEITY

It is often ignored that mast cell and basophils display a considerable degree of morphological, functional and pharmacological heterogeneity, a phenomenon that has signally stifled the generation of more effective anti-allergic therapy and in understanding their basic biology. Our sensitivities to inflammatory mediators produced by these cells also differ in comparison to other species. For example, it has been known since the1970s that the LD50 for histamine in mice is several orders of magnitude greater (2) than for humans and that fatal anaphylaxis differentially affects various vital organs between humans, dogs, rabbits and other mammals. While in humans histamine is a major biogenic amine produced by mast cells, a number of other species also produce considerable amounts of serotonin, and also even dopamine, which differentially have pro-inflammatory effects in certain species.

More recently, considerable interest was generated in 2009 when mouse basophils were shown to act as antigen presenting cells and as potential initiators of allergic or parasite-induced Th2 immune responses (3-5). In part, this was shown to involve the innate activation of basophils by protease-activated receptors (PARs) by protease allergens/antigens such as papain (4). Furthermore, murine basophils have also been ascribed to play a key role in IgG-mediated anaphylaxis (6). However, extrapolating these observations to primary human basophils is highly problematical as well as to their mast cell counterparts. For example, there is still no proof of a major antigen-presenting role for human basophils. Our own studies also found no evidence of PAR expression at all in human basophils (7) and it is also well accepted that IgG receptor engagement in human basophils has a predominantly inhibitory effect (8), in stark

contrast to mice. These discrepancies underline the major problem of species heterogeneity in shedding light on fundamental aspects of mast cell and basophil biology and thus observations made on the basis of animal models regarding these allergic effector cells must be viewed with caution.
Future developments of drugs which can selectively block the pro-inflammatory actions of mast cells and basophils must also consider potential pharmacological heterogeneity between these cell types, not only between species but, in the case of mast cells, between different subpopulations of these cells residing in different tissue locations. This is typified by the classical “mast cell stabilizing agent”, cromoglycate (and other chromone analogues), which readily inhibits IgE-dependent degranulation of rat peritoneal mast cells but not those from mice (9). Furthermore, in humans this drug only affects mucosal mast cells (of the MCT class) but not MCTC mast cells found in the skin or located close to bronchial smooth muscle in the lung or basophils (9).

METHODOLOGICAL CONSIDERATIONS IN UTILIZING PRIMARY HUMAN ALLERGIC EFFECTOR CELLS

Because of the heterogeneous properties of allergic effector cells there is a considerable, and largely unmet, need to obtain and purify primary human mast cells and basophils for diagnostic and basic research purposes. This, however, often poses logistical, ethical and financial problems which, coupled to the often burdensome techniques required to isolate these cells, has led to comparatively few studies being undertaken using primary human cells rather than animal models or the use of cell lines.
Recent advances in flow cytometry have diminished the need for highly purified mast cell and basophil populations for certain (largely diagnostic) studies but in order to carry out detailed investigations into cell-cell interactions and in understanding the signal transduction processes of these cells this still requires use of purification techniques (10). Most of these now rely on immunomagnetic selection and, ideally, using a negative selection procedure which eliminates contaminating cell types. These, often commercially available, techniques are usually performed in calcium-free conditions which further reduce any unwanted pre-activation of the allergic effector cells being enriched. However, purification by negative selection may run the risk in certain settings of selecting out any sub-populations of allergic effectors cells that express low levels of an atypical surface marker.

MARKERS AND STAINS FOR MAST CELLS AND BASOPHILS

Mast cell and basophil granules contain large amounts of sulfated proteoglycans (e.g. heparin in mast cells and chondroitin sulfate in basophils) which readily stain with toluidine blue and undergo metachromasia (a change in colour, from blue to violet in the case of this particular stain) which is unique to these cells. However, although toluidine blue, alcian blue and Leder esterase stains have been used successfully to indicate the presence of mast cells in situ they are less suited to detect degranulated cells or allow for ready differentiation between mast cells and basophils. This differentiation is now commonly done using more specific antibody-based staining techniques directed against tryptase, to identify mast cell populations, and basogranulin, for the detection of basophils (10). The Stem Cell Factor receptor Kit (CD117) is also often used as a mast cell surface marker since these cells are the only mature myeloid cell type that still express Kit. The advantages of staining mast cells for Kit is that it can still be used to recognize degranulated mast cells, although it is perhaps less specific than observing tryptase expression owing to the potential presence of haemotpoietic stem cells (albeit very low). Since basophils generally degranulate more readily than mast cells the advantage of using basogranulin as a marker for these cells is that it is a high molecular weight glycoprotein that remains detectable in the close vicinity of the basophils following degranulation.

BASOPHIL ACTIVATION TESTS (BAT)

Flow cytometric analysis of primary human basophils has become a more readily accessible approach for quantifying their responses, particularly to allergen stimulation. In this regard, BAT has now emerged as a clinical diagnostic tool which may be considered as less invasive than skin prick tests and of course poses less risk for an allergic patient in terms of anaphylaxis or further sensitization to an allergen. Another practical advantage of BAT is that basophils need not be purified, or even enriched, since these tests can be performed using anticoagulated blood samples. Alongside scatter characteristics, CD123, CCR3, IgE or CD203c can be used as positive selection markers for basophils as well as the lack of HLA-DR (negative marker) (10). Basophil activation is then most readily identified using antibodies to

detect surface CD63 expression (as an indicator of degranulation; see figure 1). CD203c is not only a specific marker for basophils (and indeed mast cells) but its surface expression can also be used as an indication for activation. However, there are a number of caveats associated with assessing CD203c since its cell surface expression is also upregulated by priming cytokines and during piecemeal degranulation. Despite its relative ease of use, flow cytometric analysis of basophils is currently less well suited for analyzing many different intracellular signaling processes. Here, Western blotting is still an important technique, which requires working with high numbers of purified basophil preparations. Although data obtained from BAT has been shown to correlate closely with the symptoms of allergy it does so less well in certain settings, e.g. in patients with systemic mastocytosis (11). There is currently also a lack of standardization in BAT and a number of technical issues which need to be considered to avoid false negative (or even positive) results. It must also be remembered that some mast cell populations can respond to certain agents in non-allergic individuals (e.g. bee and wasp venoms) which would otherwise not affect basophils and thus may be missed using BAT alone.

CONCLUSION

Despite overwhelming evidence to demonstrate the central role for mast cells and basophils in allergology their heterogeneity and their ex vivo handling still poses a considerable number of issues which clinicians and basic researchers need to take into account when working with these cells.

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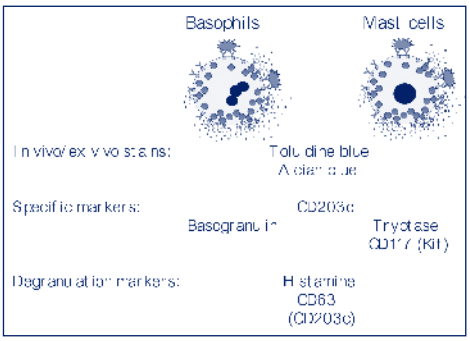

Figure 1: Summary of tools commonly used for mast cell/basophil identification and state of activation.

Clinical use of cellular test in personalized allergy management

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ABSTRACT
Through development of flow cytometry, discovery of activation markers such as CD63 and markers identifying basophil granulocytes in the last decade the basophil activation test (BAT) has become a multifaceted and accessible tool for the allergist. In patients with insect venom, food and drug allergy BAT can be part of the diagnostic evaluation in addition to history, skin testing and specific IgE determination. The basophil sensitivity can be used to monitor patients on allergen immunotherapy, anti-IgE treatment or in the natural resolution of allergy. A very important recent data demonstrated that the BAT can be used to estimate the severity and threshold of allergic reactions to peanut and insect venom and that can be efficiently upgraded with the use of recombinant allergens. The nature of BAT, as a highly quantitative ex vivo challenge test, makes them as the most important cellular test in personalized allergy management.

Keywords: Basophil granulocyte, CD63, BAT: Basophil activation test, Allergy diagnosis, Immunotherapy monitoring, Severity and threshold of allergic reaction

INTRODUCTION

The impact of BAT is due to the unique ability of basophils to degranulate upon cross-linking of the specific IgE (sIgE) bound on membrane-bound high affinity IgE-receptor (FcεRI) by allergen exposure. After discovery of the quantal upregulation of CD63 during basophil activation in 1991(1), the BAT was developed in the 90's. CD63 is a membrane protein localized to the same secretory lysosomal granule that contains histamine. Translocation of CD63 to the cell membrane during degranulation can be measured by flow cytometry.
BAT reflects a functional response as basophil activation can be induced by cross-linking of FcεRI and in case of positive response also reflects allergenic activity of those specific IgEs. Recently, a first Task force position paper (EAACI) provides an overview of the practical and technical details as well as the utility of BAT in diagnosis and management of allergic diseases (2).

Optimization of allergen concentrations

Optimization of allergen concentrations is one of the major steps in BAT testing, and proper implementation of this step allows analysis of dose-response curve metrics including EC15, EC50, CD-sens

and AUC (3). Drug allergens are typically active in the mg/ml range, and can be diluted 5- to 25-fold. Pure active ingredients or injectable intravenous drug preparations should be used when possible since solubilized tablets are complex mixtures of drugs and excipients. Protein allergens are often used in concentrations starting in the µg/mL range, and may be diluted up to 4 –7 log concentrations to ng/ml before reactivity is lost. In case of recombinant allergens, even lower concentrations (pg/ml) can be used.

Flow Cytometry in BAT

At the moment BAT with CD63 is the best clinically validated test (2), but the BAT based on CD203c could be also a reliable test. Basophils can be identified with different combinations of antibodies in flow cytometry. They were first identified as circulating IgE+ cells. However, low side scatter in combination with CD123+/HLADR-, CRTH2+, CD203c+ or CD193+(CCR3) are commonly applied combinations. Anti-FcεRI antibodies are used as IgE-mediated positive controls, buffer as negative control.

Presentation and interpretation of BAT

There are two common measures of basophil activity; basophil reactivity, the number of basophils that respond to a given stimulus, and basophil sensitivity, which is depending on allergen concentration at which basophils started to respond. Basophil sensitivity requires measurement at 4-7 allergen concentrations. The graded response to allergen is fitted to a curve of reactivity versus allergen concentration, and the eliciting concentration at which 50% of basophils respond (EC50) is determined. EC50 can be expressed as 'CD-sens' by inversion and multiplication by 100.

The problem with EC50 and their derivate CD-sens is that in case of lower responses at maximum concentrations, the EC50 values are overrated and could be misleading. For that reason more recently we started to use the area-under-the-dose curve (AUC) calculation (3). Basophil granulocytes of non-responders (about 5% of population) can remain unresponsive to stimulation through FcεRI. Results from non-responder patients should be regarded as false negatives.

DRUG ALLERGY

The diagnostic work-up of drug hypersensitivity reactions aims to identify the culprit agent, identify cross-reactive drugs and to determine a safe alternative drug. Here BAT is an additional tool and, in some instances, is the only available diagnostic tool. There are several studies including BAT in drug allergy diagnosis for beta-lactams, NMBA, quinolones, radio contrast media and pyrazolones with good sensitivity and specificity (2). BAT has also a good negative predictive value, useful in the decision to perform the provocation test as demonstrated with quinolones. Furthermore, it has a complementary role to skin tests for different drug hypersensitivities and can be particularly useful in the study of cross-reactivity between NMBA, for the identification of safe alternatives for future surgery (4).

FOOD ALLERGY

Patients with clinical allergy that developed systemic symptoms to peanut had high basophil sensitivity to peanut, and patients who tolerated peanuts or developed OAS had low basophil sensitivity to peanut (5,6). Furthermore in a recent publication, BAT reflected the allergy severity and the threshold of response to the allergen source in an OFC (7). Those studies obviously suggest that in peanut allergy, BAT significantly improved clinical diagnosis over the use of SPT and sIgE and reduced the number of OFC required.

It has been shown that basophil reactivity distinguishes patients that tolerate extensively heated forms of cow's milk and egg from patients who do not. BAT may be useful in assessing the natural resolution of food allergies that are commonly outgrown over time, such as cow's milk allergy (8), and in determining when the food can safely be reintroduced in the diet.

HYMENOPTERA VENOM ALLERGY

BAT in patients with negative standard tests

A subset of patients (4-6%) with a history of systemic reactions after Hymenoptera stings have negative venom-specific IgE and skin test results. Those patients could subsequently experience another severe

or even fatal reaction to sting. In fact, in cases of fatal sting anaphylaxis, venom-specific IgE are very low or even undetectable in more than 30% of patients BAT allows the identification of about two thirds of those patients (9, 10).

BAT in patients sensitized to bee and wasp venom "double positivity"

Up to 60% of the patients with Hymenoptera venom allergy have sIgE to both bee and wasp venom. BAT has the lowest rate of double positivity of diagnostic tests for hymenoptera allergy and repeatedly shows a positive result to only one venom in about one-quarter to one-third of patients with double sIgE positivity (2). In the case of patients with double positive BAT, the venom which the patient is markedly more sensitive might represent the primary sensitizing allergen source. We recently developed a novel diagnostic approach for venom-IgE double positive patients in which we showed that BAT AUC bee/wasp ratio-based testing could better differentiate between venom culprits than the untransformed tests. The background for this algorithm was our recent observations that BAT-AUC discriminate between LLR and SR patients and between SR-causing and non-SR causing venom in double sensitized patients.

Monitoring the effect of venom immunotherapy with basophil sensitivity:

A clear decrease in basophil sensitivity was demonstrated up to 4 years after initiation of VIT, without a change in basophil reactivity. Our previous report of an 8-year follow up of patients submitted to VIT showed that the decrease in basophil sensitivity seemed to be also associated with the induction of tolerance (11). We also showed that high basophil allergen CD63 sensitivity phenotype was a major indicator of severe adverse SRs during the build-up phase of honeybee VIT (12,13). Before honeybee VIT, measurement of basophil allergen sensitivity should be used to identify patients with a high risk for severe side-effects.

PERSPECTIVES

A major future perspective of BAT is the potential to distinguish the severity and threshold of allergic reactions ant thus significantly improved personalized allergy management. This potential was recently demonstrated in peanut (6, 7) and Hymenoptera venom allergy (13). Further studies in this field are urgently needed.

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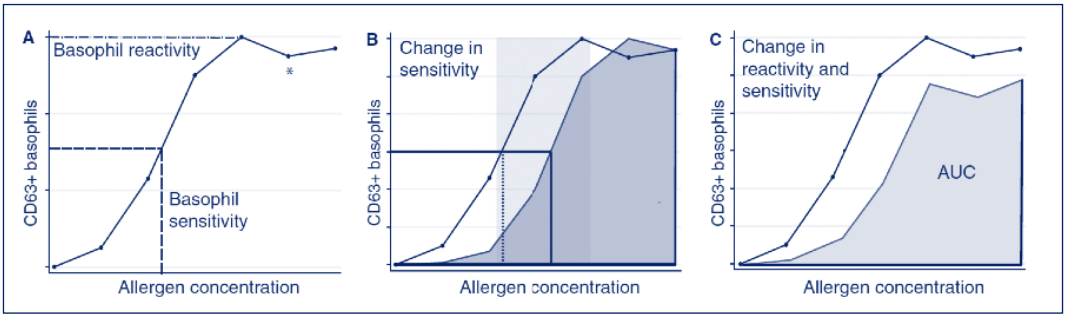

Figure 1: Assessing basophil response.

The fraction of CD63+ basophils is plotted against log allergen concentration. Adapted from (2) with permission from the authors.

A. Basophil reactivity is the dose (range) at which maximal response occurs. **Basophil sensitivity** is the dose at which half of the maximal response occurs. *At high allergen concentrations, basophil response may be suppressed.

B. A change in sensitivity toward higher allergen concentration is the most reproducible basophil biomarker for reduced clinical sensitivity to allergen to date. Attempts to reduce the number of BAT tests required to determine a significant change in basophil response have focussed on identifying an allergen concentration at which a change in sensitivity can readily be assessed (grey box).

C. Basophil response could also be assessed as area under the curve (AUC) with a log allergen axis, or a similar composite measure reflecting both reactivity and sensitivity. Variation in maximal basophil reactivity arises concurrently with, and may be inseparable from, a change in sensitivity.

Improved recombinant Api m1 and Ves v5 based IgE testing to dissect bee and yellow jacket allergy and their correlation with the severity of the sting reaction

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ABSTRACT

BACKGROUND: No study has assessed the diagnostic sensitivity of rApi m1 and rVes v5 on Immulite testing system.

OBJECTIVE: To compare the diagnostic sensitivity of commercially available venom recombinant allergens between the currently available immunoassays (ImmunoCAP [CAP] and Immulite [LITE]), and establish their correlation with the severity of the sting reaction.

METHODS: This study evaluated 95 bee venom and 110 yellow-jacket venom allergic subjects. We measured the levels of sIgE to rApi m1, rVes v5 (LITE and CAP), rApi m2 (LITE), rVes v1 (CAP) and tIgE (CAP). Forty-nine healthy subjects served as controls.

RESULTS: The diagnostic sensitivity of rApi m1 and rVes v5 was significantly higher with the LITE than with the CAP system (71% vs. 88% and 82% vs. 93%). The specificity of both assays for both allergens was between 94% and 98%. Twenty-nine patients that tested negative for rApi m1 or rVes v5 with CAP were positive with LITE, but none of the patients that tested negative with LITE were positive with CAP. The positive values of rApi m1 and rVes v5 were on average 2.7 and 2.3 times higher, with the LITE than with the CAP system. The combination of rApi m1 and rApi m2 (LITE) and the combination of rVes v5 (LITE) and rVes v1 (CAP) almost matched the sensitivity of native venoms (95% and 97%, respectively), whereas the diagnostic sensitivity of the combination of rVes v5 and rVes v1 (CAP) did not reach the sensitivity of rVes v5 (LITE) alone (90% vs. 93%). IgE levels to venom recombinants and total IgE did not correlate with the severity of sting reaction.

CONCLUSIONS & CLINICAL RELEVANCE: The use of rApi m1 and rVes v5 with the LITE system significantly enhanced diagnostic utility of venom recombinants and should improve the dissection of bee and yellow-jacket venom allergy.

Improvement of in vitro methodology for diagnosis of delayed-type hypersensitivity

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The delayed reaction or type IV hypersensitivity is T cell-mediated and includes several manifestations such as drug and maculopapular eruption, general exfoliative dermatitis or erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), drug-induced hypersensitivity syndrome, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, other bullous reactions mimicking pemphigus vulgaris or bullous pemphigoid up to vasculitis (1).
Drug hypersensitivity reactions (DHR) are the most common delayed-type hypersensitivity (DTH) and represent the important health care problem and the major problem in daily clinical practise. Pichler et al. has subdivided type IV DHR into 4 groups according to the clinical presentation and the involvement of different types of drug-responsive T-cells (Table 1) (1, 2).

Table 1: Classification of DHR according to Gell and Coombs and adapted by Pichler et al.

Type	Type of immune response	Pathophysiology	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Anaphylactic shock, Angio-oedema, Urticaria, Bronchospasm	Within 1–6 h after the last intake of the drug
II	IgG and complement	IgG and complement-dependent cytotoxicity	Cytopenia	5–15 days after the start of the eliciting drug
III	IgM or IgG and complement or FcR	Deposition of immune complexes	Serum sickness, urticaria, vasculitis	7–8 days for serum sickness/urticaria 7–21 days after the start of the eliciting drug for vasculitis
IVa	Th1 (IFNγ)	Monocytic inflammation	Eczema	1–21 days after the start of the eliciting drug
IVb	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	MPE, DRESS	1 to several days after the start of the eliciting drug for MPE 2–6 weeks after the start of the eliciting drug for DRESS
IVc	Cytotoxic T-cells (perforin, granzyme B, FasL)	Keratinocyte death mediated by CD4 or CD8	FDE, MPE, SJS/TEN, Pustular exanthema	1–2 days after the start of the eliciting drug for fixed drug eruption 4–28 days after the start of the eliciting drug for SJS/TEN
IVd	T-cells (IL-8/CXCL8)	Neutrophilic inflammation	AGEP	Typically 1–2 days after the start of the eliciting drug (but could be longer)

The diagnosis of drug and chemical induced delayed-type T-cell mediated hypersensitivity reactions is important and usually based on clinical history, skin and provocation testing. Unfortunately skin testing has low sensitivity (3) and provocation testing could lead to the reactivation of severe symptoms and consequently could be life-threatening.

In vitro tests offer safer alternatives to the often invasive provocation testing. However, the sensitivity of the majority of currently available in vitro tests is also low therefore in vitro stimulation might represent a complementary diagnostic tool. Several methods are used for in vitro determination of DTH. The most known are lymphocyte transformation test (LTT), the measurement of cytokines and the CD69 upregulation.

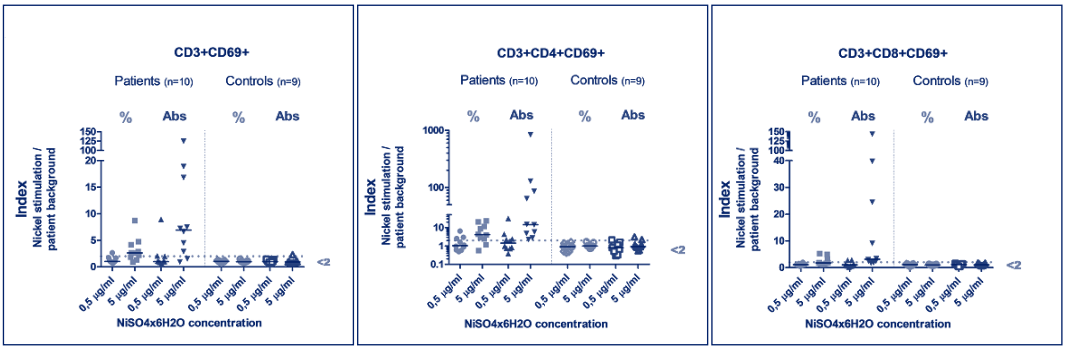
LTT measures the proliferation of the lymphocytes to an antigen. Specificity of LTT is over 90% but sensitivity is limited and depends on the type of reaction, drug and time interval between the event and analysis (4). LTT includes radioactive substances and therefore must be performed in appropriate laboratory conditions with limited accessibility causing the stagnation and failure to implement the LTT in the vast majority of laboratories.

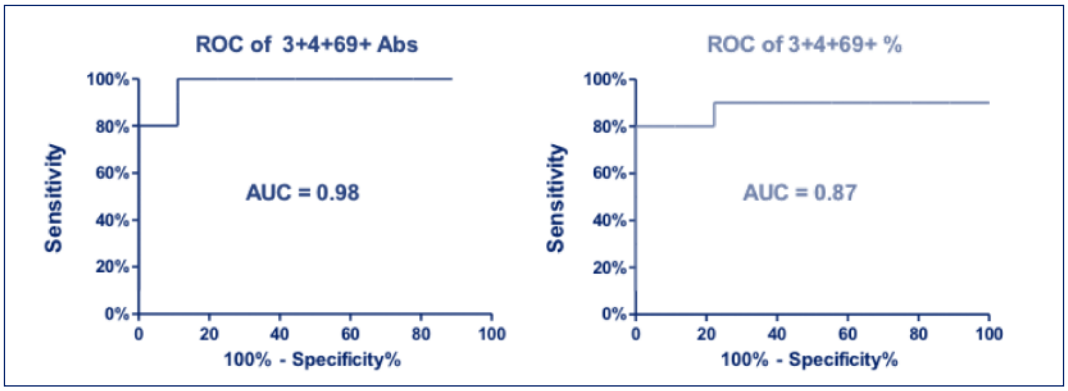
Cytokines are produced by lymphocytes after stimulation and incubation of peripheral blood mononuclear cell (PBMC) with different concentrations of drugs or/and chemicals. In vitro secretion of cytokines could be finally determined by ELISA or flow cytometry. Different subsets of T lymphocytes produce distinct cytokine expression profiles. CD4 helper T lymphocytes (Th cells) produce lymphokines such as interleukins (IL) IL-2, -4, -5, -6, -10 and interferon gamma (IFN-γ), whereas the CD8 subpopulation produces granzyme B, perforin, IFN-c and tumour necrosis factor-α (TNF-α), which induces target cell lysis and has an anti-viral activity (5). Th cells are functionally heterogeneous, with distinct cytokine patterns. Th1 cells produce IL-2 and IFN-γ, while Th2 cells produce IL-4, IL-5, IL-6 and IL-10 (6).
For DTH in vitro diagnostics the most frequently determined cytokines are: IL-2, IL-5, IL-13 and IFN-γ.

The CD69 antigen is present on activated T, B and NK lymphocytes. The CD69 antibody recognizes an early human activation of antigen. CD69 expression is measured by flow cytometry and results are present with a stimulation index. Index of more than 2 appears to discriminate well between allergic and nonallergic patients.

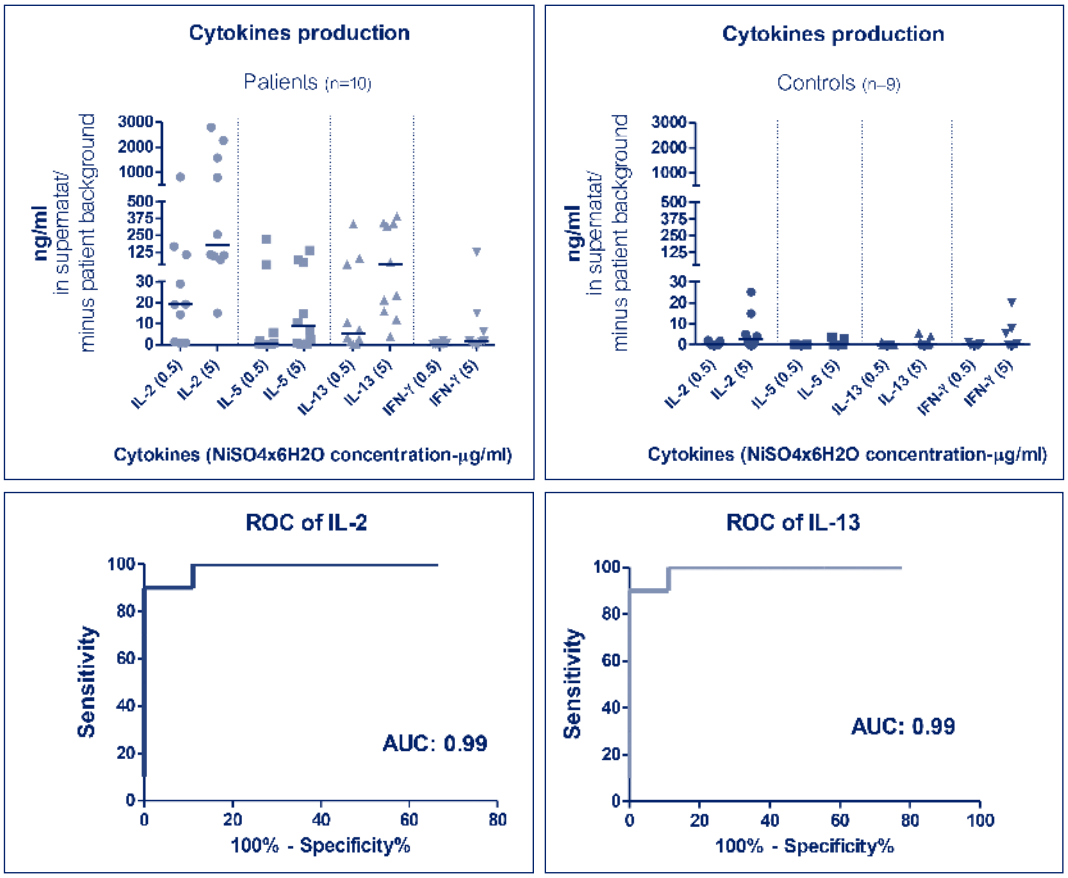
OUR EXPERIENCE:

1. Quantitative T cells analysis of CD69 up regulation in diagnosis of patients with delayed-type nickel hypersensitivity: CD69 upregulation on CD3+, CD3+CD4+ and CD3+CD8+ T cells analysed by flow cytometry after different stimulation (0.5 and 5 µg/ml of NiSO4x6H2O) and incubation protocols in 10 Nickel hypersensitive patients and in 9 healthy controls. Measurement of the absolute counts of CD69 upregulated CD3+, CD3+CD4+ and/or CD3+CD8+ T after 48 h of antigen-stimulation was shown to be useful and sensitive (7).





2. In vitro release of IL-2, IL-5 and IL-13 in diagnosis of patients with delayed-type nickel hypersensitivity: in vitro secretion of cytokines by peripheral blood mononuclear cells (PBMC) of 10 nickel hypersensitive patients and 9 healthy controls. PBMC were incubated for 48 hours with two different concentration of NiSO4x6H2O (0.5 and 5 µg/ml). IL-2, IL-5, IL-13 and IFN-γ concentrations were measured in supernatants with multiplex flow cytometry CBA Flex Array. We showed a significantly increased secretion of IL-2 (median 182 vs 3 ng/ml), IL-5 (9 vs 0 ng/ml), IL-13 (36 vs 0.5 ng/ml) in response to NiSO4x6H2O in patients with nickel hypersensitivity when compared to healthy controls. The response in the patients was concentration dependent. No difference was evident for IFN-γ . The ROC curve analysis demonstrated the highest AUC of 0.99 for IL-2 and IL-13, followed by AUC of 0.91 for IL-5 (8).



CONCLUSIONS

The measurement of IL-2 and IL-13 appeared to be a promising approach to identify antigen -reactive T cells in the peripheral blood of patients with the hypersensitivity reactions. An important innovation or improvement in measurement of cytokine productions is the introduction of new method: CBA Human Soluble Protein Flex Set System Cytometric Bead Arrays (Cytometric Bead Array; BD Biosciences, San Jose, CA). System is optimized for the detection of multiple analytes in small sample volumes with low concentrations. According to the manufacturer, the method is based on capturing of analytes with beads of known size and fluorescence. Sandwich complexes, composed of capture beads, analytes and detection reagent, can be measured using flow cytometry. Final concentration of measured analytes is extrapolated from the standard curve. The method is simple and can be performed in any well-equipped laboratory.

Second improvement is related to the determination of absolute count of CD69 upregulated CD3+, CD3+CD4+ and/or CD3+CD8+ T cells after 48 h of antigen-stimulation which seems to be more sensitive methodology, as the stimulation index calculation.

The clinical usefulness of the cytokine and CD69 approaches are currently tested in University Clinic Golnik on the clinical important issues in order to improve the diagnosis of the delayed-type hypersensitivity reactions to drugs.

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Identification of peptide mimotopes of allergens and design of mimotope-based immunotherapy

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BACKGROUND: Identification of allergen epitopes is a key component for understanding the pathogenesis of type I allergies and for developing mimotope immunotherapeutics. The term mimotope describes a peptide that mimics physicochemical properties of a natural epitope and is able to compete with native protein for antibody binding. Such peptide mimotopes expressed on a suitable immunogenic carrier offer an attractive and safer alternative compared to immunotherapy with allergen extracts or recombinant allergens, particularly in the case of severe allergies, such as peanut allergy.

METHODS: Immunoscreening of peptide libraries displayed on phage particles against affinity-purified rabbit antibodies specific to major cat allergen Fel d 1 or major peanut allergen Ara h 2 was performed. Binding of selected peptides to target antibodies and their competition for binding sites with allergen was evaluated using ELISA or immunobloting. Best binders to Fel d 1 and Ara h 2 paratopes were displayed in a large copy number on immunogenic carrier filamentous phage or *L. lactis*, respectively. Binding to allergic patients' IgE was confirmed by immunobloting. Allergic immune response and immunogenic properties of the carriers and mimotopes were evaluated in vitro by basophil activation test and measurements of cytokines released from peripheral blood mononuclear cells.

RESULTS: Five structural mimotopes of major cat allergen Fel d 1 were identified and mapped to three locations on the the surface of allergen. Mimotopes were reactive to cat-allergic patients' IgE and showed no basophil activation of the corresponding patients. Displayed on filamentous phage they elicited T cell-mediated immune response, which was predominated by the type 1 T cell response. Mimotopes alone contributed to this by promoting IL-2 production.
Mimotopes of Ara h 2 were mapped to one epitope region of allergen. The three selected and displayed on *L. lactis* were reactive to peanut allergic patients' IgE. Mimotope L7-N40 with the strongest IgE reactivity also showed high basophil activation. No allergenic activity was detected for the two structurally similar mimotopes. Mimotopes were able to elicit T cell response.

CONCLUSION: We have identified mimotopes of allergens capable of binding specific IgE and competing for paratopes with cognate allergens. Moreover mimotopes had no or low allergenic activity, and as a part of therapeutic constructs showed suitable T cell activity. Mimotopes, in combination with a suitable immunogenic carrier such as phage particles or *L. lactis*, can aid in the development of hypoallergenic vaccines for allergen-specific immunotherapy.

Association between basophils and chemotactic factors in anaphylaxis

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BACKGROUND: The specific role of basophil chemotactic factors in human anaphylaxis is not clear.

METHODS: Concentrations of three major chemotactic factors including CCR3 ligands CCL11, CCL5 and CCR2 ligand CCL2 were measured in 17 patients with anaphylaxis in three different time points (at presentation of anaphylaxis, after 7 days and after 1 month after the anaphylactic episode). Comparison group with 54 healthy controls was also included.

RESULTS: Serum CCL2 concentration was significantly increased in patients with acute allergic reaction (median 658 pg/ml) compared to 7 days (median 314 pg/ml) and 1 month (median 311 pg/ml) after the anaphylactic episode (both P=0.0002). CCL2 was also increased in patients with acute allergic reaction compared to healthy controls (P<0.0001). ROC analysis demonstrated AUC of 0.99. Importantly, the significant negative correlation (r=-0.58, P<0.0001) between serum CCL2 concentration and the absolute number of circulating basophils was demonstrated. On the other hand there were no significant differences in serum concentrations of CCL5 (46851, 49489 and 46749 pg/ml) and CCL11 (109, 108 and 96 pg/ml) (all P>0.05).

CONCLUSION: Our study indicates marked increase in the level of major basophil chemotactic factor CCL2 during anaphylaxis, which correlates with a decrease in a number of circulating basophils. These observations suggest an important and specific role for CCL2 in the pathobiology of human anaphylaxis and a novel diagnostic strategy for supporting the clinical diagnosis of anaphylaxis.

9

CLINICAL ALLERGOLOGY

Chairs: Mitja Košnik,
Natalija Edelbaher,
Sladjana Andrejević (Serbia)

Hypereosinophilia: allergist's point of view

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INTRODUCTION

The differential diagnosis of eosinophilia is broad. Eosinophils are derived from CD34+ progenitor cells in the bone marrow and differentiate in response to T-cell–derived cytokines, including granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3, and IL-5. The production of IL-5 by Th2 lymphocytes accounts for the eosinophilia accompanying Th2 cell-mediated immune responses characteristic of helminth infections and allergic diseases. Mature eosinophils can persist for up to 24 hours in the circulation before migrating into extravascular sites, where they can survive for days. For every eosinophil present in the circulation there are 300–500 in the tissues [1].

The normal eosinophil count in the peripheral blood ranges from 0.05 to 0.5×109/L. Three levels of severity of eosinophilia have been defined as follows: mild (0.5 to 1.5 × 10^9/L), moderate, (from 1.5 to 5× 10^9/L) and severe (greater than 5×10^9/L). The term hypereosinophilia (HE) should be used when marked blood eosinophilia has been documented and is persistent, with or without an additional marked tissue eosinophilia.

When patient presents with HE there are two critical questions that have to be answered: 1) is there an underlying disease or condition and 2) are there clinical signs and symptoms or laboratory abnormalities that point to the presence of accompanying HE-induced organ damage.

CLASSIFICATION

Based on underlying conditions and etiology, several variant forms of HE exist for which the following terminology has recently [2] been proposed : 1) a hereditary (familial) form (HEF), 2) HE of undetermined (clinical) significance (HEUS), 3) primary (neoplastic) HE (HEN) where eosinophils are considered to be clonal cells and 4) secondary (reactive) HE (HER) where eosinophils are considered to be nonclonal cells expanded (and activated) by a reactive process.

When organ damage accompanies HE (of any type), the term "hypereosinophilic syndrome" (HES) is appropriate, provided that organ involvement is clinically relevant and can be attributed to HE [2,3].

A number of reactive conditions and disorders can cause HE and may produce a clinical picture resembling HES. Reactive hypereosinophilia (HER) may develop in the setting of an underlying parasitic infection, drug allergy or neoplasm [3,4].

Helminthic parasites typically elicit IL-5–mediated eosinophil expansion. Eosinophilia can be constant or fluctuate over time. Histories of geographic exposures (even decades before) and recent dietary histories (eg, trichinellosis) are needed. Toxocariasis is often relatively asymptomatic, serologic testing is therefore recommended in all eosinophilic patients. Of greatest concern is underlying infection with *Strongyloides*

stercoralis. This is the only major helminthic parasite with the capacity to propagate itself internally for decades after initial infection, to cause variable eosinophilia (with or without other symptoms), and to result in disseminated infections in patients on glucocorticosteroid treatment. Although stool examinations for ova and parasites are warranted in patients with eosinophilia, these examinations are insensitive and should be screened for serum antibodies by using ELISA [3]

Allergic and immunologically mediated diseases to be considered include more common allergic diseases, although eosinophilia of greater than 1.5×109/L is uncommon in most subjects with asthma. More pronounced eosinophilia in association with asthma should prompt a consideration of the Churg-Strauss syndrome or allergic bronchopulmonary aspergillosis.

Adverse reactions to medications, both herbal and prescribed, must be considered. Drug-induced eosinophilia can develop without other manifestations of adverse drug reactions, such as rashes or drug fevers. Identifying the culprit agent in patients taking multiple drugs can be challenging. Clinicians can be guided by the type of medications (some being more likely responsible for an eosinophilic drug reaction than others, such as anticonvulsants, semisynthetic penicillins, and allopurinol) and by specific target-organ involvement: hepatitis or the drug induced rash, eosinophilia, and systemic symptoms syndrome (DRESS syndrome) with anticonvulsants; pneumonitis with nitrofurantoin, semisynthetic penicillins, and nonsteroidal antiinflammatory agents; nephritis with cephalosporins; and hypersensitivity vasculitis with allopurinol and phenytoin. In patients with drug-induced pulmonary eosinophilia, blood eosinophilia is usually, but not always, present; if absent, sputum or bronchoalveolar lavage eosinophilia is necessary to help make the diagnosis. In patients with drug-induced acute interstitial nephritis, eosinophilia is common in the involved kidneys, urine, and, at times, blood. Acute necrotizing eosinophilic myocarditis is a serious but uncommon type of hypersensitivity myocarditis, with reactions to medications responsible in some cases. A syndrome of hepatitis with eosinophilia can be a manifestation of drug reactions [3].

In addition to these relatively common causes of eosinophilia, neoplastic diseases, including varied adenocarcinomas, some forms of Hodgkin disease, T-cell lymphoma, and mastocytosis might be associated with paraneoplastic eosinophilia. Finally, eosinophilia can precede other clinical manifestations of an occult neoplasm, sometimes by many years.

Other infrequent causes include rare immunodeficiency disorders, namely hyper-IgE syndrome and Omenn syndrome.

Organ-specific eosinophilic disorders might also be associated with blood eosinophilia; these include acute and chronic eosinophilic pneumonias, eosinophilic gastroenteritides, and some principally skin diseases.

The initial work-up of a patient with HE therefore mandates careful examination of drug history, withdrawal of nonessential agents and those that are particularly suspect (eg, anticonvulsants and antimicrobials), serologic testing for selected helminths, examination of 3 stool specimens for ova and larvae, and appropriate antiparasitic treatment if results of

these tests are positive. This is usually performed in a stepwise approach. Important initial parameters that can be obtained from routine laboratory testing include a complete blood count with differential counts, peripheral blood smear looking for dysplastic eosinophils or blasts, routine chemistries (including tests of hepatic and renal function), levels of inflammatory markers, antineutrophil cytoplasmic antibody (ANCA), serum IgE, vitamin B12, and tryptase levels [3,4].

Concomitant with the evaluation described above, directed at identifying the etiology of the eosinophilia and depending in part on the signs and symptoms in the individual patient, the extent of eosinophil-mediated organ damage should be assessed. In all patients, these investigations should include a physical examination with thorough skin examination, detailed cardiologic evaluations including assays of serum troponins, electrocardiography; echocardiography, assessment of pulmonary function, chest x-ray, abdominal imaging, and gastrointestinal examinations (with endoscopy if indicated).

When an underlying cause for persistent hypereosinophilia is not identified despite thorough diagnostic evaluation, clinicians must consider HES, which comprise a heterogeneous group of uncommon disorders [5].

Recent studies have led to the identification of 2 major pathogenically identifiable variants of HES [2,3].

1) Myeloproliferative variant HES (M-HES) characterized by features that are typically encountered in other myeloproliferative diseases. The majority of patients have a cryptic interstitial deletion on chro-

mosome 4q12 that results in expression of a FIP1L1-PDGFRA (FIP1-like 1/platelet-derived growth factor receptor A fusion protein (F/P) with autonomous tyrosine kinase activity. Clinical characteristics of this variant include strong male predominance, increased serum vitamin B12 and tryptase levels, mucosal ulcers, splenomegaly, endomyocardial fibrosis and other organ-based fibrotic complications, and possible progression toward acute eosinophilic leukemia.

2) Lymphocytic variant HES (L-HES) is characterized by polyclonal eosinophil expansion in response to marked overproduction of IL-5 by deregulated T cells. These T cells can be detected on the basis of abnormal surface phenotypes are sometimes monoclonal.

Clinically, patients often present with predominant cutaneous manifestations, although other organs can be targeted as well; increased serum IgE levels; and hypergammaglobulinemia.

CASE REPORT

Finally, of special interest for allergists are patients with acute or recurrent angioedema that has occurred without any obvious trigger. There is a disorder categorized in a broad category of idiopathic HES known as a Gleich syndrome [2,4]. Episodic angioedema with eosinophilia (EAE) is a rare disorder characterized by recurrent episodes of urticaria, fever, angioedema, weight gain and dramatic eosinophilia that occur at 3-4 week intervals and resolve with spontaneous diuresis in the absence of therapy. EAE is an exceedingly rare disorder with less than 50 cases reported in the literature to date [6] By chance we had an opportunity to examine a patient with features consistent with the diagnosis of EAE [7].

A 34-year-old man was referred to our Clinic for further investigation of recurrent angioedema of the hands, feet and trunk, with onset 6 years previously. Cycles occurred every four weeks, with a complete interval resolution of symptoms. During the attacks, the patient showed drowsiness, myalgia, low-grade fever (up to 38°C) and weight gain (3-4 kg). The patient presented a personal history of mild seasonal allergic rhinitis. Patient's travel and medication histories were irrelevant. The most constant feature of his disease was an isolated peripheral blood eosinophilia up to 4900/mL, consistently greater than 40% of the absolute white cell count. Eosinophil count rose during the attacks. Serum protein electrophoresis showed polyclonal increase in gamma globulins with no paraprotein band. IgM was raised at 11 g/l. Total IgE was also markedly raised at 1417 IU/ml. FIP1L1/PDGFRA testing was negative. However, aberrant CD3-CD4+ lymphocyte populations were detected by PCR. Myeloproliferative features, including anemia, thrombocytopenia, elevated serum B12 and tryptase levels, were absent. Bone marrow aspirates demonstrated increased eosinophils, but no increase in blasts. Other investigations, including biochemistry study, stool examination and serology for parasites, ANCA, CRP, concentration and level and activity of complement were negative or normal. Serology for the hepatitis and human immunodeficiency viruses was negative. CT scans of the thorax and abdomen, gastroscopy, EKG, echocardiography electroneurography, spirometry and body pletismography all gave normal results. Bone densitometry revealed osteoporosis. Prednisone therapy was introduced at 10-20 mg/day along with cacium and vitamin D supplementation. Patient reported improvement in symptoms and steroid doses were slowly tapered off. Patient is on stable low-dose prednisone and other treatment options should be considered.

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Association between PM10 and PM2.5 exposures and their effects on asthma and other respiratory diseases at the municipalities' level in Slovenia: ecological spatial study

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INTRODUCTION: Outdoor air pollution is one of major public health concerns today. World health organization reports that in the year 2012 around 7 million people died (one in eight of total global deaths) as a result of air pollution exposure. Outdoor air pollution is strongly associated with chronic respiratory diseases. Studies have shown, that asthma and COPD have become the most common chronic disease and are one of the major causes for mortality and hospitalization. In Slovenia, several areas with high level of concentration of PM10 and PM2.5 in outdoor air pollution exist. Consequently, the aim of our study was to assess the spatial association between exposure to PM10 and PM2.5 and mortality and hospitalization from asthma and other respiratory diseases at municipality level in the entire country.

METHODS: These study was conducted as a part of Life MED HISS European project (LIFE MED HISS LIFE12 ENV/IT/000834). An ecological spatial design was used in our study. The unit of observation were 210 municipalities in Slovenia. The observed health outcomes in the analysis were mortality and hospitalization due to asthma and other respiratory diseases. Health data were obtained for the period from 2010 to 2014 and yearly average was modelled for PM10 and PM2.5 concentrations at the municipality level for the year 2011. The associations were investigated using Poisson regression models without and with spatial random effects. The statistical modelling process was prepared in two stages. Firstly, we prepared univariate models and secondly multivariate models were prepared adjusted on prevalence of: low education level, obesity, physical inactivity, alcohol consumption, present and ever smoke, passive smoke, active population, average monthly earnings.

RESULTS: The results of multivariate models show that PM10 was significantly associated with mortality due to respiratory diseases, the relative risk (RR) and 95% credibility intervals (CI) for period of observation were (1.014; 1.000 to 1.028) for each 1ug/m3 increase. Association was also found for hospitalization due to asthma in univariate model (RR = 1.019; CI = 1.002 to 1.037). PM2.5 was significantly associated with mortality due to respiratory diseases in univariate models (RR = 1.027; CI = 1.001 to 1.053).

CONCLUSION: High PM10 levels were associated with higher mortality rates due to respiratory diseases and hospitalization rates due to asthma at the municipality level in Slovenia. Future work should base on improving the exposure assessment and upgrading the statistical methods with multipollutant models.

Aspirin and NSAID hypersensitivity

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INTRODUCTION: Diagnosis and management of NSAID-induced hyperreactivity is challenge for allergologist for several reasons: most patients develop sensitivity after initially tolerating drugs, symptoms of various types of reaction may be overlapping, some reactions can be life-threatening, it is difficult to determine if the symptoms are elicited by one or multiple drugs.

UNDERLYING PATHOMECHANISMS: NSAID-induced hyperreactivity may inolve both immunological and non-immunological mechanisms. Immunological reactions are elicited by single drug and presumed to be IgE mediated. Non-immunological reactions are elicited by multiple NSAIDs because they are inhibitors of the enzymes involved in rapid, inducible lipid metabolism at cellular level (platelets, neutrophils, eosinophils). Lipid mediators (eicosanoids) are synthesized by most tissues and act as local homeostatic regulators, mediators of pain, fever, inflamation, vasular tone, etc. Stress, tissue injury, stimulation of cell to cell signaling, surgical trauma, etc., activate cytoplasmic phospholipase A2 (PLA2). This enzyme liberates polyunsaturated fatty acid – arachidonic acid (AA) from the membrane in the cell interior, as a substrate for enzymes: prostanoid-synthesizing enzyme **cyclooxygenase** (COX-1 & COX-2), oxygen oxidoreductase enzyme **lipoxygenase** (LOX) (platelet-type, reticulocyte-type, leukocyte-type and epidermis-type), and epoxygenases enzyme cytochrome P450 (CYP). Products of inducible, "suicidal enzyme" COX-2 include prostaglandins, thromboxane and prostacyclin (prostanoids), promoting inflammation, pain, fever and blood clotting. LOX products comprise leukotrienes, hepoxilins and HETEs. **Cytochrome P450** products are epoxyeicosatrienoic acids (EET) producing vascular relaxation and anti-inflammatory effects on blood vessels and kidney, promote angiogenesis, and protect ischemic myocardium and brain. All of the eicosanoid regulatory molecules tend to act locally.

Ligand/Receptor	**Target cells**
PG (PGD, PGE (EP1-EP4), PGF, PGI)	T, B, M, Neu, E/CPGE (EP1-EP4)
TXA (TPa/TBb)	Pt
LXA_4	M, Neu, EC
PAF	M, Eo, Ba, DC, Pt
5-oxo-ETE/5-hete	M, Neu, Eo
LTB_4	M, Neu, T, B

Table 1: Lipid mediators of inflammation

Disregulation of lipid metabolism is genetically determined. Genetic variants in leukotrienes-related (5-LO, 15-LO, CysLTR1) and eosinophil-related genes (CCR3, CRTH2, IL-5, IL-5R, PZRy12) are associated with NSAID-exacerbated respiratory disease (NERD). HLADPB10301 is strong genetic marker.

CLINICAL MANIFESTATIONS. NSAID can induce several distinct clinical types of adverse reaction: **NERD, NECD** (NSAID-exacerbated cutaneous disease), **NIUA** (NSAID-induced urticaria /angiooedema), **sNIUA** (single-NSAID-induced urticaria /angiooedema or anaphylaxis), **sNIDR** (single-NSAID-induced delayed reactions).

DIAGNOSTIC PROCEDURES. Kowalski et al. outlined a simplified diagnostic algorithm for NSAID-hypersensitivity: 1) the allergist should evaluate if the symptoms are typical for tolerance, intolerance or hypersensitivity, 2) the onset time of the reactions should be assessed, and 3) the pattern of clinical symptoms and underlying chronic disease should be analyzed. This informations help to suggest appropriate NSAIDs for use in challenge tests to confirm or exclude cross-reactivity with other NSAIDs. The only means of obtaining a definitive, current sensitivity diagosis is a provocative challenge for insight in drug the patient with medical need for future NSAID therapy, may safely take. For in vitro diagnosis, potential serum biomarkers may be serum periostin and dipeptidyl-peptidase 10 gene (DPP10).

CLINICAL MANAGEMENT. If medical history and evaluation confirm NSAID-hypersensitivity, drug desensitization is recommended. Despite many compounds belonging to NSAIDs, only desensitization to aspirin has been sufficiently documented. Desensitization is accomplished by continuing the challenge procedure. The most common indications for desensitization are: 1) medical need for aspirine therapy in patients with cardioovascular disordes, 2) NSAID therapy for chronic inflammatory conditions. Desensitization is absolutely contraindicated in cases of history of possible anaphylaxis, severe or threatening delayed drug hypersensitivity reactions (SJS,TEN,EM,drug reactions with eosinophilia and systemic symptoms), FEV1< 70%, in patients on therapy with ACE inhibitors and β-blockers. Protocols for drug desensitization have not been standardized. It seems that slower protocols may be more effective than rush protocols.
In future, new diagnostic methods and effective treatments should be developed for better management of patients with NSAID-hypersensitivity.

Keywords: Nonsteroidal anti-inflammatory drugs, aspirin hypersensitivity, aspirin desensitization, NSAID-induced hypersensitivity, aspirin challenge

Negative impact of elimination diets on growth and nutritional status in children with multiple food allergies

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INTRODUCTION: Impairment of growth and other nutritional deficiencies have been reported in food-allergic children. The aim of our study was to assess the food intakes and nutritional status of children with suspected or proven multiple food allergies when elimination diet was not supervised by continuing dietitian follow-up.

METHODS AND SUBJECTS: 39 children (16 girls, 23 boys) with suspected or proven food allergies were studied retrospectively. Instructions on elimination diet were given to 20 children by pediatrician allergologists (seven of them were also sent to dietitian), to three by pediatricians gastroenterologists (one of them was also sent to dietitian), to four by dermatologists, to twelve children by regional pediatricians. The majority (34) children had atopic dermatitis, 18 anaphylaxis, nine hives and six gastrointestinal symptoms. Three children had additional medical conditions that influenced nutritional status (one cromosomopathia, one histamine intolerance, one Asperger syndrome). Nutritional intakes assessment was passed on exact questioning on actual food avoidance. Children's weight, height, laboratory data for nutritional parameters were assessed.

RESULTS: In 26 (67%) children additional exact questioning revealed that their diet was extended from previously advised. Nutritional deficitis were detected in 22/23 (96% of children who did not eat cow milk/egg/wheat or cow milk/egg and in addition variable foods. 19 children (49%) had diverse nutritional deficits. Lower serum levels of levels of protein/ iron/ zinc/selenium/vitamin B12 were found in 10/10/17/14/4 children, respectively. Three children had osteoporosis and three had osteopenia. In described group the means for anthropometric measures were below the average for age (34.P for height and 32.P for weight). Three children were <-3% for relative height and two children were <-3% for relative weight.

CONCLUSIONS: The extent of food elimination diet has impact on growth and nutritional status of food-allergic children if diet is not supervised continually by experienced physician and dietitian and not equate supplemented.

Immunological and molecular background of VIT treatment failure due to SSR and the influence of omalizumab co-treatment

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BACKGROUND: Systemic side reactions (SSRs) during venom immunotherapy (VIT) frequently require emergency interventions and are cause of discontinuation of treatment –VIT failure due to SSRs.
Our objectives were to identify immunological factors associated with VIT failure due to SSRs and to evaluate the influence of omalizumab treatment for VIT continuation.

METHODS: From 2005 to 2016 1952 VIT was initiated in 1820 patients. 752 (38,5%) patients were treated with honey bee venom (HBV) and 1200 patients (61,5%) with yellow jacket venom (YJV). 132 (6,8%) patients were treated with both venoms. VIT was, despite several attempts and emergency interventions, discontinued due to SSRs 23/752 (2,9 %) HBV VIT and 0/1200 YJV VIT. Those patients were characterized according to various immunological factors including sIgE, basophil CD63 response, baseline tryptase and number of FcεRI and IgE on basophil surface. 11/23 VIT failure due to SSRs patients were pre- and co-treated with omalizumab during another attempt of VIT. We tried different schedules of omalizumab treatment (dose, time interval, duration) to establish the most successful protocol.

RESULTS: The strongest immunological factor associated with HBV VIT failure due to SSRs was high basophil CD63 response to allergen. Basophil sensitivity was significantly higher in 23 VIT failure patients in comparison to 310 patients with successful HBV VIT (median response at 0.01ug/ml: 38 vs 6.4% , 0.1 ug/ml: 79 vs 53 %, respectively). There was also significant difference in baseline tryptase (5,23 ug/ml vs 4,3 ug/ml).
Pre- and co-treatment with omalizumab markedly decreases basophil responsiveness and number of FcεRI and IgE on basophil, this cellular changes correlated with diminishing of SSR. VIT was successfully continued in 8/11 patients treated with omalizumab. Most favourable immunological and clinical outcomes were observed if omalizumab 300 mg pre-treatment was administered four-times before VIT in two weeks interval and if co-treatment was long lasting, at least 6 months during VIT.

CONCLUSIONS: Increased basophil allergen sensitivity is strongly associated with HBV VIT treatment failure due to SSRs. Pre-treatment with omalizumab decreases basophil responsiveness and enables successful initiation of VIT. Co-treatment with omalizumab should be long lasting.

Idiopathic anaphylaxis

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BACKGROUND: Idiopathic anaphylaxis (IA) is a rare disease that has no discernible cause for its occurrence. It is a diagnosis of exclusion. The insight into the natural course of the disease in Slovenia in unknown.

AIM: The main aims of our research were to determine the epidemiology of anaphylaxis, and to assess the value of new diagnostic tests used for identifying the cause of anaphylaxis, .

METHODS: To determine the epidemiology we randomly picked out from the hospital information system 200 patients with anaphylaxis and determined the cause (insect stings, food, drugs, idiopathic and other); then we generalized those results. To find patients with IA we used search form idiop* anafilaks* in BIRPIS; we also looked through patients that had determined specific IgE for antigens commonly ordered in diagnostics of anaphylaxis and ImmunoCAP ISAC made. We performed a large specter of diagnostic tests for determining the cause of anaphylaxis (skin prick tests, sIgE for alpha-gal, omega-5-gliadin,chlorhexidine, and ImmunoCAP ISAC) and also differential diagnostic tests (measuring the enzyme activity of diamine oxidase and levels of chromogranin). Three patients who are treated with omalizumab because of IA were included in our survey. To assess the value of measuring sIgE for alpha-gal we checked all patients with anaphylaxis that had positive sIgE for alpha-gal and determine, how many actually had problems after eating red meat.

RESULTS: Among the patients, the highest percentage (63%) of anaphylactic reactions were due to insect stings and the lowest percentage (3,5%) due to IA. Among 41 patients with working diagnosis IA we were able to identify the cause for anaphylaxis for 9 patients. Most useful diagnostic tests were ImmunoCAP ISAC (diagnostic for 6 patients) and skin prick test (diagnostic for 4), determining the presence of sIgE for alpha-gal and omega-5-gliadin helped us with 2 patients (patients had more than 1 positive test). For 1 patient we were able to rule out anaphylaxis. We also evaluated the diagnostic use of sIgE for alpha-gal. Amongst 17 patients with present sIgE for alpha-gal, 10 patients had a known cause of anaphylaxis, 4 had anaphylaxis after eating red meat and for 3 patients the cause of anaphylaxis is still unknown (IA). Patients that were treated with omalizumab for half of a year, had no serious reaction since the beginning of the treatment.

CONCLUSIONS: With obtaining a complete patient history, routine examinations of the patients and new diagnostic tests, the percentage of patients with IA can fall because of identifying the cause of anaphylaxis. New diagnostic tests are a useful diagnostic tool. Monoclonal antibody omalizumab was identified as a successful drug for preventing recurrent anaphylactic events.

Pre-service teachers' opinion and knowledge on management of an allergic child

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BACKGROUND: Studies showed low preparedness for managing children at risk of anaphylaxis or children with food allergy in kindergartens and schools. The purpose of our study was to explore theoretical understandings of management of an allergic child among pre-service teachers.

SUBJECTS AND METHODS: 572 pre-service primary and lower secondary school teachers (7% male; 93% female; average age 21.5 (SD=2.7) years; 319 (56%) in the 1st year and 253 (44%) in the 4th (last) year of the undergraduate pre-service teacher education programs) participated in the study. 41.8% studied subjects with more science background. 15.6% studied for pre-school teachers (Group 1), 21.9% for subject teachers (Group 2), 33% for social pedagogy, special education or art teachers (Group 3) and 29.5% for primary school teachers (Group 4). 27.8% of students were allergic themselves. Participants answered Teachers' Health Competences Development–Allergy Questionnaire (THCDAQ) which comprised 14 attitude items on managing children's health issues and ten knowledge items on managing allergic disease of a child including prevention, recognition and management of anaphylaxis, asthma and food allergy.

RESULTS: Pre-service teachers showed positive attitudes towards learning more about different children's health issues. There was an average understanding of managing allergic diseases of a child (59.4%; SD=16.1% success) with no statistically significant difference regarding the duration of education, science background or students self-allergy. Females showed statistically significantly higher knowledge on management child's allergic disease (p=.008). Students in Group 3 reached lower scores on allergy knowledge items (M=55.6, SD=16.4) than Group 2 (M=63.3, SD=15.5) and Group 4 students (M=60.2, SD=15.6) (ANOVA, F (3,568)=6.4, p=.000).

CONCLUSION: Duration of education, science background or self-allergy had no impact on knowledge of allergic disease management of a child among pre-service teachers. All pre-service teachers should be exposed to specific educational programs that can develop adequate health competences.

POSTERS

Severe acute anemia - diffuse alveolar hemorrhage: Case Report

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INTRODUCTION: Anti-GBM antibody disease is rare disease with the incidence of 0.5-1 per million and represents a spectrum of diseases caused by circulating anti-GBM antibodies which affect the basal membranes of the alveoli and glomeruli. Typical symptoms are mild fever, fatigue and pallor, frequently as a result of sideropenic anemia. Respiratory symptoms are dyspnea and cough, which can rapidly progress to hemoptysis. With the use of modern diagnostic techniques the disease is rarely immuno-serologically not proven. That happens more often with younger men, smokers, with isolated pulmonary disability – hemorrhage.

CASE REPORT: 22-year-old smoker presented with fatigue, which progressed over last week before admission to hospital. Until then, he was healthy. 4 months before he had Hb 158g/L. Examination showed only pale skin and conjunctiva and some fine late inspiratory crackles. Lab tests showed severe microcytic, hypochromic anemia (Hb 49 g/L), hemolysis was excluded. Urine tests showed blood in urine (46x10^6, normal <7) only once during 5-week hospitalization. Sonography, gastroscopy and colonoscopy were negative. Chest X-ray and CT scan showed pronounced bronchovascular densities and interstitial thickening in the form of ground glass. Immunoserology was negative, with the exception of alpha 3 collagen IV specific anti-GBM antibodies, which have been discreetly positive with IIF but ELISA neg. → because ELISA is more reliable, we concluded that antiGBM were negative.
Immunofluorescence analysis of lung biopsy tissue showed linear IgG(++) and C1(+) deposits along the basal membrane of the alveoli → anti-GBM antibody disease.

TREATMENT: With Methylprednisolone and Endoxane. Almost a year after diagnosis the patient is still anti-GBM negative, taking prescribed therapy and is significantly better.

DISCUSSION AND CONCLUSION: Seronegative anti-GBM antibody disease occurs in 2-3% of cases. Inability to proof anti-GBM antibodies is most likely caused by technical limitations of used diagnostic methods. This is suggested by a discreetly positive IIF test in our patient and by data from the literature, where many seronegative patients with diffuse alveolar hemorrhage became anti-GBM positive later in the course of the disease.
Several similar cases remind us to suspect the anti-GBM antibody disease in case of unexplained diffuse alveolar hemorrhage despite the absence of anti-GBM antibodies in routine investigations. Therefore in patients with suspected alveolar hemorrhage bronchoscopy, bronchoalveolar lavage and transbronchial biopsy taking samples for the immunohistology must be performed.

Lymphangioleiomyomatosis: Case Report

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INTRODUCTION: Lymphangioleiomyomatosis (LAM) is a rare lung disease, which occurs sporadically or in association with the genetic disease tuberous sclerosis complex. LAM affects mostly premenopausal women with incidence of 1 in 400,000 adult females. Patients usually develop progressive dyspnoea and recurrent pneumothorax, chylous collections and occasional haemoptysis. Extra pulmonary lymphangioleiomyomas can result in abdominal and pelvic lymphatic obstructions. LAM is often associated with angiomyolipoma in the kidneys, and an increased frequency of meningioma.

CASE REPORT:
43-year-old female, non-smoker, was treated for 3 years due to progressive dyspnoea. For 2 years she was managed as an asthma patient unresponsive to inhalation therapy with progressive deterioration in obstruction as well as diffusion capacity. A few months ago, the breathing problems exacerbated. Lung function: VC 3470ml (85%), FEV1 1420ml (44%), Tiff. 42%, after the bronchodilator FEV1 increased by 40%.
HRCT lung reveals diffuse, very numerous, round, thin edge cysts ranging in size from few mm to about 2 cm in all slabs, causing a collapse of the parenchyma similar to emphysema. Disease is progressed. The image is characteristic of LAM.
Abdominal CT shows adenocystic structural changes by the pelvic vasculature and before the large blood vessels up to the left renal hilum (retroperitoneal cystic lymphangiomas?), and a slightly bulkier uterus (part of LAM?).
Sample from transbronchial biopsy of lung tissue captured lung parenchyma with small cystic spaces, surrounded with proliferated spindle cells with unimorph fascicular growth that are ER and HMB45 positive.
Desaturation to 82% after 6 min walk test. Normal heart ultrasound, no indirect signs of pulmonary hypertension.

TREATMENT:
Patient rejects suggested treatment with sirolimus (rapamycin). She is currently taking Foster NEXThaler 100µg /6µg two inhalations twice a day and Ventolin if necessary. Limitation of physical extertion was advised. She is in the process of disability retirement. She is regularly monitored in the pulmonary outpatient clinic. Evaluated as a potential candidate for a lung transplant.

DISCUSSION AND CONCLUSION:
Although great progress has been made in researching the disease, there is no cure for LAM. However, treatment with the drug sirolimus as well as everolimus may improve lung function in some women with LAM. For women with advanced lung disease, long term oxygen therapy is required. For very advanced stages of the disease, a lung transplant may be considered - it prolongs life expectancy but does not cure the disease.

Exercise induced bronchoconstriction or vocal cord dysfunction in elite competitive swimmer

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OBJECTIVE: Exercise induced bronchoconstriction (EIB) is defined as reversible narrowing of distal airways that follows vigorous exercise in the presence or absence of clinically recognised asthma. The mechanisms responsible for epithelial damage and EIB in swimmers remain incompletely understood. The increased oxidative stress observed in swimmers airways and reduced antioxidant capacity may promote the release of inflammatory mediators and sensitisation of airway smooth muscle, contributing to the development of EIB in swimmers.

STUDY DESIGN: A case report.

SUBJECTS: A 28 years old competitive elite female swimmer, participant of three Olympic games, started to have first respiratory symptoms after A cut qualification for Olympics in 2016. Swimmer was for many years regularly checked at Clinic Golnik. Clinically and functionally recognised asthma was treated with inhaled corticosteroid. Allergic rhinitis with hypersensitivity to the house dust mite, nasal eosinophilia, gastritis and gastroesophageal reflux were clinically proven and treated. Echocardiography of several perforated atrial septum was performed and demonstrated clinically not significant.

CLINICAL PROBLEM: Difficulties began in October 2015 during altitude training. Shortness of breath during exercise with coexisting feeling that the air cannot be fully inhaled was observed. Clinical investigation followed by laboratory tests, pulmonary function, echocardiography, exercise challenge test, PEF measurements in the pool during training and competition and gastroscopy didn't explain the symptoms. Therapy with inhaled corticosteroids, long-acting sympathicomimetic, short-acting sympathicomimetic, gastritis and gastroesophageal reflux was received. Despite the therapy, symptoms persisted.

RESULTS: In February 2016 stress testing was carried out with simultaneous videolaringoskopy. Dysfunction of the vocal cords movement was demonstrated during exercise. After introducing appropriate foniatric therapy, shortness of breath no longer persisted and preparations for the Olympic games continued.

CONCLUSIONS: In athletes with difficult to control asthma or unexplained shortness of breath during exercise, attention has to be devoted to identifying asthma confounders and coexisting conditions such as exercise-induced glottic or supraglottic laryngeal obstruction, including vocal cord dysfunction, a paradoxical closure of vocal cords during inspiration.

Clinical and microbiological characteristics of patients with non-cystic fibrosis bronchiectasis

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BACKGROUND: Despite bronchiectasis not being a rare disease, it seems to be a neglected pathology within pneumology. Project EMBARC (European Multicentre Audit and Research Collaboration), founded by European Respiratory Society, is a European prospective observational study, which deals with clinical, microbiological, radiologic and functional data about patients with bronchiectasis (patients with cystic fibrosis excluded), with the goal of encouraging research and international scientific collaboration in this field. We entered the project along with 20 other countries. The aim of our study was to focus on clinical characteristics and microbiological analysis of sputum and their correlation in adult patients with non-cf bronchiectasis in Slovenia. We hypothesized that our subjects will present with airflow obstruction and that lower FEV1 results will be associated with more symptoms and increased sputum production. We also anticipated that the presence of *P. aeruginosa* will correlate with decreased lung function and higher frequency of hospitalizations.

METHODS: This retrospective study was conducted on a sample of 152 patients with non-cf bronchiectasis, who were examined between 27.5.2014 and 29.7.2015 at Golnik University Clinic. The data was entered into the EMBARC register and statistically analysed.

RESULTS: The median age of patients was 67 years, of which 51 % were male and 49 % female. They produced median daily sputum of 5 ml and had a median FEV1 of 1,805 L (74%) and median FVC of 3,317 L (102%). We saw statistically significant correlation ($p < 0,001$) between FEV1 and dyspnoea. The analysis of correlation between FEV1 and sputum volume ($p = 0,7$) and dyspnoea and sputum volume ($p = 0,56$) was not statistically significant. Lung function of patients colonized with *P. aeruginosa* was lower (FEV1 = 57 %, $p = 0,012$) (FVC = 91,7 %, $p = 0,019$) compared to uncolonized patients. The median of hospitalizations in colonized patients in one year was 1 compared to uncolonized patients with 0 hospitalizations ($p = 0,276$).

CONCLUSIONS: Subjects with the median age of 67 years, produced 5 ml of sputum daily (median). Lung function showed mild obstruction. Lower FEV1 significantly correlated with increased levels of dyspnoea, however not with increasing volume of sputum. We proved significantly worse lung function in patients colonised with *P. aeruginosa* compared to uncolonized patients. There was also a trend observed toward more frequent hospitalisations in colonized patients, but the difference did not reach statistical significance.

Bronchiectasis and asthma: Case Report

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Patient presentation: 61 yr female, ex-smoker 15 pack years (quitted 30 years ago) treated for asthma > 15 years. Nasal polyposis (surgery 2005). Bilateral bronchiectasis (CT 2009, 2015), P. aeruginosa colonization; obestity hypoventilation syndrome- NIV (bipap) and oxygen treatment. Other diseases: fibrothorax dex (post empyema treatment 2009), kyphosis, obesity (BMI 38) , arterial hypertension. Aspirin allergy
Lung function: FVC 2070 (64%), FEV1 970 (38%), TI 47%, Bronchodilatatory test: FVC 2210 (68%), FEV1 1040 (41%), TI 47%, DICO 61%, VA 2650 (55%), KCO 1,75 (112%)-
Heart US: diastolic dysfunction, normal systolic function
For the last 8 years: 3-4 hospitalisations a year due to respiratory failure, atributed to worsening of multiple diseases she is supposed to have.
Treated with oxygen, bronchodilators, corticosteroids, antibiotics and diuretics. Short time improvements.
In 2014 she was diagnosed with OHS due to persistent hypoxemia with hypercapnia. Bipap and therapy with supplemental oxygen was introduced. Patient mostly did not use noninvasive ventilation due to intensive persistent productive cough.
2016: ICU treatment: mechanical ventilation due to P. aeruginosa exacerbation with hypercapnic respiratory failure. Improvement following antibiotic and bronchodilation treatment was slow.
In depth review of patient history and additional diagnostic tests were done: specific IgE for A. fumigatus 5,63 (normal value <0,35), specific IgG for aspergilus f, thermoactynomyces, micropolyspora and candida albicans were normal, total igE 452 (after glucocorticoid treatment), no present eosinophilia but several recordings of eosinophilia up to 13% (0,76 10>9/l) in the past.
CT thorax: central bronchiectasis, thickened bronchial walls, mucoid impaction, middle lobe atelectasis. Expert radiologist opinion: ABPA.
Intensive respiratory physiotherapy with cough assistance and glucocorticoid treatment led to marked improvement. She was successfully weaned of mechanical ventilation. Additionally she was treated with voriconazole.

Discussion: Allergic bronchopulmonary aspregilosis (ABPA) is an IgE mediated hypersensitivity response to *A. fumigatus* colonization of the tracheobronchial tree. It presents as asthma-like exacerbations and possibly leads to irreparable lung damage – bronchiectasis and fibrosis.
We believe patient presented in this case has ABPA despite the fact she does not meet all the inclusion criteria. Comorbidities- fibrothorax and obesity additionally worsen her clinical condition.
We believe bronchial clearance and standard therapy for ABPA is the cornerstone treatment for this patient. Due to colonisation with P. aeruginosa and repeated exacerbations inhalatory antipseudomonal antibiotic would be of a beneficial value.
Noninvasive ventilation might be contraindicated due to impaired bronchial clearance.

Case Report: asthma with caustic injuries of the airways

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PREFACE: Asthma is one of the commonest diseases of the respiratory system. It manifests as dyspnea, cough and feeling of tightness in the chest. The fundamental investigations to differentiate it from other lung diseases are pulmonary function tests. The reversibility of obstruction is distinctive of asthma.

CASE REPORT: A 25-year-old nonsmoking man was admitted to Clinic Golnik for the first time for supposed deterioration of asthma during an influenza infection. He has been receiving treatment for asthma for years, but it wasn't clear whether his asthma has been properly diagnosed or not. Apart from asthma his history was also significant for aspirating iron sulfate when he was 6 months old. This fact rose suspicion, whether his past diagnosis of asthma was correct. Spirometry at that time showed a large component of fixed obstruction with post-bronchodilator FEV1 of 4,0l (65% of norm) and FEV1/FVC ratio of 62%. HRCT imaging showed entrapment of air in exhalation with mediastinal shift to the left and obstruction of large airways of the right lung as a result of caustic injuries. The patient underwent bronchoplasty of the right main bronchus, after which the pre-bronchodilator FEV1/FVC ratio rose to 69%, which is 10% more than the previous best measure.
After the procedure the respiratory difficulties had improved and the patient reduced the use of bronchodilator. The metacholine test was negative and exhaled NO measured 36ppb.
A sample of mucosa of the left main bronchus taken at bronchoscopy showed chronic eosinophilic inflammation. We concluded that the patient has asthma. He was given low doses of inhalatory corticosteroids for use at home. In the follow-up time of one year there were no deteriorations of respiratory difficulties.
During the course of diagnostic testing and preoperative management, the patient had to be hospitalized for 3 respiratory infections, which had a prolonged course.

DISCUSSION: Apart from asthma, the patient also had a component of fixed obstruction because of scarring after the caustic injury. The injury prevented cleansing of bronchial secretions, it caused inflammation distally and it probably triggered worsening of asthma. The spirometry findings are a consequence of both diseases. After the bronchoplasty the patient's respiratory difficulties improved.

CONCLUSION: Airway obstruction can be caused by a variety of diseases. A correctable cause of obstruction should be excluded, especially if there were airway injuries in the past.

Prevalence of multidrug resistant Gram-negative bacteria in tertiary hospital care during 5-year period

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BACKGROUND: Infections caused by multidrug resistant Gram-negative bacteria are difficult to treat and are mayor cause of health-care and community-acquired infections. Resistance to β-lactam antibiotics in Gram-negative bacteria is rapidly increasing worldwide. The rapid global spread of MDR Gram-negative bacteria has been facilitated by mobile genetic elements harbouring genes, which are encoding extended-spectrum β-lactamases (ESBLs) and carbapenemases. Aim of our study was to determine trends in prevalence of MDR Gram-negative bacteria in 5-year period in University Clinic Golnik.

METHODS: This retrospective study, covering the period from January 1st, 2011 to November 15th, 2015, was carried out in tertiary hospital University Clinic Golnik. Clinical samples were collected from hospital wards and ICU. Isolates of the most frequent five Gram-negative bacteria were chosen for analysis, in total 4615 bacterial isolates. Antimicrobial susceptibility testing was performed using the disc diffusion method following the guidelines of Clinical and Laboratory Standards Institute. All isolates that were resistant to three or more distinct groups of antibiotics were defined as MDR. All antibiotics evaluated in our study were routinely tested in Laboratory for Respiratory Microbiology in University Clinic Golnik.

RESULTS: Out of 4615 isolates, 2428 of them were identified as *Escherichia* coli, 1044 as *Pseudomonas aeruginosa*, 710 as *Klebsiella pneumoniae*, 318 as *Enterobacter spp.* and 115 as *Acintobacter spp.* The most common isolate was *E. coli.* There was a progressive increase of MDR *E. coli* isolates from 22,2% in the first year of the study to 34,5% in the last year of the study. *P. aeruginosa*, the second most common bacteria isolated during the study, showed no significant change in frequency of MDR isolates, which was 3,2% during study period. On analysing *K. pneumoniae* isolates, there was no significant change of MDR isolates. Frequency of MDR isolates during the study was 47,8% with the highest percentage 57,9% in year 2012. Frequency of MDR *Enterobacter spp.* isolates remained relatively stable and was 12,0% during the study period. There was a significant increase of MDR *Acinetobacter spp.* isolates from 12,5% in the first year of the study to 52,2% in the last year of the study.

CONCLUSION: In this study, we observed slight increase in prevalence of MDR *E. coli* and significant increase in prevalence of MDR *Acinetobacter spp*. In prevalence of MDR isolates of *Enterobacter spp.*, *P. aeruginosa* and *K. pneumoniae* we observed no significant change during study period. Data presented in our study confirm the worldwide trend of increasing multidrug resistance in some Gram-negative bacteria.

MRSA and ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*: A five-year retrospective study in a tertiary care, teaching hospital

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BACKGROUND: Methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamases (ESBL) in *Enterobacteriaceae continue* to be a major challenge in clinical setups worldwide. Knowledge about their prevalence is essential to guide towards appropriate antibiotic treatment. The aim of our retrospective analysis was to evaluate the prevalence of MRSA and ESBL-producing strains of *Escherichia coli (E. coli)* and *Klebsiella pneumoniae (K. pneumoniae)* at University Clinic of Respiratory and Allergic Diseases Golnik (UCRAD).

METHODS: In the Laboratory for Respiratory Microbiology at UCRAD Golnik a total of 5514 *S. aureus* isolates and 3138 isolates comprising *E. coli* (n=2428) and *K. pneumoniae* (n=710) were recovered from various clinical samples over a five-year period from January 2011 to November 2015. Antimicrobial susceptibility testing of the isolates was performed by the standard disc diffusion method, along with screening for MRSA and ESBL production by screening tests.

RESULTS: MRSA comprised 10.1% (556) of all *S. aureus* isolates (5514). During the five-year period prevalence of MRSA was slightly fluctuating from 9.0% in 2011, 10.0% in 2012, 7.8% in 2013, 10.6% in 2014 to 15.2% in 2015.
Out of 3138 isolates of *E. coli* and *K. pneumoniae* screened for ESBL production, 1055 (33.6%) were found to be ESBL-producers. Among 2428 *E. coli* isolates 697 (28.7%) were ESBL-positive, while ESBL-producing *K. pneumoniae* occured in 358 (50.4%) of 710 isolates. The frequency of ESBL-positive *E. coli* was steadily increasing in a five-year period from 22.2% in 2011 to 34.8% in 2015, while in *K. pneumoniae* isolates no such trend was seen. The percentage of ESBL-positive *K. pneumoniae* peaked in 2012 to 57.9% followed by a substantial decline in 2014 to 31.8% and an increase to 43.3% in the last year.

CONCLUSION: In conclusion, the data show that during the five-year period from 2011 till 2015 the percentage of MRSA was fluctuating, with the lowest prevalence in 2013 (7.8%) and the highest in the last year (15.2%). Among ESBL-producing strains of *E. coli* and *K. pneumoniae* we observed fluctuation of ESBL-positive *K. pneumoniae* isolates, but the prevalence of ESBL-producing strains of *E. coli* was slowly rising from year to year. Nevertheless MRSA and ESBL-producing strains pose a serious problem and should be identified quickly so that the appropriate antibiotic usage and infection control measures can be implemented to prevent the spread of these strains.

Microbiological findings of broncholavage speciment in chronic mucopurulent bronchitis

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BACKGROUND: Chronic bronchitis is largely a long life disease. The quality of life is decreased for those who suffer from chronic bronchitis. The principal symptom of bronchitis is a prolonged cough. A prolonged cough with or without expectoration is often a suggestion to do a bronchoscopy, which can lead to a proper diagnosis of chronic bronchitis. The aim of this study is to analyze microbiological findings of broncholavage specimens of bronchoscopy.

METHODS: Microbiological findings of broncholavate specimen were analyzed in a time frame of one year. Indications for bronchoscopy, diagnoses obtained by bronchoscopy, and in vitro efficacy of antibiotics were analyzed. Concomitant bronchoscopic diagnoses were analyzed, as well comparing the validity of bronchoscopy with other diagnostic procedures.

RESULTS: In a one year period, 546 bronchoscopic procedures were performed. 78 (27 female and 51 male, mean age 61,65±14,21years) cases were diagnosed with chronic mucopurulent bronchitis. In the broncholavage specimens of 6 cases, positive bacterial culture were found (Pseudomonas aeruginosa 2 cases, Staphylococcus aureus 2 cases, Acynetobacter 1 case and Klebsiella 1 case). In 11 of 546, saprophyte flora was found. In 5 cases, Candida albicans was found. Due to the diagnosed disease, bronchitis was not a great sign to do a bronchoscopy. Other diseases were identified: TB was present in 8 cases, pulmonary abscess in 2 cases, bronchial carcinoma in 5 cases, TB of hilar lymph nodes in 1 case, specific pleuritis in 3 cases, 4 cases of pneumonia. The bacterial findings were sensitive to antibiotic treatment while in hospital care. Endoscopic pictures have also overlapped with catharal bronchitis and inhalations of steroids were recommended.

CONCLUSION: Chronic bronchitis, of any type, is not a positive indicator to preform a bronchoscopy. Diagnoses of chronic mucopurulent bronchitis, and vital information such as microbial findings and concomitant diseases, are very common findings in doing bronchoscopies.

Temporary hypoferremia in patients with community-acquired pneumonia

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Transferrin is main negative acute phase protein. The mechanisms by which transferrin and serum iron concentration decreased during the infection are multifactorial.

The prospective study included 129 patients (52 female, 77 male) with simple Community-acquired pneumonia (CAP) (mean age 64,8 ± 13.3 years), hospitalized from april 2014 to april 2016 y. The aim of the study was to calculate correlation of CRP, serum iron and transferrin during the antibiotic treatment of CAP. The patients did not use the supplementary iron therapy. We measured the C-reactive protein (CRP), serum iron, total iron binding capacity (TIBC), and calculated transferrin (Trf (g/l) = TIBC (μmol/l) / 25,1 (μmol/g)). Blood samples were analyzed on the 1. day (group I) and after 5-7 days of hospitalization (group II).

CRP (140.24 ± 103.36 mg/L) showed decrease in group II (74.96±69.09 mg/L) ($p<0.001$). Transferrin was higher in group II (1.294±0.258 vs. 1.567±0.273 g/L) ($p<0.01$). Serum iron increase in group II (4.89±3.23 vs. 10.04 ± 4.6 μmol/L) ($p<0.001$). Serum iron showed negative linear correlation with CRP ($r=-0,525$; $p<0.01$) and positive correlation with transferrin ($r =+0.533$; $p<0.01$). Serum CRP falls rapidly in group II, while transferrin and serum iron were increased.
Iron deficiency is common in patients with CAP. It positively correlates with transferrin, and negatively with CRP. The inflammatory response associated with infection shifts iron from the circulation into storage. Iron supplementation during CAP is unnecessary.

Keywords: serum iron, community acquired pneumonia, hypoferremia

Mortality of tuberculosis patients in Slovenia between 2005 and 2015

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BACKGROUND: Worldwide, tuberculosis (TB) remains one of the most lethal infectious diseases. In 2014, 1.5 million people died of it. TB is also one of the main causes of high mortality in developing countries, where lethality of this disease is extremely high. On the other hand, in developed countries the mortality of TB patients is low. However it is higher in groups of elderly, comorbid patients and those infected with resistant bacteria.
In this study, we were interested in mortality of TB patients in Slovenia in period from 2005 to 2015, the rate of TB related death (TB as main cause od death), the rate of non-TB related death (co-morbidity as main cause od death) and the most common co-morbidity which caused death. We were also interested in discovering how many deceased patients with tuberculosis began the treatment with anti-tuberculosis medications and in how many the diagnosis was determined post-mortem.

METHODS: We performed a retrograde analysis of data from TB patients registered in Registry of Tuberculosis in the period 2005 – 2015. To identify other diseases as a cause of death we considered International Classification of Diseases.

RESULTS: 2016 new TB patients were registered in Slovenia in the period 2005 – 2015. From these, 14% died (6 % male, 9 % female). The average age at death was 73 years (68years male, 77years female).
Among all deaths, 35 % were TB related (34 % male, 36 % female). The average age was 71 years (67years male, 74years female).
The rest 65 % of deceased died due to other disease (non-TB related death), most commonly due to cardio-vascular diseases (30 %), other respiratory diseases (14 %) and malignancy (14 %).
Most of TB patients with ante-mortem diagnosed disease began treatment with anti-tuberculosis medications (99 %). In only 37 % of deceased the diagnosis was made post-mortem.

CONCLUSION: Mortality of TB patients in Slovenia is comparable with other developed European countries. Rate of non-TB related death is increasing in these countries. The main cause is aging of population and increasing prevalence of co-morbidities.
Among all co-morbidities cardio-vascular diseases overwhelm as main cause of death. Mortality of TB patients is higher for females than males, due to longer life expectancy of females. Furthermore TB appears later in females than in males, therefore clinical picture of disease is less significant and immune response less active.
As expected the proportion of deaths with ante-mortem diagnosis is higher than post-mortem.

Analysis of clinical isolates of Nontuberculous Mycobacteria (M. intracellulare and M. abscessus)

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BACKGROUND: Nontuberculous mycobacteria (NTM) are ubiquitous opportunistic pathogens that can cause pulmonary disease among immunocompromised (especially with cystic fibrosis patients (CF)) as well as immunocompetent patients. Two important groups belong to NTM: MAC (Mycobacterium avium complex) and MABSC (Mycobacterium abscessus complex). Taxonomy among these groups is rapidly changing due to development of better molecular methods. Our partly prospective and partly retrospective study was done with purpose to answer on two questions: (i) how many isolates that belonged to M. intracellulare now belong to new species M. chimaera; (ii)which of 3 new subspecies of M. abscessus is predominant among Slovenian isolates and which subspecies is the most frequently isolated from respiratory tract of Slovenian patients with CF.

METHODS: Our molecular genetic analysis was performed on 131 clinical isolates of NTM (128 patients) from Slovenian National NTM Collection Golnik. Twenty-seven M. abscessus and 99 M. intracellulare isolates, which were obtained in our lab from January 2007 till August 2016 were analyzed. Amplification and line-probe hybridization method (GenoType Mycobacterium NTM-DR, Hain Lifescience, Nehren, Germany) divided M. abscessus into three subspecies: M. abscessus subsp. abscessus, M. abscessus subsp. massiliense, M. abscessus subsp. bolletii) and assigned isolates that before belonged to M. intracellulare to M. chimaera.

RESULTS: In total of 27 isolates of M. abscessus, 20 (74%) were identified as M. abscessus subsp. abscessus, 3 (11%) belonged to M. abscessus subsp. massiliense and 4 (15%) isolates belonged to M. abscessus subsp. bolletii. At least 7 of MABSC isolates were found as clinically important and 6 of them belonged to M. abscessus subsp. abscessus. In total of 97 M. intracellulare isolates, 46 (47%) were assigned to M. chimaera. Among M. intracellulare/ M. chimaera at least 20 isolates were clinically important and 15 of them belonged to M. intracellulare. Furthermore, 7 NTM isolates were recovered from 6 patients with CF where 4 isolates were identified as M. abscessus subsp. abscessus and 3 as M. chimaera.

CONCLUSION: Our results show that most of the Slovenian isolates of M. abscessus group belong to M. abscessus subsp. absecessus and it was also predominant mycobacteria isolated among patients with cystic fibrosis. M. intracellulare is in our country more frequent as M. chimaera and probably also more virulent since 75% of isolates were clinically relevant. Meanwhile at CF patients 3 isolates of M. chimaera were isolated and no M. intacellulare was detected.

Recombinant IgE and BAT AUC ratio based diagnostic algorithm distinguishes between bee and wasp allergy

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BACKGROUND: Diagnosis of insect sting allergy is often difficult. We aimed to establish better in-vitro diagnostic algorithms for identification of the disease-causing insect.

METHOD: Hundred and seventy-seven consecutive sting allergic patients were included. Testing for sIgE to venoms and SSMA (rApi m1 and rVes v5) and the BAT were performed for each participant; the majority was also tested with skin tests.

RESULTS: One hundred and thirty-three patients with unequivocal culprit history were analysed. In the case of venom sIgE single positivity (sIgE+/-; n=73), the agreement between different test results and culprit histories was excellent (90%-96%).

In the venom double positive group (sIgE+/+; n=56), we constructed diagnostic algorithms that relied on the ratio of bee/wasp SSMA and/or BAT area under the curve (AUC) test pair results. All of the algorithms outperformed the standard cut-off tests when used separately or stepwise. The best algorithm was the SSMA and BAT AUC algorithm, which correctly diagnosed more than 80% of patients in comparison to the diagnostic approaches that used standard cut-offs (50% BAT-only/SSMA-only; 60% stepwise). The significant improvement was confirmed with ROC curve analyses.
In the venom double negative (sIgE-/-; n=4) group, sensitization was confirmed in all patients with the BAT but in only 1 patient with SSMA-antibodies.

CONCLUSION: We established a novel ratio based diagnostic approach that significantly enhanced diagnostic accuracy, raising it to more than 80% of correctly diagnosed Hymenoptera venom allergic patients (compared to only 50% with the standard [SSMA or BAT] approaches) in a diagnostically challenging venom double positive group.

Global transcriptome profiling during acute anaphylactic reaction reveals involvement of complex networks of signaling, interactions and recruitment of distinct immune cell types

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Anaphylaxis is a severe, systemic, life-threatening allergic reaction that occurs with rapid onset affecting multiple organs, and is difficult to predict, diagnose, and treat. It mainly involves the activation of mast cells and/or basophils, followed by the release of mediators of anaphylaxis. To better characterize the mechanisms leading to potentially lethal events, analysis of global transcriptional alterations in peripheral blood samples of patients during acute anaphylaxis was performed.

We performed RNAseq based characterization of human transcriptome on total RNA population in whole blood samples of 15 patients with acute allergic reaction. The sampling points were at the time of presentation to the emergency department followed by sampling 7 days and 1 month after the anaphylactic episode. We performed extensive characterization of differential gene expression, cell-specific transcriptional alterations, analysis of alternative splicing patterns in anaphylaxis and functional characterization of detected alterations.

Whole transcriptome expression analysis revealed striking alterations of gene expression during acute anaphylaxis in comparison to 7 days and 1 month after the episode reflecting cellular and subcellular mechanisms taking place during acute anaphylaxis, most notably in categories of cellular movement, cell-to-cell signaling, interaction and immune cell trafficking as well as inflammatory response. Furthermore, when comparing the transcriptional differences during acute anaphylaxis with expression signatures of peripheral immune cells, significant under-expression of basophil and/or mast cell signatures and over-expression of eosinophil and neutrophil signatures were detected.

This finding improve our understanding of biological mechanisms underlying anaphylaxis, since our data suggests that complex networks of signaling, interactions and recruitment of several different immune cells lead to the development of this life-threatening allergic reaction.

Hypersensitivity to analgetics: 10 years Golnik experience

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BACKGROUND: Analgesics are the second most common cause of drug-induced hypersensitivity reactions. Diagnosis of NSAID hypersensitivity relies on patient's medical history and oral provocation tests (OPT). Basophil activation test (BAT) is thus far unverified and not used in everyday clinical practice. Aim. Finding out the ratio between five types of NSAID hypersensitivity; checking the diagnostics procedure of NSAID hypersensitivity; finding out whether BAT test gives different results in hypersensitivity to COX-1 inhibitors and in selective-type NSAID-induced hypersensitivity.

METHODS: We selected patients from the hospital informational system, which had taken OPT test between 2004 and 2015. All with a positive OPT and those with a convincing history of NSAID hypersensitivity were classified in five types of hypersensitivity. 50 patients with positive OPT or immediate hypersensitivity reactions to a single NSAID had BAT test performed.

RESULTS: We selected 1842 patients (1271 women). 198 (7,1%) had positive OPT. 851 OPT were performed with aspirin. 708 patients had aspirin hypersensitivity in their medical history, 86 out of 449 provocations were positive. 549 patients had paracetamol hypersensitivity in their medical history, 28 had positive OPT with paracetamol. Ratio between five classes of NSAID hypersensitivity: NSAIDs exacerbated respiratory disease 10,9%; NSAIDs exacerbated cutaneous disease 10,7%; NSAIDs induced urticarial-angioedema 30,8%; single NSAID-induced urticarial/angioedema/anaphylaxis 46,5% (55,5% diclofenac, 29,8% pyrazolone); NSAIDs-induced delayed hypersensitivity reactions 1,3%. 8 out of 77 patients with positive OPT, which had used other analgesics after their test, had another positive reaction. 114 patients had done BAT test, all with aspirin. The results between those with NSAID hypersensitivity and the healthy people did not statistically different ($p<0,05$).

CONCLUSIONS: Single NSAID-induced urticaria/angioedema or anaphylaxis is the most common type of NSAID hypersensitivity. Only 25,7% of patients had completed diagnostic procedure and were applicable for classification in phenotypes. Patients with a convincing history of NSAID hypersensitivity rarely take OPT test to prove hypersensitivity. BAT test was of no diagnostic use.

Schnitzler's syndrome: autoinflammatory disease presenting as chronic urticaria-two case reports

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INTRODUCTION: Chronic urticaria is a skin disease characterised by wheals and angioedema lasting more than 6 weeks. Reported prevalence in the European population is 0.5-1%. Wheal-like skin changes can occur in other diseases, which must be differentiated from chronic urticaria: autoimmune connective tissue disorders, urticarial vasculitis, autoinflammatory diseases, and other rare causes.
CASE REPORTS: Both patients were referred for suspected chronic urticaria. They reported periodic onset of slightly itchy generalised wheals that disappeared within 24 hours, accompanied by systemic symptoms: myalgia, arthralgia with joint stiffness, malaise. Both patients reported unsatisfactory response to antihistamine medication and a need for chronic intermittent steroid treatment. The diagnostic process revealed elevated markers of inflammation (CRP, SR) and an elevated total protein count. Based on the clinical manifestation and laboratory findings we suspected an autoinflammatory disease. Specific laboratory tests excluded autoimmune connective tissue disorders, autoimmune thyroiditis, chronic infections, and urticarial vasculitis. We identified monoclonal gammopathy. Both patients met the criteria for Schnitzler's syndrome and are on the anti-IL-1 anakinra treatment practically asymptomatic.
DISCUSSION: Schnitzler's syndrome is a rare autoinflammatory disease (150 described cases). It is characterised by recurrent wheals in combination with signs and symptoms of systemic inflammation and monoclonal IgM/IgG gammopathy in serum. The frequency of symptoms among patients varies from days to years. It typically manifest at the age of 50. Spontaneous remission is rare. Diagnosis is made years or decades after initial symptoms due to rarity and limited awareness. Long-term complications include secondary amyloidosis and lymphoproliferative disorders (most often Waldenstrom's macroglobulinemia). Pathogenesis is still unknown but assumed to be linked to overactive IL-1. At present, there are no guidelines on a standard therapy, but case reports show successful treatment with anti-IL-1 therapies, with complete remission of symptoms in the majority of cases. Anakinra is a recombinant competitive antagonist of receptor for IL-1, inhibiting the inflammatory cascade by binding. Major side effects include neutropenia with associated serious infections and thrombocytopenia; therefore, regular differential blood count should be performed.
CONCLUSION: Autoinflammatory diseases are a rare but important differential diagnosis of chronic urticaria. It is important to consider autoinflammatory diseases in patients with a periodical onset of wheals with unsatisfactory antihistamine therapy, accompanied by signs and symptoms of systemic inflammation, myalgia, arthralgia, joint stiffness, malaise, lymphadenopathy, mouth ulcers, gastrointestinal symptoms, or neurologic symptoms. Laboratory findings reveal elevated markers of inflammation, monoclonal gammopathy, proteinuria, elevated SAA. Due to their rarity, chronic urticaria and autoinflammatory diseases are best handled in specialised centres.

Efficacy of wasp venom immunotherapy in hornet venom-allergic patients

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BACKGROUND: Venom immunotherapy is a successful way of treating patients who have developed systemic IgE-mediated reaction to hymenoptera sting. Not only are the wasp stings much more common in our environment than hornet stings, but it is also known that there is cross reactivity between wasp and hornet venom. Therefore, the patients with a systemic IgE-mediated reaction after hornet sting are usually treated with a wasp VIT. In our working hypothesis we assumed that the patients, who had experienced anaphylactic reaction after hornet sting, can be successfully treated with wasp VIT. As a result, their immune system develops tolerance to hornet venom.

METHODS: Our research is based on an observational cohort clinical study with retrospective collection of data. It was conducted with the help of 202 patients who have developed a severe anaphylactic reaction after hornet sting and were treated with wasp VIT in Hospital Golnik between January 1st 1996 and December 31st 2005. Data about the patients was collected with Birpis information system of Hospital Golnik and Slovenian telephone directory database. We conducted a survey with the patients who have been treated with VIT and were possibly stung by a wasp or hornet after the treatment. The data we had collected was then processed with the help of a computer.

RESULTS: Out of 202 patients that were taken into consideration, 130 of them provided their answers for the survey. After having finished the VIT treatment, 94 patients have been stung by a wasp and/or a hornet. Also, wasp stings were much more common than hornet stings. After having been stung by a wasp or a hornet, 17 patients have anaphylactic reaction and 11 of them were large local reactions. 6 (6,4%) patients have developed systemic hypersensitivity reaction, which means that immune tolerance has not been achieved. All except two patients that have developed an anaphylactic reaction to insect stings after having been treated with VIT, reported eased symptoms of a reaction. The other two patients reported a similar reaction to the one before the VIT treatment.

CONCLUSIONS: According to the results, we can say that wasp VIT treatment is a successful way of treating the patients who are sensitized to the venom of a hornet. Our working hypothesis is therefore confirmed.

Patient knowledge of correct self-administration of adrenalin auto-injector after hymenoptera venom anaphylaxis

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BACKGROUND: Correct self-administration of adrenalin is crucial in the management of possible repeated anaphylaxis. Several reports have shown the lack of patient's knowledge about the use of auto-injectors. With this study we wanted to assess the influence of education by different health care workers on the knowledge of self-administration and proper performance of self-administration of auto-injectors.

METHODS: 63 patients with a history of anaphylaxis after hymenoptera sting were included in the study. In the first group 32 patients had regular contact with health care workers at specialized allergy center because they were receiving venom immunotherapy. In the second group 31 patients that were not treated with immunotherapy were included. Questionnaire to assess patients' knowledge of correct administration of auto injectors was used. Correct administration was checked with supervised self-administration of placebo auto-injector. Checklist was used to rate the self-administration.

RESULTS: Patients that were treated with immunotherapy had better knowledge of correct indications for auto injector use ($p<0,01$) but there were no significant difference in knowledge of correct site of administration. Patients trained by specialized allergy nurse or doctor also had better knowledge of correct indication for auto injector use, compared to patients trained in the pharmacy ($p<0,01$). But supervised self-administrations of placebo auto-injectors weren't more accurate in patients with frequent contact with healthcare workers compared with the control group ($p=0,124$).

CONCLUSIONS: Although patients that were educated about adrenalin auto injector use by specialised allergy nurse or doctor and had frequent contact with health care workers at specialized allergy centre had better knowledge of correct place and timing of auto injector use, the demonstration of use with placebo auto injector was not better.

Primary pulmonary hypertension: a two year observation: Case Report

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BACKGROUND: Primary pulmonary hypertension is a gradual increase in pulmonary artery pressure. The etiology of this disorder is still unknown, but recent studies have shown that the possible cause may be a dysfunction of pulmonary vascular endothelium. This disease usually affects young and healthy people, and is twice as common in women versus men. Up to date, there is no casual treatment. One year survival rate in untreated patients is 68%, dropping to 34% for a five year survival rate.

CASE PRESENTATION: Patient O.E., 27 years old, contacts a doctor because of progressive fatigue intolerance, NYHA II/III. Problems started approximately 2 years ago, fatigue gradually increasing from high effort activity to all activity. A month before contacting the doctor, patient's exhaustion was significant. The patient is a smoker, smoking approximately 10 cigarettes a day. Family history and physical examination suggests no notable history of disease. In addition to the usual diagnostic tests (EKG, RTG p/c; laboratory tests), specific pulmonary and cardiac tests were performed.
The Echocardiography shows an increase in right cavity volumes and an increase in pulmonary artery pressure, measured at tricuspid regurgitation with a value of 75 mmHg. CT angiography of pulmonary arteries shows no signs of intraluminal thrombotic masses, with dilatation of truncus pulmonalis (3.8 cm), right pulmonary artery (3.03 cm) and left pulmonary artery (2.74 cm). Immunology exams (ANCA, ANA etc.), spirometry, coronary necrosis markers, Deep-dimer were all within normal values. Right heart catheterization confirmed an increase in pulmonary artery pressure, measuring at 85/35 mmHg, with normal values for PCWP (9/3 mmHg). Considering all findings primary pulmonary hypertension is suspected.
A drug treatment was started, including calcium channel blockers, sildenafil, diuretics, oral anticoagulants, and mobile home oxygenation. Regular check-ups were performed during the two years treatment. During the check-ups, there have not been any signs of deterioration only fatigue intolerance persisted.
The patient has had regular check-ups regarding echocardiography, which has not shown any significant changes related to the original condition. The calculated RVSP is about 75 mmHg. Control of CT angiography of pulmonary artery: truncus pulmonalis (3.9 cm), right pulmonary artery (3.0 cm), and left pulmonary artery (2.8 cm), which represents almost identical values compared to two years ago.

CONCLUSION: Adequate treatment (medicaments, oxygenation every day, adherence to doctor's guidelines) can significantly slow down the progression of primary pulmonary hypertension.
Keywords: primary pulmonary hypertension, echocardiograpy

Paliativna oskrba neozdravljivo bolnih na intenzivnem oddelku

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Intenzivne enote predstavljajo visokotehnološko okolje, ki je v prvi vrsti namenjeno zdravljenju kritično bolnih. Zaradi izrednega razvoja medicine je populacija bolnikov, ki se zdravi v intenzivnih enotah, čedalje starejša in ima številne pridružene bolezni, kar ima za posledico, da se v intenzivnih enotah obravnava čedalje več bolnikov s slabo napovedjo izida kritične bolezni. Pri takih bolnikih je smiselnost nadaljnjega intenzivnega zdravljenja vprašljiva. Ob prenehanju intenzivnega zdravljenja mora nujno slediti dobra paliativna oskrba, ki pa je intenzivnih enotah zaradi neznanja in neozaveščenosti s tega področja ter zaradi usmerjenosti intenzivne medicine - reševati življenje za vsako ceno, težko izvedljiva.

V Univerzitetni kliniki za pljučne bolezni in alergijo Golnik lahko izpostavimo zelo dobro sodelovanje med intenzivnim oddelkom in specialističnim paliativnim timom, ki je lociran na oddelku za neakutno obravnavo na negovalnem oddelku. Tim specialistične paliativne oskrbe obišče bolnika v intenzivni enoti, kjer sledi pogovor z bolnikom in timom v intenzivni enoti. Običajno sledi družinski sestanek, na katerem so poleg bolnika, svojcev in članov paliativnega tima, prisotni tudi člani tima iz intenzivnega oddelka. Na sestanku se pogovorimo o stanju bolnika, diagnozi, prognozi in nadaljnji obravnavi. Svojce in bolnika seznanimo s paliativno oskrbo in se dogovorimo o premestitvi bolnika na negovalni oddelek.

V večini primerov gre za bolnike na invazivni ali na neinvazivni mehanični ventilaciji, pri katerih nadaljnje intenzivno zdravljenje zaradi napredovale bolezni predvsem obremeni bolnika, ne doprinese pa k boljšemu izidu kritične bolezni. Nadaljnje načrtovanje oskrbe in oskrba bolnika potekajo v tesnem sodelovanju paliativnega tima, tima iz intenzivnega oddelka ter bolnika in njegovih bližnjih. Tako zagotavljamo bolniku in svojcem najbolj strokovno in kakovostno oskrbo, ki jo v danem trenutku potrebujejo, obenem pa tudi razbremenimo intenzivni oddelek.

Izobraževanje iz paliativne oskrbe v slovenskih izobraževalnih ustanovah

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Celostna paliativna oskrba je ena od osnovnih pacientovih pravic, saj prinaša dobrobit pacientom in njihovim bližnjim. V državnem programu Ministrstva za zdravje Republike Slovenije (2010) je razvoj paliativne oskrbe opredeljen kot državna prioriteta na področju zdravstvene dejavnosti. V tem dokumentu pa je eno izmed vodil za oblikovanje in uvajanje predlaganega programa uvesti dodiplomsko in podiplomsko izobraževanje zdravstvenih delavcev in zdravstvenih sodelavcev iz paliativne oskrbe. Na področju zdravstva skorajda ni delovnega področja, da se zdravstveni delavec ne bi srečevali z neozdravljivo bolnim ali umirajočim.

V prispevku je prikazan pregled umeščenosti vsebin iz paliativne oskrbe v srednjem in visokošolskem izobraževanju na 1., 2. in 3. stopnji na področju zdravstvene nege v Sloveniji.

Vsebine so v naših izobraževalnih inštitucijah s področja zdravstvene nege v izobraževalne programe vključene v različnih obsegih in oblikah. V nekaterih primerih se iz paliativne oskrbe izobražuje v okviru onkološke in gerontološke zdravstvene nege ali pa kot izbirni predmet oziroma modul. Vsebine s področja paliativne oskrbe se izvajajo v obliki predavanj, kliničnih vaj in klinične prakse ter seminarskih vaj. Pri pregledu stanja ugotovimo, da se izobraževanje iz paliativne oskrbe v slovenskih izobraževalnih ustanovah s področja zdravstvene nege izvaja v različnem obsegu in v različnih oblikah. Izobraževanje iz paliativne oskrbe je še vedno pomanjkljivo. Zato je potrebno vlagati tako v izobraževanje kot v raziskovanje v dodiplomskem in podiplomskem študiju. Ravno tako je potrebna specializacija iz paliativne oskrbe (Kamnik, Pajnkihar, Habjanič, 2014).

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Komunikacija in kontinuirano spremljanje bolnika v paliativni oskrbi

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Pri obravnavi bolnika z neozdravljivo boleznijo in njihovih bližnjih predstavlja temelj obravnave dobra komunikacija, saj je osnova za izgradnjo odnosov s pacientom, ob tem pa se moramo zavedati, da je njihovo doživljanje in funkcioniranje spremenjeno zaradi stresnega doživljanja ob soočanju s težko boleznijo in umiranjem. Komunikacija se začne ob prvem srečanju z bolnikom in poteka ves čas obravnave vse do smrti, z njegovimi bližnjimi pa tudi v procesu žalovanja. V paliativni oskrbi je pomembno kontinuirano spremljanje bolnika in svojcev ne glede na mesto obravnave.

V bolnišnici se prične komunikacija z bolnikom s strani članov paliativnega tima, nadaljuje z vključevanjem svojcev na družinskem sestanku, po odpustu bolnika iz bolnišnice pa s spremljanjem bolnika in svojcev s pomočjo koordinatorja odpusta. O odpustu vsakega bolnika, ki je odpuščen v domače okolje, obvestimo patronažno medicinsko sestro.

Tako, kot je bistvenega pomena komunikacija z bolnikom in svojci, tako je pomembna tudi komunikacija med člani timov, ki oskrbujejo bolnika.

V Univerzitetni kliniki za pljučne bolezni in alergijo Golnik je bilo v letih od junija 2013 do julija 2015 pri 75% obravnavanih bolnikih v okviru specialističnega paliativnega tima izveden družinski sestanek. Pri četrtini obravnavanih bolnikov je bilo izvedeno informiranje bolnika in svojcev s strani zdravnika, zatem tudi s strani ostalih članov paliativnega tima. Družinskega sestanka pri teh bolnikih v večini primerov ni bilo možno organizirati zaradi slabega zdravstvenega stanja bolnikov oziroma prepozne vključitve v paliativno oskrbo.

Vsakega bolnika v paliativni oskrbi po odpustu iz bolnišnice v Kliniki Golnik spremljamo s pomočjo koordinatorja odpusta. Koordinacija poteka kontinuirano do bolnikove smrti. Koordinator odpusta je dipl. m. s., članica specialističnega paliativnega tima. Po potrebi se v koordinacijo vključujejo tudi drugi člani paliativnega tima. Od leta 2011 pa do septembra 2015 je bilo pri 332 bolnikih, obravnavanih v paliativni oskrbi in odpuščenih iz bolnišnice, izvedeno 1282 telefonskih klicev koordinatorja odpusta.

V okviru zagotavljanja kontinuirane oskrbe bolnikov v paliativni oskrbi je potrebno zagotoviti stalno dosegljivost izvajalcev paliativne oskrbe, tako bolnikom in svojcem ob odpustu iz bolnišnice posredujemo telefonske kontakte vseh, ki jih bolniki v nadaljevanju oskrbe potrebujejo; članov specialističnega paliativnega tima, osebnega zdravnika in patronažne medicinske sestre, oskrbe na domu, Društva hospic. Posredujemo tudi 24 ur dosegljivo telefonsko številko.

Bolnik z neozdravljivo boleznijo in njegovi bližnji nas lahko potrebujejo vsak trenutek, tega se moramo zavedati v vseh timih paliativne oskrbe ne glede na to, kje delujemo. Zato se moramo med seboj tesno povezati, sodelovati in se organizirati tako, da bo zagotovljena kontinuirana paliativna oskrba bolnika.

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Zdravljenje lahko nadaljujete s polnim odmerkom (150 mg 2x/ dan) ali z zmanjšanim odmerkom (100 mg 2x/ dan). Če bolnik ne prenaša odmerka po 100 mg 2x/ dan, je treba zdravljenje z zdravilom Ofev ukiniti. V primeru prekinitev zaradi zvišanja vrednosti AST ali ALT na > 3x zgornjo mejo normalnih vrednosti (ULN), se lahko zdravljenje po vrnitvi vrednosti aminotransferaz na izhodiščno raven nadaljuje z zmanjšanim odmerkom, nato pa se lahko poveča na polni odmerek. *Starejši:* Verjetneje je, da bodo bolniki, stari 75 let ali več, potrebovali zmanjšanje odmerka za obvladovanje neželenih učinkov. *Ledvična okvara*: Varnosti, učinkovitosti in farmakokinetike nintedaniba pri bolnikih s hudo ledvično okvaro (očistek kreatinina < 30 ml/min) niso proučevali. *Jetrna okvara:* Zdravljenja bolnikov z zmerno (Child Pugh B) in hudo (Child Pugh C) jetrno okvaro se ne priporoča. *Pediatrična populacija:* Varnost in učinkovitost zdravila Ofev pri otrocih, starih 0 do 18 let, nista bili dokazani. Podatkov ni na voljo. *Način uporabe:* Zdravilo Ofev je namenjeno peroralni uporabi. Kapsule je treba zaužiti s hrano, pogoltniti cele z vodo; ne sme se jih žvečiti ali drobiti. **Kontraindikacije:** Preobčutljivost na nintedanib, arašide ali sojo ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** *Driska*: Zdraviti jo je potrebno takoj, ko se pojavijo prvi znaki, včasih je treba zdravljenje prekiniti. Zdravljenje lahko nadaljujete z zmanjšanim odmerkom ali s polnim odmerkom. Pri trdovratni hudi driski, je treba zdravljenje ukiniti. *Navzea in bruhanje:* Pri trdovratnih simptomih, ki kljub podporni oskrbi ne izginejo, je morda treba odmerek zmanjšati ali zdravljenje prekiniti. Zdravljenje se lahko nadaljuje z zmanjšanim odmerkom ali s polnim odmerkom. Pri trdovratnih simptomih je treba zdravljenje z zdravilom Ofev ukiniti. *Delovanje jeter:*Zdravljenje za bolnike z zmerno (Child Pugh B) ali hudo (Child Pugh C) jetrno okvaro ni priporočljivo. Dajanje nintedaniba je bilo povezano z zvišano ravnjo jetrnih encimov (ALT, AST, ALKP in GGT) z možnim večjim tveganjem za bolnice. Dajanje nintedaniba je bilo povezano tudi z zvišanjem ravni bilirubina. Pred uvedbo zdravljenja in nato periodično ali kot je klinično indicirano je treba določiti ravni jetrnih aminotransferaz in bilirubina. Če so izmerjene vrednosti aminotransferaz(AST ali ALT) > 3 x ULN, se priporoča zmanjšanje odmerka ali prekinitev zdravljenja, bolnika pa je treba natančno spremljati. Ko se aminotransferaze vrnejo na izhodiščne vrednosti, se lahko zdravljenje nadaljuje s polnim odmerkom ali z zmanjšanim odmerkom, nato pa postopoma zvišuje do polnega odmerka. Če so zvišane vrednosti jetrnih testov povezane s kliničnimi znaki ali simptomi poškodbe jeter, je treba zdravljenje trajno ukiniti. Raziskati je treba alternativne vzroke za zvečane jetrnih encimov. *Krvavitev:* Zaviranje receptorja vaskularnega endotelijskega rastnega faktorja VEGFR lahko poveča tveganje za krvavitev. Bolniki z znanim tveganjem za krvavitve, vključno z bolniki z dedno nagnjenostjo h krvavitvam ali tisti, ki so pred začetkom zdravljenja z zdravilom prejemali polne odmerke antikoagulantov se lahko zdravijo le, če so pričakovane koristi večje od možnih tveganj. *Arterijski trombembolični dogodki:* Pri zdravljenju bolnikov z večjim srčnožilnim tveganjem, vključno z znano koronarno arterijsko boleznijo, je potrebna previdnost. Če se pri njih pojavijo znaki ali simptomi akutne miokardne ishemije, je treba razmisliti o prekinitvi zdravljenja. *Venska trombembolija:* Zaradi mehanizma delovanja nintedaniba je lahko pri bolnikih tveganje za trombembolične dogodke večje. *Predrtje prebavil:* Zaradi mehanizma delovanja nintedaniba je lahko pri bolnikih tveganje za predrtje prebavil večje. Posebno pozornost je treba nameniti zdravljenju bolnikov s predhodno abdominalno operacijo. Zdravilo Ofev se lahko uvede najmanj 4 tedne po abdominalni operaciji. Zdravljenje je treba trajno ukiniti pri bolnikih, pri katerih se pojavi predrtje prebavil. *Hipertenzija:* Dajanje zdravila Ofev lahko zviša krvni tlak. Sistemski krvni tlak je treba meriti periodično in kot je klinično indicirano. *Zapleti s celjenjem rane:* Zaradi mehanizma delovanja lahko nintedanib poslabša celjenje ran. Zdravilo Ofev je dovoljeno uvesti ali v primeru perioperativne prekinitve nadaljevati njegovo jemanje le na podlagi klinične ocene ustreznega celjenja rane. *Sočasno dajanje s pirfenidonom:* Razmerja med koristjo in tveganjem pri sočasni uporabi s pirfenidonom ni bilo mogoče ugotoviti. *Učinek na interval QT:* Previdnost je potrebna pri dajanju nintedaniba bolnikom, pri katerih se lahko razvije podaljšanje intervala QTc. *Alergijska reakcija:* Pri bolnikih z znano alergijo na arašidove beljakovine je tveganje za resne reakcije na izdelke s sojo povečano. *Vožnja:* Zdravilo ima blag vpliv na sposobnost vožnje in upravljanja s stroji. **Interakcij:** *P-glikoprotein (P-gp):* Sočasno dajanje z močnim zaviralcem P-gp, je povečalo izpostavljenost nintedanibu. Močni induktorji P-gp lahko zmanjšajo izpostavljenost nintedanibu. *Encimi citokroma (CYP):* Na podlagi presnove s CYP velja, da je verjetnost medsebojnega delovanja zdravil z nintedanibom majhna. **Plodnost, nosečnost in dojenje:** Ženskam v rodni dobi je treba svetovati, naj med zdravljenjem z zdravilom Ofev ne zanosijo. Svetovati jim je treba, naj med zdravljenjem z zdravilom Ofev in še najmanj 3 mesece po zadnjem odmerku uporabljajo ustrezno kontracepcijo. Za preprečevanje nosečnosti je potrebno kot drugo obliko kontracepcije uporabiti še pregradno metodo. Ker lahko nintedanib pri ljudeh poškoduje plod, se ga med nosečnostjo ne sme uporabljati. Med zdravljenjem z zdravilom Ofev je treba prenehati z dojenjem. Ni znakov vpliva na plodnost pri moških. **Neželeni učinki:** *Zelo pogosti:* driska, navzea, bolečine v trebuhu, zvečana vrednost jetrnih encimov. *Pogosti:* zmanjšana telesna masa, zmanjšan tek, bruhanje, zvečana vrednost ALT, zvečana vrednost AST, zvečana vrednost GGT. *Občasni:* hipertenzija, hiperbilirubinemija, zvečana vrednost ALKP v krvi. **Preveliko odmerjanje**: Zdravljenje je treba prekiniti in takoj uvesti ustrezne splošne podporne ukrepe. **Način in režim izdaje:** Rp/ Spec. **Imetnik dovoljenja za promet z zdravilom:** Boehringer Ingelheim International GmbH, Binger Strasse 173, D-55216 Ingelheim am Rhein, Nemčija. **Za podrobnejše informacije o zdravilu glejte** Povzetek glavnih značilnosti zdravila 01/2015.

*potrjena eksacerbacija je bila vnaprej določena v združeni analizi občutljivosti. Čas, ko je prvi raziskovalec poročal eksacerbacijo, je bil sekundarni cilj, ki je bil dosežen v TOMORROW in INPULSIS-2®, ne pa v INPULSIS-1.[61,2] • FVC, forsirana vitalna kapaciteta; HRCT, high-resolution computed tomography.

Literatura: 1. Povzetek glavnih značilnosti zdravila Ofev® 2015. **2.** Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med.* 2014;380(22):2071-2082. **3.** Costabel U et al. Effect of baseline FVC on decline in lung function with nintedanib: results from the INPULSIS™ trials. Poster presented at the European Respiratory Society International Congress; Munich, Germany, September 6-10, 2014. Available at: http://www.ers-education.org/events/international-congress.aspx?idParent=132533. Accessed December 14, 2014. **4.** Cottin V et al. Effect of baseline emphysema on reduction in FVC decline with nintedanib in the INPULSIS trials. Abstract presented at the 18th International Colloquium on Lung and Airway Fibrosis; Mont Tremblant, Canada, September 20-24, 2014. Available at: http://iclaf.com/conference/index.php/2014/ICLAF/paper/view/151. Accessed December 14, 2014. **5.** Kolb M, Richeldi L, Kimura T, Stowasser S, Hallmann C, du Bois RM. Eff ect of baseline FVC on decline in lung function with nintedanib in patients with IPF: results from the INPULSIS® trials. Poster presented at the 110th American Thoracic Society Conference; Denver, Colorado, May 15-20, 2015.

Boehringer Ingelheim RCV,
Podružnica Ljubljana, Šlandrova 4b, 1231 Ljubljana Črnuče

OF 04/november 2015 Samo za strokovno javnost. Datum priprave informacije: november 2015

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KAKOVOSTNA IN KOLIČINSKA SESTAVA: Ena filmsko obložena tableta vsebuje 10 mg/15 mg/20 mg rivaroksabana. Pomožne snovi: Jedro tablete: mikrokristalna celuloza, premreženi natrijev karmelozat, laktoza monohidrat, hipromeloza, natrijev lavrilsulfat, magnezijev stearat. Filmska obloga: makrogol 3350, titanov dioksid (E171), rdeči železov oksid (E172). **TERAPEVTSKE INDIKACIJE: 10 mg:** – Preprečevanje venske trombembolije (VTE) pri odraslih bolnikih po načrtovani kirurški zamenjavi kolka ali kolena. **15 mg/20 mg:** – Preprečevanje možganske kapi in sistemske embolije pri odraslih bolnikih z nevalvularno atrijsko fibrilacijo in enim ali več dejavniki tveganja, kot so kongestivno srčno popuščanje, hipertenzija, starost ≥ 75 let, sladkorna bolezen, predhodna možganska kap ali prehodni ishemični napad. – Zdravljenje globoke venske tromboze (GVT) in pljučne embolije (PE) ter preprečevanje ponovne GVT in PE pri odraslih. **ODMERJANJE IN NAČIN UPORABE:** *Preprečevanje venske trombembolije pri odraslih bolnikih po načrtovani kirurški zamenjavi kolka ali kolena:* Priporočeni odmerek je 10 mg rivaroksabana peroralno enkrat na dan. Prvi odmerek naj bi bolnik prejel 6 do 10 ur po kirurškem posegu, če je zagotovljena ustrezna hemostaza. Po velikem kirurškem posegu na kolku se priporoča 5 tedenska zaščita. Po velikem kirurškem posegu na kolenu se priporoča 2 tedenska zaščita. *Preprečevanje možganske kapi in sistemske embolije:* Priporočeni odmerek je 20 mg enkrat na dan, kar je tudi priporočeni največji odmerek. *Zdravljenje GVT in preprečevanje ponovne GVT in PE:* Priporočeni odmerek za začetno zdravljenje akutne GVT ali PE je prve tri tedne 15 mg dvakrat na dan, nato pa 20 mg enkrat na dan kot nadaljevanje zdravljenja in preprečevanje ponovne GVT in PE. *Bolniki z načrtovano kardioverzijo:* Zdravilo Xarelto se lahko uvede ali z zdravljenjem nadaljuje pri bolnikih, pri katerih je potrebna kardioverzija. Pri bolnikih s kardioverzijo, vodeno s transezofagealnim ehokardiogramom (TEE), ki predhodno niso bili zdravljeni z antikoagulanti, je treba zdravljenje z zdravilom Xarelto začeti najmanj 4 ure pred kardioverzijo za zagotovitev ustrezne antikoagulacije. Pri vseh bolnikih je treba pred kardioverzijo pridobiti potrditev, da je bolnik jemal zdravilo Xarelto tako, kot je predpisano. **KONTRAINDIKACIJE:** Preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov; klinično pomembna aktivna krvavitev; poškodbe ali stanja z visokim tveganjem za velike krvavitve; sočasno zdravljenje s katerimkoli drugim antikoagulacijskim zdravilom npr. nefrakcioniranim heparinom, nizkomolekularnimi heparini (enoksaparinom, dalteparinom in drugimi), derivati heparina (fondaparinuksom in drugimi), peroralnimi antikoagulanti (varfarinom, apiksabanom, dabigatranom in drugimi) razen v primerih zamenjave zdravljenja z ali na rivaroksaban ali kadar se nefrakcionirani heparini uporabljajo v odmerkih, ki so potrebni za vzdrževanje prehodnosti centralnega venskega ali arterijskega katetra; bolezen jeter, ter hkrati motnje koagulacije in klinično pomembno tveganje za krvavitve, vključno z jetrno cirozo razreda Child – Pugh B in C; nosečnost in dojenje. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Ves čas zdravljenja se priporoča klinično spremljanje v skladu s smernicami vodenja antikoagulacijskega zdravljenja. Zdravljenje z zdravilom Xarelto je treba prenehati, če se pojavijo hude krvavitve. S starostjo se tveganje za krvavitve lahko poveča. *Uporaba zdravila Xarelto se ne priporoča:* pri bolnikih s hudo okvaro ledvic (očistek kreatinina < 15 ml/min); pri bolnikih, ki sočasno jemljejo tudi močne zaviralce CYP3A4 in P-gp, t.j. azolne antimikotike za sistemsko zdravljenje ali zaviralce proteaz HIV, pri bolnikih, kjer je tveganje za krvavitve povečano, se je treba izogibati sočasni uporabi močnih induktorjev CYP3A4, razen če se bolnika skrbno spremlja glede znakov in simptomov tromboze. *Zaradi malo podatkov se uporaba zdravila Xarelto ne priporoča:* pri otrocih in mladostnikih, mlajših od 18 let; pri bolnikih, sočasno zdravljenih z dronedaronom; Samo za 15mg/20mg: pri bolnikih z umetnimi srčnimi zaklopkami ali pri bolnikih s pljučno embolijo, ki so hemodinamsko nestabilni ali so morda na trombolizi ali pljučni embolektomiji. *Previdna uporaba zdravila Xarelto:* Pri stanjih bolnikov, kjer obstaja povečano tveganje za krvavitve. Pri bolnikih s hudo okvaro ledvic (očistek kreatinina 15 – 29 ml/min) ali pri bolnikih z okvaro ledvic, ki sočasno uporabljajo druga zdravila, ki povečajo plazemsko koncentracijo rivaroksabana; pri bolnikih, ki sočasno prejemajo zdravila, ki vplivajo na hemostazo; pri nevraksialni anesteziji ali spinalni/epiduralni punkciji. Samo za 15 mg/20 mg: za bolnike z zmerno ali hudo okvaro ledvic veljajo posebna priporočila za odmerjanje. Ta priporočila veljajo tudi za bolnike z GVT in PE, pri katerih je ocenjeno tveganje za krvavitve večje od tveganja za ponovno GVT in PE. Pri bolnikih, pri katerih obstaja tveganje za pojav razjed v prebavilih, je treba razmisliti tudi o ustreznem profilaktičnem zdravljenju. V vsakdanji praksi med zdravljenjem z rivaroksabanom ni potrebno spremljanje kazalcev koagulacije. Če je klinično indicirano, se lahko vrednosti rivaroksabana izmeri s kalibriranim kvantitativnim merjenjem aktivnosti anti-Xa. Zdravilo Xarelto vsebuje laktozo. **NEŽELENI UČINKI:** *Pogosti:* anemija, omotica, glavobol, krvavitev v očesu, hipotenzija, hematom, epistaksa, hemoptiza, krvavitev iz dlesni, krvavitve v prebavilih, bolečine v prebavilih in trebuhu, dispepsija, navzea, zaprtje, driska, bruhanje, srbenje, osip, ekhimoza, krvavitve v koži in podkožju, bolečine v udih, krvavitve v urogenitalnem traktu (menoragijo so opazili zelo pogosto pri ženskah <55 let pri zdravljenju GVT, PE ali preprečevanju ponovne GVT ali PE), okvara ledvic, zvišana telesna temperatura, periferni edem, splošna oslabelost in pomanjkanje energije, povečane vrednosti transaminaz, krvavitev po posegu, kontuzija, sekrecija iz rane. *Občasni:* trombocitemija, alergijska reakcija, alergijski dermatitis, cerebralna in intrakranialna krvavitev, sinkopa, tahikardija, suha usta, moteno delovanje jeter, urtikarija, hemartroza, slabo počutje, povečane vrednosti: bilirubina, alkalne fosfataze v krvi, LDH, lipaze, amilaze, GGT. *Redki:* zlatenica, krvavitve v mišicah, lokaliziran edem, povečane vrednosti konjugiranega bilirubina, vaskularna pseudoanevrizma. *Neznana pogostnost:* utesnitveni sindrom ali akutna odpoved ledvic po krvavitvi; *Opazovanja v obdobju trženja:* angioedem in alergijski edem, holestaza, hepatitis (vključno s hepatocelularno poškodbo), trombocitopenija. **Način izdajanja zdravila:** Izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** Bayer Pharma AG, D-13342 Berlin, Germany **Za nadaljnje informacije o zdravilu Xarelto, se lahko obrnete na:** Bayer d.o.o., Bravničarjeva 13, 1000 Ljubljana **Verzija:** EU/5 (06/2015)

Reference: 1. Patel M.R., Mahaffey K.W., Garg J. *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883–91. **2.** Camm J., Amarenco P., Haas S. *et al.* XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J.* 2016;37(14):1145–53. **3.** Tamayo S., Peacock F., Patel M.R. *et al.* Characterizing major bleeding in patients with nonvalvular atrial fibrillation: A pharmacovigilance study of 27,467 patients taking rivaroxaban. *Clin Cardiol.* 2015;38(2):63–8. **4.** Xarelto Povzetek glavnih značilnosti zdravila, dec 2015.

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KOPB: Simptomatsko zdravljenje bolnikov s hudo obliko KOPB (FEV < 50 % predvidenega normalnega FEV) in s ponavljajočimi se poslabšanji v anamnezi, pri katerih se kljub zdravljenju z dolgodelujočimi bronhodilatatorji pojavljajo znatni simptomi. **Odmerjanje in način uporabe** Zdravilo DuoResp Spiromax ni indicirano za uporabo pri otrocih, starih 12 let ali manj, ali mladostnikih, starih od 13 do 17 let. *Astma:* Zdravilo DuoResp Spiromax ni primerno za začetno zdravljenje astme. Zdravljenje z zdravilom ni ustrezno pri odraslih bolnikih z blago obliko astme, ki ni ustrezno nadzorovana z inhalacijskim kortikosteroidi in inhalacijskimi kratkodelujočimi agonisti adrenoreceptorjev β_2, ki se uporabljajo po potrebi. Odmerek je treba titrirati do najmanjšega odmerka, pri katerem je še ohranjen učinkovit nadzor nad simptomi. Ko v običajni praksi dosežemo ustrezen nadzor simptomov z odmerjanjem nižje jakosti zdravila dvakrat na dan, lahko titracijo do manjšega še učinkovitega odmerka opravimo tudi z zmanjšanjem pogostnosti odmerjanja na enkrat na dan. ***DuoResp Spiromax 160 mcg/4,5 mcg:*** *Zdravilo DuoResp Spiromax za vzdrževalno zdravljenje* Bolnikom je treba svetovati, da naj imajo svoj ločeni inhalator s hitrodelujočim bronhodilatatorjem kot olajševalcem vedno na razpolago za hitro obvladanje simptomov. Odrasli (18 let in več): 1–2 vdiha dvakrat na dan. Pri nekaterih bolnikih bodo morda potrebni največ 4 vdihi dvakrat na dan. *Zdravilo DuoResp Spiromax za vzdrževalno in olajševalno zdravljenje* Bolniki redno jemljejo dnevni vzdrževalni odmerek zdravila DuoResp Spiromax, ob pojavu simptomov pa po potrebi dodatne odmerke zdravila DuoResp Spiromax. Vzdrževalno in olajševalno zdravljenje z zdravilom DuoResp Spiromax je primerno predvsem za bolnike: -z neustrezno nadzorovano astmo, ki pogosto potrebujejo inhalator z olajševalcem; -s poslabšanjem astme v preteklosti, pri katerem je bila potrebna medicinska intervencija. *Priporočeni odmerki:* Odrasli (18 let in več): priporočen vzdrževalni odmerek je 2 vdiha na dan, bodisi 1 vdih zjutraj in 1 vdih zvečer ali pa 2 vdiha zjutraj ozirома 2 vdiha zvečer. Za nekatere bolnike je primeren vzdrževalni odmerek 2 vdiha dvakrat dnevno. Ob pojavu simptomov naj bolniki po potrebi naredijo še 1 dodaten vdih. Če so simptomi po nekaj minutah še vedno prisotni, naj naredijo še 1 vdih. Naenkrat ne smejo narediti več kot 6 vdihov. Celotni dnevni odmerek, večji od 8 vdihov, v običajnih okoliščinah ni potreben. Kljub temu je lahko v določenih omejenih časovnih obdobjih celotni dnevni odmerek 12 vdihov. Bolniki, ki uporabljajo več kot 8 vdihov dnevno, morajo obiskati zdravnika. Zdravnik jih bo ponovno pregledal in ocenil njihovo vzdrževalno zdravljenje. *KOPB:* Odrasli (18 let in več): 2 vdiha dvakrat na dan. ***DuoResp Spiromax 320 mcg/9mcg:*** *Astma:* Treba uporabljati le kot vzdrževalno zdravljenje. Odrasli (18 let in več): 1 vdih dvakrat na dan. *KOPB:* Odrasli (18 let in več): 1 vdih dvakrat na dan. *Starejši bolniki (≥ 65 let):* Ni posebnih zahtev za odmerjanje. *Bolniki z okvaro ledvic ali jeter:* Podatkov ni na voljo. **Kontraindikacije** Preobčutljivost na zdravilni učinkovini ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi** Če bolnik ugotavlja, da je zdravljenje neučinkovito, ali če preseže največji priporočeni odmerek zdravila DuoResp Spiromax, mora poiskati zdravniško pomoč. Nenadno in progresivno poslabšanje nadzora simptomov astme ali KOPB je lahko za bolnika življenjsko nevarno, zato je potreben nujen zdravniški pregled. Bolnikom svetujte, naj imajo inhalator z olajševalcem vedno pri roki.Bolnike je treba opozoriti, naj uporabljajo vzdrževalni odmerek zdravila DuoResp Spiromax kot olajševalec se uporablja v primerih, ko se pojavijo simptomi, ne pa redno v profilaktične namene, na primer pred telesnim naporom. V takih primerih je treba razmisliti o uporabi hitrodelujočega bronhodilatatorja. Simptomi astme Bolnikom se ne sme uvesti zdravila med poslabšanjem astme ali v obdobju pomembnega ozirома akutnega poslabšanja simptomov astme. Med zdravljenjem z zdravilom se lahko pojavijo resni neželeni učinki, povezani z astmo, in poslabšanje bolezni. Če po uvedbi zdravila simptomi astme niso nadzorovani ali se poslabšajo, naj bolniki nadaljujejo z zdravljenjem in poiščejo zdravniško pomoč. Med zdravljenjem se lahko pojavi paradoksni bronhospazem, ki ga prepoznamo po okrepitvi piskanja v pljučih in težkega dihanja,takoj po vdihu zdravila. V tem primeru je treba zdravljenje z zdravilom takoj prekiniti. Paradoksni bronhospazem se odziva na hitrodelujoč inhalacijski bronhodilatator in ga moramo zdraviti takoj. Sistemski učinki Pri uporabi vseh inhalacijskih kortikosteroidov se lahko pojavijo sistemski učinki, še posebno, če so bili predpisani veliki odmerki za dlje časa. Med možnimi sistemskimi učinki so Cushingov sindrom, Cushingoidne značilnosti, supresija nadledvične žleze, zmanjšanje kostne mineralne gostote, katarakta in glavkom ter redkeje vrsta psiholoških in vedenjskih učinkov, vključno s psihomotorno hiperaktivnostjo, motnjami spanja, anksioznostjo, depresijo ali agresijo. Učinki na kostno gostato Treba je razmisliti o možnih učinkih na kostno gostato, še posebej pri bolnikih, ki prejemajo večje odmerke za daljša obdobja in imajo sočasne dejavnike tveganja za osteoporozo. Delovanje nadledvične žleze Če obstaja kakršen koli razlog za sum na motnjo delovanja nadledvične žleze zaradi prejšnje sistemskega zdravljenja s steroidi, je pri prehodu na zdravljenje s fiksno kombinacijo budezonida/formoterolijevega fumarata potrebna previdnost. Kortikosteroidi v visokih odmerkih Klinično pomembna adrenalna supresija se lahko pojavi tudi pri bolnikih, ki so imeli podaljšano zdravljenje z visokimi odmerki inhalacijskih kortikosteroidov, še posebej v odmerkih, višjih od priporočenih. Zato je treba razmisliti o dodatni uporabi sistemskih kortikosteroidov v obdobjih stresa, kot so npr. hude okužbe ali pred neurgentnimi kirurškimi posegi. Hitro zmanjšanje odmerka steroidov lahko povzroči akutno adrenalno krizo. Simptomi in znaki, ki se lahko pojavijo pri akutni adrenalni krizi, so včasih nejasni, lahko pa vključujejo anoreksijo, bolečine v trebuhu, izgubo telesne teže, utrujenost, glavobol, navzeo, bruhanje, motnje zavesti, konvulzije, hipotenzijo in hipoglikemijo. Zdravljenje z dopolnilnimi sistemskimi steroidi ali inhalacijskim budezonidom ne smemo nenadno prekiniti. Prehod s peroralnega zdravljenja Med prehodom s peroralnega zdravljenja na zdravljenje s fiksno kombinacijo budezonida/formoterolijevega fumarata se običajno pojavi splošno manjše delovanje sistemskih steroidov, kar lahko povzroči pojav alergijskih ali artritičnih simptomov, kot so npr. rinitis, ekcem in bolečine v mišicah in sklepih. Za te težave je treba uvesti posebno zdravljenje. Peroralne okužbe Da bi lahko na najmanjšo možno mero zmanjšali tveganje za orofaringealno okužbo s kandido, bolniku naročite, naj si po vsakem vzdrževalnem odmerku spere usta z vodo. Ob pojavu orofaringealne kandidoze si morajo bolniki sprati usta tudi po vsaki inhalaciji po potrebi. Previdnost pri posebnih boleznih Kombinacijo budezonida in formoterolijevega fumarat dihidrata v fiksnih odmerkih predpisujte previdno pri bolnikih s tirotoksikozo, feokromocitomom, sladkorno boleznijo, nezdravljeno hipokaliemijo, hipertrofično obstruktivno kardiomiopatijo, idiopatsko subvalvularno aortno stenozo, hudo hipertenzijo, anevrizmo ali drugimi hudimi kardiovaskularnimi boleznimi, kot so na primer ishemična srčna bolezen, tahiaritmije ali hudo srčno popuščanje. Pomožne snovi To zdravilo vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze, ne smejo jemati tega zdravila. Pomožna snov laktoza vsebuje majhne količine mlečnih beljakovin, ki lahko povzročijo alergijske reakcije. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Močni zaviralci CYP3A4 (npr. ketokonazol, itrakonazol, vorikonazol, posakonazol, klaritromicin, telitromicin, nefazodon in zaviralci proteaze HIV) bodo zelo verjetno povečali plazemsko koncentracijo budezonida, zato se je treba izogibati sočasni uporabi. Če to ni mogoče, pazite, da bo časovni razmik med uporabo zaviralca in budezonida kolikor je mogoče dolg. Pri bolnikih, ki jemljejo močne zaviralce CYP3A4, kombinacija budezonida in formoterolijevega fumarata dihidrata v fiksnih odmerkih kot vzdrževalno in olajševalno zdravljenje ni priporočeno. Antagonisti receptorjev receptorjev β lahko oslabijo ali zavrejo delovanje formaterola. **Neželeni učinki** Najpogostejši neželeni učinki so farmakološko pričakovani neželeni učinki zdravljenja z agonisti adrenergičnih receptorjev β_2, kot so tremor in palpitacije. *Pogosti:* Okužbe s kandido v ustih in žrelu, glavobol, tremor, palpitacije, blaga draženje grla, kašljanje in hripavost.
Imetnik dovoljenja za promet z zdravilom Teva Pharma B.V., Swensweg 5, 2031 GA Haarlem, Nizozemska **Način in režim izdaje zdravila** *Rp* - Predpisovanje in izdaja zdravila je le na recept **Datum zadnje revizije besedila** september 2015

Reference: 1. Rychlik R, Kreimendahl F. Presented at the 7th IPCRG World Conference, 2014. **2.** Plusa T, Bijos´ P. Int Rev Allergol Clin Immunol Family Med, 2015; 21(1): 21–24. **3.** DuoResp Spiromax® SmPC, september 2015.

** Uporaba zdravila DuoResp Spiromax® je dovoljena zgolj pri bolnikih, starih 18 let ali več.
* Navodila za bolnika moramo uporabljati v skladu z navodili za uporabo zdravila.

Dodatne informacije o nagradi za odličnost pri oblikovanju v medicini so na voljo na: http:/www.canontradeshows.com/expo/awards/awards.
www.duoresp.com

Datum priprave informacije: september 2016. Za podrobnejše informacije o zdravilu, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki je objavljen na spletni strani Evropske agencije za zdravila http://www.ema.europa.eu ali se obrnite na zastopnika imetnika dovoljenja za promet z zdravilom v Sloveniji, Pliva Ljubljana d.o.o., Pot k sejmišču 35, 1231 Ljubljana-Črnuče, tel: 01 58 90 399, e-mail: info@tevasi.si. Samo za strokovno javnost.

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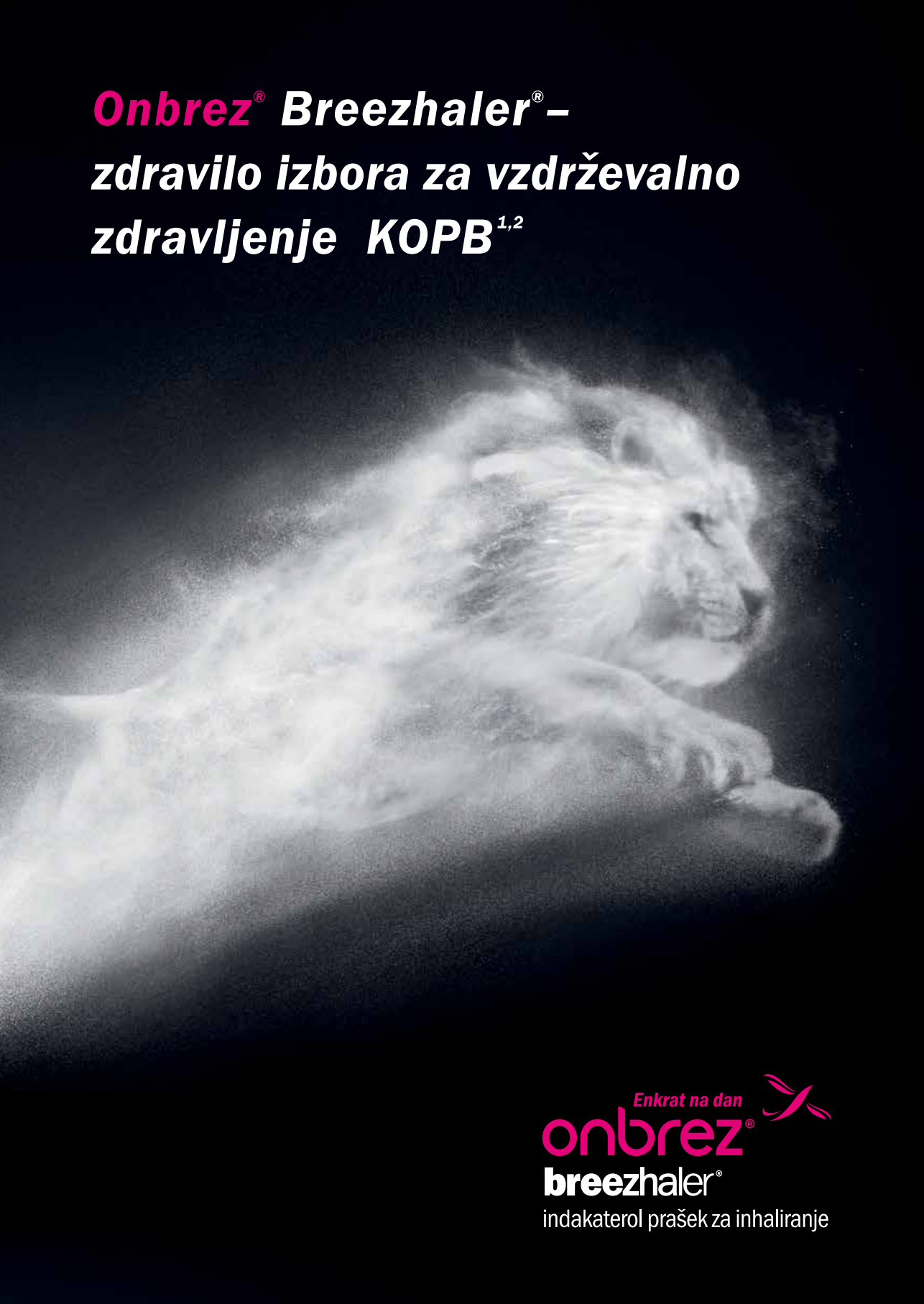

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- **Zdravilo Onbrez Breezhaler je indicirano za vzdrževalno bronhodilatatorno zdravljenje obstrukcije dihalnih poti pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo.[3]**
- **Zdravila Onbrez Breezhaler se ne sme uporabljati pri astmi, saj ni podatkov o dolgoročnih rezultatih pri zdravljenju astme.[3]**
- **Priporočeni odmerek je vdih vsebine ene 150 mikrogramske kapsule enkrat na dan z uporabo inhalatorja Onbrez Breezhaler. Odmerek je mogoče zvišati po nasvetu zdravnika.[3]**

Glejte navodila za predpisovanje, v celoti navedena v Povzetku glavnih značilnosti zdravila.

ONBREZ® BREEZHALER® 150 in 300 mikrogramov prašek za inhaliranje, trde kapsule

Sestava: Ena trda kapsula s praškom za inhaliranje vsebuje indakaterolijev maleat v količini, ki ustreza 150 mikrogramom indakaterola. Ena trda kapsula s praškom za inhaliranje vsebuje indakaterolijev maleat v količini, ki ustreza 300 mikrogramom indakaterola.
Indikacije: Zdravilo Onbrez Breezhaler je indicirano za vzdrževalno bronhodilatatorno zdravljenje obstrukcije dihalnih poti pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo (KOPB). **Odmerjanje:** Odrasli: Priporočeni odmerek je vdih vsebine ene 150-mikrogramske kapsule enkrat na dan z uporabo inhalatorja Onbrez Breezhaler. Odmerek je mogoče zvišati samo po nasvetu zdravnika. Pokazalo se je, da vdih vsebine ene 300-mikrogramske kapsule enkrat na dan z uporabo inhalatorja Onbrez Breezhaler dodatno klinično koristi pri zadihanosti še posebno bolnikom s hudo KOPB. Najvišji odmerek je 300 mikrogramov enkrat na dan. Pediatrična populacija: Pri pediatrični populaciji (starost pod 18 let) uporaba ni primerna. Posebne skupine bolnikov: Pri starejših bolnikih, pri bolnikih z blago in zmerno okvaro jeter ter pri bolnikih z okvaro ledvic prilagajanje odmerjanja ni potrebno. O uporabi pri bolnikih s hudo okvaro jeter ni na voljo nobenih podatkov. Način uporabe: samo za inhaliranje. Kapsul zdravila Onbrez Breezhaler se ne sme pogoltniti. Kapsule je treba vzeti iz pretisnega omota šele tik pred uporabo. Kapsule zdravila Onbrez Breezhaler so namenjene samo uporabi z inhalatorjem Onbrez Breezhaler. Vedno je treba uporabiti inhalator Onbrez Breezhaler, ki je priložen novemu pakiranju zdravila. Bolnike je treba poučiti, kako naj si pravilno aplicirajo zdravilo. Bolnike, pri katerih ne pride do izboljšanja dihanja, je treba vprašati, ali zdravilo morda pogoltnejo namesto da bi ga inhalirali. **Kontraindikacije:** preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov.
Opozorila/previdnostni ukrepi: Astma: zdravila se ne sme uporabljati pri astmi. Preobčutljivost: poročali so o primerih takojšnje preobčutljivostne reakcije po odmerjanju zdravila Onbrez Breezhaler. Če pride do znakov, ki kažejo na alergijsko reakcijo (zlasti oteženega dihanja ali požiranja, otekanja jezika, ustnic in obraza, urtikarije ali izpuščaja), je treba zdravljenje z zdravilom Onbrez Breezhaler takoj ukiniti in uvesti drugo zdravilo. Paradoksni bronhospazem: tako kot uporaba drugih inhalacijskih zdravil lahko uporaba zdravila Onbrez Breezhaler povzroči paradoksni bronhospazem, ki lahko ogroža življenje. Če pride do paradoksnega bronhospazma, je treba takoj prenehati jemanje zdravila Onbrez Breezhaler in ga nadomestiti z drugačnim zdravljenjem. Poslabšanje bolezni: zdravilo Onbrez Breezhaler ni indicirano za zdravljenje akutnih epizod bronhospazma. Če pride med zdravljenjem do poslabšanja KOPB, je treba ponovno pregledati bolnika in oceniti shemo zdravljenja KOPB. Sistemski učinki: kot velja za druge agoniste adrenergičnih receptorjev beta-2, je potrebna previdnost pri uporabi pri bolnikih s srčno-žilnimi boleznimi (s koronarno boleznijo, po akutnem miokardnem infarktu, z aritmijami, s hipertenzijo), pri bolnikih s konvulzivnimi motnjami ali s hipertiroidizmom in pri bolnikih, ki so neobičajno odzivni na agoniste adrenergičnih receptorjev beta-2. Učinki na srčno-žilni sistem: tako kot drugi agonisti adrenergičnih receptorjev beta-2 lahko pri nekaterih bolnikih tudi indakaterol klinično pomembno vpliva na srčno-žilni sistem, kar se kaže kot povečan srčni utrip, zvišan krvni tlak in/ali povzročanje drugih simptomov. Če pride do takega vpliva, je včasih treba zdravljenje prekiniti. Za agoniste adrenergičnih receptorjev beta-2 so poleg tega poročali, da povzročajo elektrokardiografske (EKG) spremembe, vendar klinični pomen teh opažanj ni znan. Iz navedenih razlogov je pri uporabi dolgodelujočih agonistov adrenergičnih receptorjev beta-2 , kot je zdravilo Onbrez Breezhaler, pri bolnikih z ugotovljenim ali domnevnim podaljšanjem intervala QT in pri tistih, ki prejemajo zdravila z vplivom na interval QT, potrebna previdnost. Hipokaliemija: agonisti adrenergičnih receptorjev beta-2 lahko pri nekaterih bolnikih povzročijo pomembno hipokaliemijo, zaradi katere lahko pride do neželenih učinkov na srčno-žilni sistem. Pri bolnikih s hudo KOPB lahko hipoksija in sočasna zdravila še poglobijo hipokaliemijo, kar lahko poveča možnost za razvoj aritmij. Hiperglikemija: v kliničnih študijah so bile klinično opazne spremembe v koncentraciji glukoze v krvi večinoma za 1-2 % bolj pogoste pri bolnikih, ki so jemali zdravilo Onbrez Breezhaler v priporočenih odmerkih kot pri bolnikih, ki so jemali placebo. Po začetku zdravljenja je treba pri bolnikih s sladkorno boleznijo še natančneje spremljati koncentracije glukoze v plazmi. Pomožne snovi: kapsule vsebujejo laktozo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. Nosečnost: Uporaba je med nosečnostjo upravičena le, če pričakovane koristi prevladajo nad možnimi tveganji. Dojenje: odločiti se je treba med prenehanjem dojenja in prenehanjem/prekinitvijo zdravljenja z zdravilom Onbrez Breezhaler, pri čemer je treba pretehtati prednosti dojenja za otroka in prednosti zdravljenja za mater. Plodnost: Skoraj nobene možnosti ni, da bi indakaterol pri vdihu najvišjega priporočenega odmerka vplival na sposobnost za razmnoževanje ali plodnost pri ljudeh. **Interakcije:** Sočasna uporaba drugih simpatikomimetičnih zdravil lahko okrepi neželene učinke zdravila Onbrez Breezhaler. Ne sme se uporabljati v povezavi z drugimi dolgodelujočimi agonisti adrenergičnih receptorjev beta-2 oziroma z zdravili, ki vsebujejo dolgodelujoče agoniste adrenergičnih receptorjev beta-2. Sočasno zdravljenje z derivati metilksantina, s steroidi ali z diuretiki, ki ne zadržujejo kalija, lahko okrepi možne hipokaliemične učinke agonistov adrenergičnih receptorjev beta-2, zato je pri sočasni uporabi potrebna previdnost. Ne sme se jemati skupaj z zaviralci adrenergičnih receptorjev beta (tudi s kapljicami za oči), razen če so za sočasno uporabo nujni razlogi. Zaradi izkušenj glede varnosti pri uporabi zdravila Onbrez Breezhaler v kliničnih študijah, zaviranje delovanja dveh dejavnikov, ki sta bistveno vpletena v izločanje indakaterola (CYP3A4 in P-gp), ni zaskrbljujoče. **Neželeni učinki:** Zelo pogosti: okužba zgornjih dihal, nazofaringitis. Pogosti: sinusitis, sladkorna bolezen in hiperglikemija, glavobol, omotičnost, ishemična bolezen srca, palpitacije, kašelj, orofaringealna bolečina, vključno z vnetjem žrela, rinoreja, srbenje/izpuščaj, mišični krči, mišičnoskeletna bolečina, bolečina v prsnem košu, periferni edem, tremor (pri odmerku 600 mg na dan). Občasni: preobčutljivost, parestezije, atrijska fibrilacija, tahikardija, paradoksni bronhospazem, bolečine v mišicah.
Način/režim izdajanja: Rp - predpisovanje in izdaja zdravila le na recept. **Imetnik dovoljenja za promet:** Novartis Europharm Limited, Frimley Business Park Camberley GU16 7SR, Velika Britanija. **Opozorilo: Pred predpisovanjem natančno preberite zadnji odobreni povzetek glavnih značilnosti zdravila. Podrobnejše informacije so na voljo pri:** Novartis Pharma Services Inc., Verovškova ulica 57, 1000 Ljubljana, Slovenija. Datum zadnje revizije skrajšanega povzetka glavnih značilnosti: oktober 2014.

Literatura: 1. GOLD: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Posodobljeno 2016. **2.** Matera GB, Rogliani P, Cazzola P. Indacaterol for the treatment of chronic obstructive pulmonary disease. Expert Opin Pharmacother. 2015; 16(1):107-115. **3.** Povzetek glavnih značilnosti zdravila Onbrez® Breezhaler®, oktober 2014.

Datum priprave informacije: januar 2016.

NOVARTIS

Novartis Pharma Services Inc., Podružnica v Sloveniji,
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▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih.

SEEBRI® BREEZHALER® 44 mikrogramov prašek za inhaliranje, trde kapsule

Sestava: Ena kapsula vsebuje 63 mikrogramov glikopironijevega bromida, kar ustreza 50 mikrogramom glikopironija. En odmerek glikopironijevega bromida, ki pride skozi ustnik inhalatorja, vsebuje 55 mikrogramov glikopironijevega bromida, kar ustreza 44 mikrogramom glikopironija.
Indikacije: Zdravilo Seebri Breezhaler je indicirano kot vzdrževalno bronhodilatatorno zdravljenje za lajšanje simptomov pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo (KOPB).
Odmerjanje: *Odrasli:* Priporočeni odmerek je inhalacija vsebine ene kapsule enkrat na dan z uporabo inhalatorja Seebri Breezhaler. *Otroci (mlajši od 18 let):* Zdravilo Seebri Breezhaler ni primerno za uporabo pri pediatrični populaciji (v starosti pod 18 let) za indikacijo KOPB. *Posebne skupine bolnikov:* Pri starejših bolnikih ter pri bolnikih z blago in zmerno okvaro ledvic prilagajanje odmerjanja ni potrebno. Pri bolnikih z okvaro jeter niso izvedli nobenih študij. Glikopironij se iz telesa izloča pretežno preko ledvic, zato pri bolnikih z okvaro jeter ni pričakovati bistveno povečane izpostavljenosti zdravilu. Bolniki s hudo okvaro ledvic in bolniki, ki imajo končno ledvično odpoved in potrebujejo dializno zdravljenje, smejo uporabljati zdravilo Seebri Breezhaler samo v primeru, da pričakovana korist presega potencialno tveganje. *Način uporabe:* Samo za inhaliranje. Kapsule so namenjene samo uporabi z inhalatorjem Seebri Breezhaler. Kapsul se ne sme pogoltniti. Bolnike je treba poučiti, kako naj si pravilno aplicirajo zdravilo. Bolnike, pri katerih ne pride do izboljšanja dihanja, je treba vprašati, ali zdravilo morda pogoltnejo namesto da bi ga inhalirali.
Kontraindikacije: Preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov.
Opozorila/previdnostni ukrepi: • *Akutna uporaba:* Zdravilo ni namenjeno akutni uporabi. • *Preobčutljivost:* Poročali so o primerih takojšnje preobčutljivostne reakcije po odmerjanju zdravila Seebri Breezhaler. Če se pojavijo znaki, ki kažejo na alergijsko reakcijo, zlasti angioedem (vključno z oteženim dihanjem ali požiranjem, otekanjem jezika, ustnic in obraza), urtikarija ali izpuščaj, je treba zdravljenje z zdravilom Seebri Breezhaler takoj ukiniti in uvesti drugo zdravilo. • *Paradoksni bronhospazem:* V kliničnih študijah z zdravilom Seebri Breezhaler niso opažali paradoksnega bronhospazma, opažali pa so ga pri uporabi drugih inhalacijskih zdravil. Paradoksni bronhospazem je lahko življenjsko nevaren. Če pride do paradoksnega bronhospazma, je treba takoj prenehati z jemanjem zdravila Seebri Breezhaler in ga nadomestiti z alternativnim zdravljenjem. • *Antiholinergično delovanje:* Zdravilo Seebri Breezhaler je treba uporabljati previdno pri bolnikih z glavkomom zaprtega zakotja ali z zastojem urina. • *Bolniki s hudo okvaro ledvic:* Pri bolnikih s hudo okvaro, med katere sodijo tudi tisti s končno ledvično odpovedjo, ki potrebujejo dializno zdravljenje, je mogoče zdravilo Seebri Breezhaler uporabljati samo v primeru, da pričakovana korist presega potencialno tveganje. Te bolnike je treba skrbno opazovati glede morebitnih neželenih učinkov. • *Bolniki z anamnezo kardiovaskularne bolezni:* Bolniki z nestabilno ishemično boleznijo srca, s popuščanjem levega prekata, z anamnezo miokardnega infarkta, z aritmijo (z izjemo tistih s kronično stabilno atrijsko fibrilacijo), z anamnezo sindroma dolgega intervala QT in bolniki s podaljšanim intervalom QTc (trajanje intervala s korekcijo Fridericia >450 ms pri moških in >470 ms pri ženskah) niso bili vključeni v klinične študije, zato je obseg izkušenj pri teh skupinah bolnikov omejen. Pri uporabi zdravila Seebri Breezhaler pri teh skupinah bolnikov je potrebna previdnost. • *Pomožne snovi:* Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. • *Nosečnost:* Glikopironij je v nosečnosti mogoče uporabiti samo v primeru, da pričakovana korist za bolnico upravičuje potencialno tveganje za plod. • *Dojenje:* O uporabi glikopironija v času dojenja je smiselno razmišljati samo v primeru, da pričakovana korist za bolnico presega potencialno tveganje za otroka. *Plodnost:* Rezultati študij na živalih ne vzbujajo pomislekov glede plodnosti tako pri moških kot pri ženskah.
Interakcije: Sočasne uporabe zdravila Seebri Breezhaler in drugih zdravil, ki vsebujejo antiholinergične učinkovine, niso proučevali, zato tovrstna sočasna uporaba ni priporočena.
Neželeni učinki: • *Pogosti:* suha usta, nazofaringitis, nespečnost, glavobol, gastroenteritis, okužba sečil. • *Občasni:* dispepsija, zobni karies, bolečine v okončinah, mišičnoskeletna bolečina v prsnem košu, izpuščaj, pruritus, utrujenost, astenija, kongestija sluznice obnosnih votlin, produktiven kašelj, vnetje grla oziroma žrela, krvavitev iz nosu, rinitis, cistitis, hiperglikemija, disurija, zastoj urina, atrijska fibrilacija, palpitacije, hipestezija, preobčutljivost, angioedem. • *Pogostnost neznana:* paradoksni bronhospazem.
Način/režim izdajanja: Rp - predpisovanje in izdaja zdravila le na recept.
Imetnik dovoljenja za promet: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, Velika Britanija
Opozorilo: Pred predpisovanjem natančno preberite zadnji odobreni povzetek glavnih značilnosti zdravila.
Podrobnejše informacije so na voljo pri: Novartis Pharma Services Inc., Verovškova ulica 57, 1000 Ljubljana, Slovenija.
Zadnja revizija besedila: september 2015

Literatura:
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NOVARTIS

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Po 5 minutah deluje, 24 ur učinkuje[1,2,3]

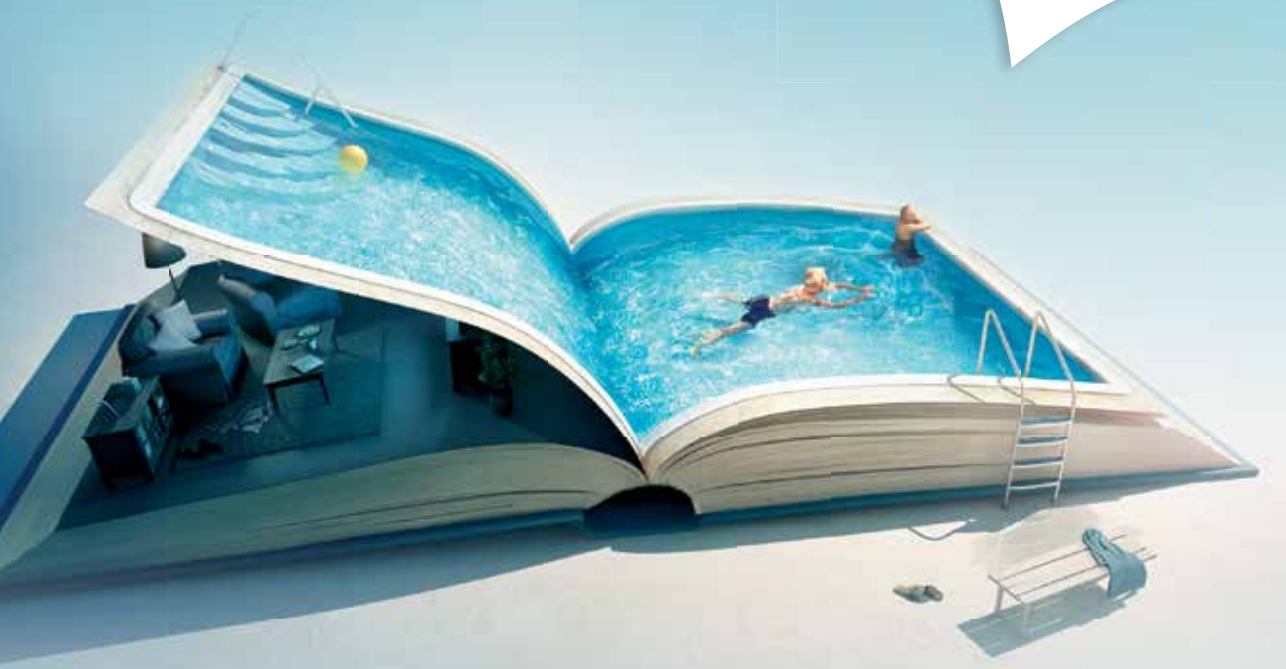
Zagotavlja jutranjo učinkovitost[2]

Zmanjša pogostnost in podaljša čas do prve eksacerbacije*[,1,2,3]

* zmerne oziroma hude eksacebracije

Danes je *dober dan*

PRVI
dvojni dolgodelujoči bronhodilatator z enkrat-dnevnim odmerjanjem†*



ULTIBRO® BREEZHALER®

NOVO POGLAVJE V ZDRAVLJENJU BOLNIKOV S KOPB.

- **Prva kombinacija dveh dolgodelujočih bronhodilatatorjev v enem inhalatorju.[1]**
- **Učinkovitejši kot tiotropij# in kombinacija salmeterol/flutikazon†.[1-4]**
- **Po 5 min deluje, 24 ur učinkuje.[1,2,4]**
- **Dobro prenosljiv in varen.[1-5]**

#Zdravilo Ultibro® Breezhaler® je bilo učinkovitejše kot odprto uporabljen tiotropij pri izboljšanju pljučne funkcije (merjeno s FEV_1), pri zmanjšanju zadihanosti (merjeno s TDI), pri povečanju deleža dni, ko so bolniki lahko izvajali svoje običajne aktivnosti, pri zmanjšanju porabe hitrih olajševalcev, pri izboljšanju kvalitete življenja (merjeno s SGRQ), pri zmanjšanju pogostnosti vseh akutnih poslabšanj KOPB skupaj (blagih, zmernih in hudih)
† Zdravilo Ultibro® Breezhaler® je bilo učinkovitejše kot kombinacija salmeterol/flutikazon pri izboljšanju pljučne funkcije (merjeno s FEV_1), pri zmanjšanju zadihanosti (merjeno s TDI), pri povečanju deleža dni brez dnevnih simptomov, pri zmanjšanju porabe hitrih olajševalcev, pri bolnikih brez zmernih ali hudih akutnih poslabšanj v predhodnem letu.
* prvi dvojni dolgodelujoči bronhodilatator z enkrat-dnevnim odmerjanjem odobren v Evropski uniji.
FEV_1= forsirani ekspiratorni volumen v prvi sekundi
TDI= indeks spreminjanja dispneje v času
SGRQ= vprašalnik St. George's Respiratory Questionnaire
KOPB= kronična obstruktivna pljučna bolezen

ENKRAT NA DAN
ultibro®
breezhaler®
indakaterol/glikopironij
prašek za inhaliranje

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih.

ULTIBRO® BREEZHALER® 85 mikrogramov/43 mikrogramov prašek za inhaliranje, trde kapsule

Sestava: Ena kapsula vsebuje 143 µg indakaterolijevega maleata, kar ustreza 110 µg indakaterola, in 63 µg glikopironijevega bromida, kar ustreza 50 µg glikopironija. En odmerek, ki pride skozi ustnik inhalatorja, vsebuje 110 µg indakaterolijevega maleata, kar ustreza 85 µg indakaterola, in 54 µg glikopironijevega bromida, kar ustreza 43 µg glikopironija.

Indikacije: Zdravilo Ultibro Breezhaler je indicirano kot enkrat dnevno vzdrževalno bronhodilatatorno zdravljenje za lajšanje simptomov pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo (KOPB).

Odmerjanje: Priporočeni odmerek je inhalacija vsebine ene kapsule enkrat na dan z uporabo inhalatorja Ultibro Breezhaler. Zdravilo Ultibro Breezhaler je priporočeno uporabiti vsak dan ob istem času. V primeru izpuščenega odmerka je treba zdravilo vzeti čimprej še isti dan. Bolnikom je treba naročiti, naj ne vzamejo več kot enega odmerka v istem dnevu.

Posebne skupine bolnikov: Populacija starejših: Starejši bolniki (stari 75 let ali več) lahko uporabljajo zdravilo Ultibro Breezhaler v priporočenem odmerku. *Okvara ledvic:* Bolniki z blago do zmerno okvaro ledvic lahko uporabljajo zdravilo Ultibro Breezhaler v priporočenem odmerku. Bolniki s hudo okvaro ledvic in bolniki, ki imajo končno ledvično odpoved in potrebujejo dializno zdravljenje, ga smejo uporabljati samo v primeru, da pričakovana korist presega potencialno tveganje. *Okvara jeter:* Bolniki z blago in zmerno okvaro jeter lahko uporabljajo zdravilo Ultibro Breezhaler v priporočenem odmerku. O uporabi zdravila Ultibro Breezhaler pri bolnikih s hudo okvaro jeter ni na voljo nobenih podatkov, zato je pri teh bolnikih potrebna previdnost. *Pediatrična populacija:* Zdravilo Ultibro Breezhaler ni primerno za uporabo pri pediatrični populaciji (v starosti pod 18 let) za indikacijo KOPB. Varnost in učinkovitost zdravila Ultibro Breezhaler pri otrocih nista bili dokazani. Podatkov ni na voljo. *Način uporabe:* Samo za inhaliranje. Kapsul se ne sme pogoltniti. Kapsule so namenjene samo uporabi z inhalatorjem Ultibro Breezhaler. Bolnike je treba poučiti, kako naj si pravilno aplicirajo zdravilo.

Kontraindikacije: Preobčutljivost na zdravilni učinkovini ali katero koli pomožno snov.

Opozorila/previdnostni ukrepi: Zdravila Ultibro Breezhaler se ne sme uporabljati sočasno z drugimi zdravili, ki vsebujejo dolgodelujoče agoniste beta adrenergičnih receptorjev ali dolgodelujoče antagoniste muskarinskih receptorjev, torej z zdravili iz obeh skupin, v kateri sodita učinkovini zdravila Ultibro Breezhaler. Astma: Zdravila Ultibro Breezhaler se ne sme uporabljati za zdravljenje astme, saj o uporabi pri tej indikaciji ni na voljo nobenih podatkov. Dolgodelujoči agonisti beta-2 adrenergičnih receptorjev lahko pri uporabi za zdravljenje astme povečajo tveganje za resne neželene dogodke, ki so povezani z astmo, med drugim za smrt zaradi astme. Zdravilo ni namenjeno akutni uporabi: Zdravilo Ultibro Breezhaler ni indicirano za zdravljenje akutnih epizod bronhospazma. Preobčutljivost: Poročali so o primerih takojšnje preobčutljivostne reakcije po odmerjanju indakaterola oziroma glikopironija, ki sta učinkovini zdravila Ultibro Breezhaler. Če pride do znakov, ki kažejo na alergijsko reakcijo, zlasti če pride do angioedema (oteženega dihanja ali požiranja, otekanja jezika, ustnic in obraza), urtikarije ali izpuščaja, je treba zdravljenje takoj ukiniti in ga nadomestiti z alternativnim zdravljenjem. Paradoksni bronhospazem: V kliničnih študijah z zdravilom Ultibro Breezhaler niso opažali paradoksnega bronhospazma, opažali pa so ga pri uporabi drugih inhalacijskih zdravil. Paradoksni bronhospazem je lahko življenjsko nevaren. Če pride do paradoksnega bronhospazma, je treba zdravljenje takoj ukiniti in ga nadomestiti z alternativnim zdravljenjem. Antiholinergično delovanje v povezavi z glikopironijem: Pri uporabi zdravila Ultibro Breezhaler pri bolnikih z glavkomom zaprtega zakotja in pri bolnikih z zastojem urina je potrebna previdnost, ker ni na voljo nobenih podatkov. Bolniki s hudo okvaro ledvic: Pri bolnikih z blago in zmerno okvaro ledvic so opažali zmerno povečanje povprečne celotne sistemske izpostavljenosti glikopironiju (AUC_{tau}) za največ 1,4-krat, pri bolnikih s hudo okvaro ledvic in končno ledvično odpovedjo pa za največ 2,2-krat. Pri bolnikih s hudo okvaro ledvic (z ocenjeno hitrostjo glomerulne filtracije manj kot 30 ml/min/1,73 m^2), med katere sodijo tudi tisti s končno ledvično odpovedjo, ki potrebujejo dializno zdravljenje, je mogoče zdravilo Ultibro Breezhaler uporabljati samo v primeru, da pričakovana korist presega potencialno tveganje. Te bolnike je treba skrbno opazovati glede morebitnih neželenih učinkov. Kardiovaskularni učinki: Pri uporabi zdravila Ultibro Breezhaler pri bolnikih s kardiovaskularnimi boleznimi (s koronarno boleznijo, po akutnem miokardnem infarktu, z aritmijami, s hipertenzijo) je potrebna previdnost. Agonisti beta-2 adrenergičnih receptorjev lahko klinično pomembno vplivajo na kardiovaskularni sistem, kar se kaže kot povečan srčni utrip, zvišan krvni tlak in/ali pojav drugih simptomov. Če pride do takega vpliva pri uporabi tega zdravila, je včasih treba zdravljenje prekiniti. Poleg tega so za agoniste beta-2 adrenergičnih receptorjev poročali, da povzročajo elektrokardiografske (EKG) spremembe (na primer: zmanjševanje vala T, podaljšanje intervala QT in depresijo segmenta ST). Iz navedenih razlogov je pri uporabi dolgodelujočih agonistov beta-2 adrenergičnih receptorjev pri bolnikih z ugotovljenim ali domnevnim podaljšanjem intervala QT in pri tistih, ki prejemajo zdravila z vplivom na interval QT, potrebna previdnost. Bolniki z nestabilno ishemično boleznijo srca, s popuščanjem levega prekata, z anamnezo miokardnega infarkta, z aritmijo (z izjemo tistih s kronično stabilno atrijsko fibrilacijo), z anamnezo sindroma dolgega intervala QT ali s podaljšanim intervalom QTc (s trajanjem intervala po metodi s korekcijo Fridericia >450 ms) niso bili vključeni v klinične študije, zato pri teh skupinah bolnikov z uporabo zdravila ni nobenih izkušenj. Pri uporabi zdravila Ultibro Breezhaler pri teh skupinah bolnikov je potrebna previdnost. Hipokaliemija: Agonisti beta-2 adrenergičnih receptorjev lahko pri nekaterih bolnikih povzročijo pomembno hipokaliemijo, zaradi katere lahko pride do neželenih kardiovaskularnih učinkov. Znižana koncentracija kalija v serumu je običajno le prehodna in zaradi nje ni treba nadomeščati kalija. Pri bolnikih s hudo KOPB lahko hipoksija in sočasna zdravila še poslabšajo hipokaliemijo, kar lahko poveča možnost za razvoj aritmij. Hiperglikemija: Inhaliranje visokih odmerkov agonistov beta-2 adrenergičnih receptorjev lahko povzroči zvišanje koncentracije glukoze v plazmi. Pri sladkornih bolnikih je treba po začetku zdravljenja z zdravilom Ultibro Breezhaler še bolj natančno spremljati koncentracije glukoze v plazmi. Splošne težave: Pri uporabi zdravila Ultibro Breezhaler je potrebna previdnost pri bolnikih s konvulzivnimi motnjami ali s hipertiroidizmom in pri bolnikih, ki so neobičajno odzivni na agoniste beta-2 adrenergičnih receptorjev. Pomožne snovi: Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. Zdravilo Ultibro Breezhaler nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja s stroji. Nosečnost: Ni podatkov o uporabi zdravila Ultibro Breezhaler pri nosečnicah. Indakaterol lahko zavira porod zaradi relaksantnega učinka na gladko mišičje maternice. Iz tega razloga je zdravilo Ultibro Breezhaler v nosečnosti mogoče uporabiti samo v primeru, da pričakovana korist za bolnico upravičuje potencialno tveganje za plod. Dojenje: Ni znano, ali se indakaterol, glikopironij in njuni presnovki izločajo v materino mleko. O uporabi zdravila Ultibro Breezhaler v času dojenja je smiselno razmišljati samo v primeru, da pričakovana korist za bolnico presega potencialno tveganje za otroka. Plodnost: Rezultati študij vpliva na sposobnost razmnoževanja in drugi podatki iz študij na živalih ne vzbujajo pomislekov glede plodnosti tako pri moških kot pri ženskah.

Interakcije: Sočasna uporaba peroralno inhaliranih indakaterola in glikopironija v stanju dinamičnega ravnovesja obeh učinkovin ni vplivala na farmakokinetične lastnosti niti prve niti druge od obeh učinkovin. Sočasna uporaba ni priporočljiva: *Antagonisti beta adrenergičnih receptorjev:* Antagonisti beta adrenergičnih receptorjev lahko oslabijo ali zavrejo učinke agonistov beta-2 adrenergičnih receptorjev, zato se zdravila Ultibro Breezhaler ne sme uporabljati skupaj z antagonisti beta adrenergičnih receptorjev (kar pomeni tudi s kapljicami za oči), razen če za sočasno uporabo obstajajo nujni razlogi. Kadar je potrebno, je treba izbrati kardioselektivne antagoniste beta adrenergičnih receptorjev, vendar jih je treba uporabljati previdno. *Antiholinergična zdravila:* Sočasne uporabe zdravila Ultibro Breezhaler z drugimi zdravili, ki vsebujejo antiholinergične učinkovine, niso proučevali in zato ni priporočena. *Simpatikomimetična zdravila:* Sočasna uporaba drugih simpatikomimetičnih zdravil (samih ali v sklopu kombinacije zdravil) lahko okrepi neželene učinke indakaterola. Pri sočasni uporabi je potrebna previdnost: *Zdravila, ki lahko povzročijo hipokaliemijo:* Sočasno zdravljenje z derivati metilksantina, s steroidi ali z diuretiki, ki ne varčujejo s kalijem, lahko okrepi možne hipokaliemične učinke agonistov beta-2 adrenergičnih receptorjev, zato je pri sočasni uporabi potrebna previdnost. Pri sočasni uporabi je treba vzeti v obzir: *Interakcije na podlagi presnove in prenašalcev:* Zaviranje delovanja dveh dejavnikov, ki sta bistveno vpletena v izločanje indakaterola - CYP3A4 in P-glikoproteina (P-gp), do dvakrat poveča sistemsko izpostavljenost indakaterolu. Povečanje izpostavljenosti zaradi interakcij ni zaskrbljujoče, in sicer zaradi izkušenj glede varnosti pri uporabi indakaterola v kliničnih študijah s trajanjem do enega leta v odmerkih, ki so dosegali tudi dvakratni najvišji priporočeni odmerek indakaterola. *Cimetidin in drugi zaviralci transporta organskih kationov:* Pri sočasni uporabi glikopironija in cimetidina ali drugih zaviralcev transporta organskih kationov ni pričakovati klinično pomembnih interakcij.

Neželeni učinki: *Zelo pogosti:* okužbe zgornjih dihal; *Pogosti:* nazofaringitis, okužba sečil, sinusitis, rinitis, omotičnost, glavobol, kašelj, orofaringealna bolečina, vključno z draženjem žrela, dispepsija, zobni karies, gastroenteritis, mišičnoskeletna bolečina, zvišana telesna temperatura, bolečina v prsnem košu; *Občasni:* preobčutljivost, angioedem, sladkorna bolezen in hiperglikemija, nespečnost, parestezije, glavkom, ishemična bolezen srca, atrijska fibrilacija, tahikardija, palpitacije, paradoksni bronhospazem, krvavitev iz nosu, suha usta, srbenje/izpuščaj, mišični krči, bolečine v mišicah, bolečine v okončinah, zapora sečnega mehurja in zastoj urina, periferni edemi, utrujenost.

Način in režim izdajanja: Rp- predpisovanje in izdaja zdravila je le na recept.

Imetnik dovoljenja za promet: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, Velika Britanija.

Pomembno opozorilo: Pred predpisovanjem preberite navodila za predpisovanje, v celoti navedena v Povzetku glavnih značilnosti zdravila.

Podrobnejše informacije so na voljo: Novartis Pharma Services Inc., Verovškova ulica 57, 1000 Ljubljana, Slovenija

Datum zadnje revizije besedila: *januar 2015*

Literatura:

1. Povzetek glavnih značilnosti zdravila Ultibro® Breezhaler® 85 mikrogramov/43 mikrogramov prašek za inhaliranje, trde kapsule, oktober 2015.
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3. Wedzicha JA, Decramer M, Ficker JH, in sod. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199-209.
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5. Dahl R, Chapman KR, Rudolf M in sod. Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. Respir Med. 2013 Oct;107(10):1558-67.

Samo za strokovno javnost.
Datum priprave informacije: januar 2016.
ULT-AD1-01/16-SI

NOVARTIS

Novartis Pharma Services Inc., Podružnica v Sloveniji,
Verovškova 57, 1000 Ljubljana, Telefon: 01 300 75 50

Vzdrževalno bronhodilatacijsko zdravljenje za bolnike s KOPB in dispnejo.

DAJTE BOLNIKOM TAKOJŠNJE REZULTATE,[1,2] KI JIH POTREBUJEJO.

ANORO® ▼ELLIPTA®
umeklidinij/vilanterol
zadihajte...

Zdravilo Anoro Ellipta je treba pri bolnikih s hudimi srčno-žilnimi boleznimi uporabljati previdno.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

ANORO▼ 55 mikrogramov/22 mikrogramov prašek za inhaliranje, odmerjeni
Ena inhalacija zagotavlja oddani odmerek (odmerek, ki pride iz ustnika inhalatorja) 65 mikrogramov umeklidinijevega bromida, kar ustreza 55 mikrogramom umeklidinija, in 22 mikrogramov vilanterola (v obliki trifenatata). To ustreza odmerjenemu odmerku 74,2 mikrogramov umeklidinijevega bromida, kar ustreza 62,5 mikrogramom umeklidinija in 25 mikrogramov vilanterola (v obliki trifenatata). Pomožne snovi: laktoza monohidrat, magnezijev stearat. **Terapevtske indikacije:** Zdravilo ANORO je indicirano za vzdrževalno bronhodilatacijsko zdravljenje za olajšanje simptomov pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo (KOPB). Zdravilo ANORO je treba uporabljati enkrat na dan, vsak dan ob istem času, za ohranjanje bronhodilatacije. Največji odmerek je ena inhalacija zdravila ANORO 55/22 mikrogramov enkrat na dan. **Odmerjanje in način uporabe:** Zdravilo ANORO je namenjeno samo za inhalacijsko uporabo. Priporočeni odmerek je ena inhalacija zdravila ANORO 55/22 mikrogramov enkrat na dan. **Kontraindikacije:** Preobčutljivost na zdravilni učinkovini ali katero koli pomožno snov (laktoza monohidrat in magnezijev stearat). **Posebna opozorila in previdnostni ukrepi:** Kombinacije umeklidinij/vilanterol se ne sme uporabljati pri bolnikih z astmo, ker ta kombinacija pri tej populaciji bolnikov ni raziskana. Če se pojavi paradoksni bronhospazem, je treba zdravljenje s kombinacijo umeklidinij/vilanterol takoj prekiniti in po potrebi uvesti drugo zdravljenje. Po uporabi antagonistov muskarinskih receptorjev in simpatikomimetikov, vključno s kombinacijo umeklidinij/vilanterol, se lahko pojavijo učinki na srce in ožilje, npr. motnje srčnega ritma, kakršni sta atrijska fibrilacija in tahikardija. Zato je treba kombinacijo umeklidinij/vilanterol pri bolnikih s hudo kardiovaskularno boleznijo uporabljati previdno. Zdravilo Anoro Ellipta je treba uporabljati previdno pri bolnikih z retenco urina, glavkomom z ozkim zakotjem, pri bolnikih s konvulzivnimi motnjami ali tirotoksikozo, hipokaliemijo, hiperglikemijo ali hudo okvaro jeter. Bolnikom z blago ali zmerno okvaro jeter odmerka ni treba prilagoditi. Kombinacija umeklidinij/vilanterol ni indicirana za zdravljenje akutnih epizod bronhospazma. Povečevanje uporabe kratkodelujočih bronhodilatatorjev za olajšanje simptomov kaže na slabšanje urejenosti bolezni. Če se stanje KOPB med zdravljenjem s kombinacijo umeklidinij/vilanterol poslabša, je treba znova oceniti tako bolnika kot shemo zdravljenja KOPB. Potrebno se je posvetovati z zdravnikom. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študije medsebojnega delovanja so izvedli samo pri odraslih. Sočasni uporabi z zaviralci adrenergičnih receptorjev beta (tako neselektivnih kot selektivnih) se je treba izogibati, razen če obstajajo nujni razlogi za njihovo uporabo. V primeru sočasne uporabe z močnimi zaviralci CYP3A4 (npr. ketokonazol, klaritromicin, itrakonazol, ritonavir, telitromicin) je priporočljiva previdnost. Sočasne uporabe kombinacije umeklidinij/vilanterol in drugih dolgodelujočih muskarinskih antagonistov, dolgodelujočih agonistov adrenergičnih receptorjev beta$_2$ ali zdravil, ki vsebujejo katero od teh učinkovin, niso preučevali in zato te uporabe ne priporočajo. Sočasno hipokaliemično zdravljenje z metilksantinskimi derivati, steroidi ali diuretiki, ki ne ohranjajo kalija, lahko stopnjuje možni hipokaliemični učinek agonistov adrenergičnih receptorjev beta$_2$, zato je pri uporabi potrebna previdnost. **Plodnost, nosečnost in dojenje:** Kombinacijo umeklidinij/vilanterol se sme uporabljati le, če je pričakovana korist večja od možnega tveganja. **Neželeni učinki:** Pogosti: okužba sečil, sinuzitis, nazofaringitis, vnetje žrela (faringitis), okužba zgornjih dihal, glavobol, kašelj, orofaringealna bolečina, zaprtost, suhost ust. Občasni: atrijska fibrilacija, supraventrikularna tahikardija, idioventrikularni ritem, tahikardija, supraventrikularne ekstrasistole, palpitacije, tremor, disgevzija in izpuščaj. Redki: anafilaksa, angioedem in urtikarija. **Ime in naslov imetnika dovoljenja za promet:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex, TW8 9GS, Velika Britanija. **Datum zadnje revizije besedila:** 10/2015

Predpisovanje in izdaja zdravila je le na recept.

▼Za to zdravilo se izvaja dodatno spremljanje varnosti, kar označuje navzdol obrnjen črn trikotnik. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Sami lahko k temu prispevate s poročanjem o kateremkoli domnevnem neželenem učinku zdravila. Prosimo, da o domnevnih neželenih učinkih, ki jih opazite pri zdravljenju z zdravilom Anoro Ellipta, poročate v skladu s Pravilnikom o farmakovigilanci zdravil za uporabo v humani medicini (UL RS, št. 57/14), na način kot je objavljeno na spletni strani www.jazmp.si. Izpolnjen obrazec o domnevnem neželenem učinku zdravila pošljite nacionalnemu centru za farmakovigilanco: UKC Ljubljana, Interna klinika, Center za zastrupitve, Zaloška cesta 2, SI-1000 Ljubljana, faks: 01 434 76 46, ali na e-naslov: farmakovigilanca@kclj.si.

Za vse nadaljnje informacije o tem zdravilu se lahko obrnete na: GSK d.o.o., Ljubljana, Ameriška ulica 8, 1000 Ljubljana, tel: + 386 (0)1 280 25 00, medical.x.si@gsk.com

SLO/UCV/0004/16
Datum priprave materiala: februar 2016.
Datum naslednje revizije materiala: februar 2018.

Literatura:
1. Donohue JF *et al. Respir Med* 2013; 107: 1538–1546. **2.** Singh S *et al. Thorax* 2015; 70 (Suppl 3); A1-A254.

Zdravilo Relvar® Ellipta® je kombinacija IGK/LABA, namenjena bolnikom (starim 12 let ali več), ki niso urejeni z IGK in SABA "po potrebi".[1]

Astma

Ali vaši bolniki potrebujejo učinkovito terapijo, ki ustreza realnosti vsakdanjega življenja?

- **Stalna 24-urna učinkovitost** v samo enem odmerku na dan [1,2]
- V pripomočku, ki je **preprost za uporabo** [3]

Zelo pogosti neželeni učinki: glavobol in nazofaringitis. Pogosti neželeni učinki: pljučnica, okužba zgornjih dihal, bronhitis, gripa, kandidoza ust in žrela, orofaringealna bolečina, sinuzitis, faringitis, rinitis, kašelj, disfonija, bolečine v trebuhu, artralgija, pireksija, bolečine v hrbtu, zlomi, mišični krči. Podobno kot pri ostalih zdravilih, ki imajo IGK, je povečana verjetnost pljučnice pri bolnikih s KOPB, zdravljenih z zdravilom Relvar.[1]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Relvar Ellipta ▼ 92 mikrogramov/22 mikrogramov prašek za inhaliranje, odmerjeni
Relvar Ellipta ▼ 184 mikrogramov/22 mikrogramov prašek za inhaliranje, odmerjeni
Ena inhalacija zdravila Relvar Ellipta 92/22 mikrogramov zagotavlja oddani odmerek (odmerek, ki zapusti ustnik) 92 mikrogramov flutikazonfuroata in 22 mikrogramov vilanterola (v obliki trifenatata). To ustreza odmerjenemu odmerku 100 mikrogramov flutikazonfuroata in 25 mikrogramov vilanterola (v obliki trifenatata). Ena inhalacija zdravila Relvar Ellipta 184/22 mikrogramov zagotavlja oddani odmerek (odmerek, ki zapusti ustnik) 184 mikrogramov flutikazonfuroata in 22 mikrogramov vilanterola (v obliki trifenatata). To ustreza odmerjenemu odmerku 200 mikrogramov flutikazonfuroata in 25 mikrogramov vilanterola (v obliki trifenatata). Pomožne snovi: laktoza monohidrat, magnezijev stearat. **Terapevtske indikacije:** Relvar Ellipta (obe jakosti): Astma: Redno zdravljenje astme pri odraslih in mladostnikih, starih 12 let ali več, ki bolezni nimajo ustrezno obvladane, ob uporabi inhalacijskih kortikosteroidov in inhalacijskih kratkodelujočih agonistov adrenergičnih receptorjev beta$_2$ "po potrebi" in za katere je primerna uporaba kombiniranega zdravila (dolgodelujočega agonista adrenergičnih receptorjev beta$_2$ in inhalacijskega kortikosteroida). Relvar Ellipta 92 mikrogramov/22 mikrogramov prašek za inhaliranje, odmerjeni: KOPB (kronična obstruktivna pljučna bolezen): Simptomatsko zdravljenje odraslih s KOPB, ki imajo FEV$_1$ < 70 % predvidenega normalnega (po bronhodilatatorju), z anamnezo poslabšanj kljub rednemu zdravljenju z bronhodilatatorjem. **Odmerjanje in način uporabe:** Zdravilo Relvar Ellipta je namenjeno samo za inhalacijsko uporabo. *Astma: Odrasli in mladostniki, stari 12 let ali več:* Za bolnike, ki potrebujejo nizek do srednji odmerek inhaliranega kortikosteroida v kombinaciji z dolgodelujočim agonistom adrenergičnih receptorjev beta$_2$, pride v poštev začetni odmerek zdravila Relvar Ellipta 92/22 mikrogramov enkrat na dan. Če bolniki z zdravilom Relvar Ellipta 92/22 mikrogramov bolezni nimajo ustrezno obvladane, pride v poštev zvišanje odmerka na 184/22 mikrogramov; to lahko prinese dodatno izboljšanje urejenosti astme. Za bolnike, ki potrebujejo višji odmerek inhaliranega kortikosteroida v kombinaciji z dolgodelujočim agonistom adrenergičnih receptorjev beta$_2$, pride v poštev zdravilo Relvar Ellipta 184/22 mikrogramov. Zdravnik mora bolnike redno kontrolirati, da ostane jakost uporabljane kombinacije flutikazonfuroat/vilanterol optimalna in se spremeni le po nasvetu zdravnika. Odmerek je treba titrirati do najnižjega odmerka, ki učinkovito obvladuje simptome. *KOPB: Odrasli, stari 18 let ali več:* Ena inhalacija zdravila Relvar Ellipta 92/22 mikrogramov enkrat na dan. Zdravilo Relvar Ellipta 184/22 mikrogramov ni indicirano pri bolnikih s KOPB. Odmerek 184/22 mikrogramov v primerjavi z odmerkom 92/22 mikrogramov nima dodatnih koristi, obstaja pa lahko večje tveganje za pljučnico in sistemske neželene učinke, povezane s kortikosteroidi. **Kontraindikacije:** Preobčutljivost na zdravilni učinkovini ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Flutikazonfuroat/vilanterol je treba uporabljati previdno pri bolnikih s pljučno tuberkulozo, s hudo kardiovaskularno boleznijo ali motnjami srčnega ritma, hipertiroidizmom, nekorigirano hipokaliemijo, pri bolnikih, ki so nagnjeni k nizkim vrednostim kalija v serumu, bolnikih s kroničnimi ali nezdravljenimi okužbami in z anamnezo sladkorne bolezni. Po uporabi zdravila se lahko pojavi paradoksni bronhospazem. Takšno stanje je treba nemudoma zdraviti s hitrodelujočim inhalacijskim bronhodilatatorjem. Uporabo zdravila Relvar Ellipta je treba takoj prekiniti, bolnika pregledati in uvesti drugo zdravljenje, če je potrebno. Pri bolnikih z zmerno do hudo okvaro jeter je treba uporabiti odmerek 92/22 mikrogramov. Flutikazonfuroat/vilanterol se ne sme uporabljati za zdravljenje simptomov akutne astme ali akutnega poslabšanja KOPB; za to je potreben kratkodelujoč bronhodilatator. Če bolnikova uporaba kratkodelujočih bronhodilatatorjev za olajšanje naraščа, to kaže na slabšanje urejenosti bolezni in bolnikovo stanje je treba znova oceniti. Bolniki zdravljenja astme ali KOPB s flutikazonfuroatom/vilanterolom ne smejo končati brez zdravniškega nadzora, ker se lahko simptomi po prenehanju ponovijo. Med zdravljenjem s flutikazonfuroatom/vilanterolom se lahko pojavijo z astmo povezani neželeni učinki in poslabšanja. Bolnikom je treba naročiti, naj v primeru, da simptomi astme po uvedbi zdravila Relvar Ellipta niso obvladani ali se poslabšajo, zdravljenje nadaljujejo, a naj se hkrati posvetujejo z zdravnikom. *Sistemski učinki kortikosteroidov:* Med uporabo vseh inhalacijskih kortikosteroidov se lahko pojavijo sistemski učinki, zlasti med dolgotrajno uporabo velikih odmerkov. Ti učinki so veliko manj verjetni kot med uporabo peroralnih kortikosteroidov. Med možnimi sistemskimi učinki so Cushingov sindrom, Cushingoidne značilnosti, supresija nadledvičnih žlez, zmanjšanje mineralne gostote kosti, upočasnitev rasti pri otrocih in mladostnikih, katarakta in glavkom ter, redkeje, različni psihološki ali vedenjski učinki, med njimi psihomotorična hiperaktivnost, motnje spanja, anksioznost, depresija ali agresivnost (zlasti pri otrocih). Pri bolnikih s KOPB, ki so prejemali inhalacijske kortikosteroide, so opažali večjo pojavnost pljučnice. Med dejavniki tveganja za pljučnico pri bolnikih s KOPB so trenutno kajenje, višja starost, nizek indeks telesne mase (ITM) in huda KOPB. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študije medsebojnega delovanja so izvedli le pri odraslih. Sočasni uporabi z antagonisti adrenergičnih receptorjev beta$_1$ (tako neselektivnih kot selektivnih) se je treba izogibati, razen če obstajajo nujni razlogi za njihovo uporabo. Previdnost je potrebna med sočasno uporabo z močnimi zaviralci CYP3A4 (npr. ketokonazol, ritonavir). Sočasna uporaba drugih simpatikomimetičnih zdravil (samih ali kot sestavin kombiniranega zdravljenja) lahko stopnjuje neželene učinke flutikazonfuroata/vilanterola. Zdravila Relvar Ellipta se ne sme uporabljati skupaj z drugimi dolgodelujočimi agonisti adrenergičnih receptorjev beta, ali z zdravili, ki vsebujejo dolgodelujoče agoniste adrenergičnih receptorjev beta$_2$. **Nosečnost in dojenje:** Uporaba pri nosečnicah pride v poštev le, če je pričakovana korist za mater večja od možnega tveganja za plod. Odločiti se je treba bodisi za prenehanje dojenja bodisi za prenehanje zdravljenja s flutikazonfuroatom/vilanterolom, upoštevaje koristi dojenja za otroka in korist zdravljenja za žensko. **Neželeni učinki:** *Zelo pogosti (≥ 1/10):* glavobol, nazofaringitis. *Pogosti (≥ 1/100 do < 1/10):* pljučnica, okužba zgornjih dihal, bronhitis, gripa, kandidoza ust in žrela, orofaringealna bolečina, sinuzitis, faringitis, rinitis, kašelj, disfonija, bolečine v trebuhu, artralgija, pireksija, bolečine v hrbtu, zlomi, mišični krči. *Občasni (≥ 1/1000 do < 1/100):* ekstrasistole. *Redki (≥ 1/10.000 do < 1/1000):* palpitacije, tahikardija, tremor, anksioznost, preobčutljivostne reakcije, vključno z anafilakso, angioedemom, izpuščajem in urtikarijo. **Imetnik dovoljenja za promet:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, Velika Britanija. **Datum zadnje revizije besedila:** 06/2016.

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti, kar označuje navzdol obrnjen črn trikotnik. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Sami lahko k temu prispevate s poročanjem o kateremkoli domnevnem neželenem učinku zdravila. Prosimo, da o domnevnih neželenih učinkih, ki jih opazite pri zdravljenju z zdravilom Relvar Ellipta, poročate v skladu s Pravilnikom o farmakovigilanci zdravil za uporabo v humani medicini (UL RS, št. 57/14), na način kot je objavljeno na spletni strani www.jazmp.si. Izpolnjen obrazec o domnevnem neželenem učinku zdravila pošljite nacionalnemu centru za farmakovigilanco: UKC Ljubljana, Interna klinika, Center za zastrupitve, Zaloška cesta 2, SI-1000 Ljubljana, faks: 01 434 76 46, ali na e-naslov:farmakovigilanca@kclj.si. Relvar Ellipta je bila razvita v sodelovanju z družbo Innoviva.
Za vse nadaljnje informacije o tem zdravilu se lahko obrnete na: GSK d.o.o., Ljubljana, Ameriška ulica 8, 1000 Ljubljana, tel: + 386 (0)1 280 25 00, medical.x.si@gsk.com
SLO/FFT/0005/16

Literatura:
1. Povzetek glavnih značilnosti zdravila Relvar Ellipta 6/2016.
2. Bleecker ER et al. JACI In Practice. 2014; 2(5): 553–561.
3. Svedsater H et al. Prim Care Resp Med. 2014; 24: 14019.

INNOVIVA | gsk

RELVAR® ▼ ELLIPTA®
(flutikazonfuroat in vilanterol, prašek za inhaliranje)
Praktična učinkovitost

[1] Povzetek glavnih značilnosti zdravila Tarceva. Dostopano septembra 2016 na: http://www.ema.europa.eu/docs/sl_SI/document_library/EPAR_-_Product_Information/human/000618/WC500033994.pdf

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Ime zdravila: Tarceva 25 mg/100 mg/150 mg filmsko obložene tablete. **Kakovostna in količinska sestava:** Ena filmsko obložena tableta vsebuje 25 mg, 100 mg ali 150 mg erlotiniba (v obliki erlotinibijevega klorida). **Terapevtske indikacije:** Nedrobnocelični rak pljuč: Zdravilo Tarceva je indicirano za prvo linijo zdravljenja bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč z EGFR-aktivirajočimi mutacijami. Zdravilo Tarceva je indicirano tudi za vzdrževalno zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč z EGFR-aktivirajočimi mutacijami in stabilno boleznijo po kemoterapiji v prvi liniji zdravljenja. Zdravilo Tarceva je indicirano tudi za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč po neuspehu vsaj ene predhodne kemoterapije. Pri predpisovanju zdravila Tarceva je treba upoštevati dejavnike, povezane s podaljšanim preživetjem. Koristnega vpliva na podaljšanje preživetja ali drugih kliničnо pomembnih učinkov zdravljenja niso dokazali pri bolnikih z EGFR-negativnimi tumorji (glede na rezultat imunohistokemije). Rak trebušne slinavke: Zdravilo Tarceva je v kombinaciji z gemcitabinom indicirano za zdravljenje bolnikov z metastatskim rakom trebušne slinavke. Pri predpisovanju zdravila Tarceva je treba upoštevati dejavnike, povezane s podaljšanim preživetjem. Koristnega vpliva na podaljšanje preživetja niso dokazali za bolnike z lokalno napredovalo boleznijo. **Odmerjanje in način uporabe:** Zdravljenje z zdravilom Tarceva mora nadzorovati zdravnik z izkušnjami pri zdravljenju raka. Pri bolnikih z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč, ki še niso prejeli kemoterapije, je treba testiranje za določanje mutacij EGFR opraviti pred začetkom zdravljenja z zdravilom Tarceva. Zdravilo Tarceva vzamemo najmanj eno uro pred zaužitjem hrane ali dve uri po tem. Kadar je potrebno odmerek prilagoditi, ga je treba zmanjševati v korakih po 50 mg. Pri sočasnem jemanju substratov in modulatorjev CYP3A4 bo morda potrebna prilagoditev odmerka. Pri dajanju zdravila Tarceva bolnikom z jetrno okvaro je potrebna previdnost. Če se pojavijo hudi neželeni učinki, pride v poštev zmanjšanje odmerka ali prekinitev zdravljenja z zdravilom Tarceva. Uporaba zdravila Tarceva pri bolnikih s hudo jetrno ali ledvično okvaro ter pri otrocih ni priporočljiva. Bolnikom kadilcem je treba svetovati, naj prenehajo kaditi, saj so plazemske koncentracije erlotiniba pri kadilcih manjše kot pri nekadilcih. Nedrobnocelični rak pljuč: Priporočeni dnevni odmerek zdravila Tarceva je 150 mg. Rak trebušne slinavke: Priporočeni dnevni odmerek zdravila Tarceva je 100 mg, v kombinaciji z gemcitabinom. Pri bolnikih, pri katerih se kožni izpuščaj v prvih 4 do 8 tednih zdravljenja ne pojavi, je treba ponovno pretehtati nadaljnje zdravljenje z zdravilom Tarceva. **Kontraindikacije:** Preobčutljivost na erlotinib ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pri določanju bolnikovega statusa mutacij EGFR je pomembno izbrati dobro validirano in robustno metodologijo, da se izognemo lažno negativnim ali lažno pozitivnim rezultatom. *Kadilci:* Bolnikom, ki kadijo, je treba svetovati, naj prenehajo kaditi, saj so plazemske koncentracije erlotiniba pri kadilcih zmanjšane v primerjavi s plazemskimi koncentracijami pri nekadilcih. Verjetno je, da je velikost zmanjšanja klinično pomembna. *Intersticijska bolezen pljuč:* Pri bolnikih, pri katerih se akutno pojavijo novi in/ali poslabšajo nepojasnjeni pljučni simptomi, kot so dispneja, kašelj in vročina, je treba zdravljenje z zdravilom Tarceva prekiniti, dokler ni znana diagnoza. Bolnike, ki se sočasno zdravijo z erlotinibom in gemcitabinom, je treba skrbno spremljati zaradi možnosti pojava toksičnosti, podobni intersticijski bolezni pljuč. Če je ugotovljena intersticijska bolezen pljuč, zdravilo Tarceva ukinemo in uvedemo ustrezno zdravljenje. *Driska, dehidracija, neravnovesje elektrolitov in ledvična odpoved:* Pri približno polovici bolnikov, ki so se zdravili z zdravilom Tarceva, se je pojavila driska (vključno z zelo redkimi primeri, ki so se končali s smrtnim izidom). Zmerno do hudo drisko zdravimo z loperamidom. V nekaterih primerih bo morda potrebno zmanjšanje odmerka. V primeru hude ali dolgotrajne driske, navzeje, anoreksije ali bruhanja, povezanih z dehidracijo, je treba zdravljenje z zdravilom Tarceva prekiniti in dehidracijo ustrezno zdraviti. O hipokaliemiji in ledvični odpovedi so poročali redko. Posebno pri bolnikih z dejavniki tveganja (zlasti sočasnim jemanjem kemoterapevtikov in drugih zdravil, simptomi ali boleznimi ali drugimi dejavniki, vključno z visoko starostjo) moramo, če je driska huda ali dolgotrajna oziroma vodi v dehidracijo, zdravljenje z zdravilom Tarceva prekiniti in bolnikom zagotoviti intenzivno intravensko rehidracijo. Dodatno je treba pri bolnikih s prisotnim tveganjem za razvoj dehidracije spremljati ledvično delovanje in serumske elektrolite, vključno s kalijem. *Hepatitis, jetrna odpoved:* Pri uporabi zdravila Tarceva so poročali o redkih primerih jetrne odpovedi (vključno s smrtnimi). K njenemu nastanku je lahko pripomogla predhodno obstoječa jetrna bolezen ali sočasno jemanje hepatotoksičnih zdravil. Pri teh bolnikih je treba zato premisliti o rednem spremljanju jetrnega delovanja. Dajanje zdravila Tarceva je treba prekiniti, če so spremembe jetrnega delovanja hude. *Perforacije v prebavilih:* Bolniki, ki prejemajo zdravilo Tarceva, imajo večje tveganje za razvoj perforacij v prebavilih, ki so jih opazili občasno (vključno z nekaterimi primeri, ki so se končali s smrtnim izidom). Pri bolnikih, ki sočasno prejemajo zdravila, ki zavirajo angiogenezo, kortikosteroide, nesteroidna protivnetna zdravila (NSAID) in/ali kemoterapijo na osnovi taksanov, ali so v preteklosti imeli peptični ulkus ali divertikularno bolezen, je tveganje večje. Če pride do tega, je treba zdravljenje z zdravilom Tarceva dokončno ukiniti. *Kožne bolezni, pri katerih so prisotni mehurji in luščenje kože:* Poročali so o primerih kožnih bolezni z mehurji in luščenjem kože, vključno z zelo redkimi primeri, ki so nakazovali na Stevens-Johnsonov sindrom/toksično epidermalno nekrolizo in so bili v nekaterih primerih smrtni. Zdravljenje z zdravilom Tarceva je treba prekiniti ali ukiniti, če se pri bolniku pojavijo hude oblike mehurjev ali luščenja kože. Pri bolnikih s kožnimi boleznimi z mehurji in luščenjem kože je treba preveriti prisotnost okužbe kože in jih zdraviti v skladu z lokalnimi smernicami. *Očesne bolezni:* Bolniki, pri katerih se pojavijo znaki in simptomi, ki nakazujejo na keratitis in so lahko akutni ali se poslabšujejo: vnetje očesa, solzenje, občutljivost na svetlobo, zamegljen vid, bolečine v očesu in/ali rdeče oči, se morajo takoj obrniti na specialista oftalmologije. V primeru, da je diagnoza ulcerativnega keratitisa potrjena, je treba zdravljenje z zdravilom Tarceva prekiniti ali ukiniti. V primeru, da se postavi diagnoza keratitisa, je treba skrbno razmisliti o koristih in tveganjih nadaljnega zdravljenja. Zdravilo Tarceva je treba pri bolnikih, ki so v preteklosti imeli keratitis, ulcerativni keratitis ali zelo suhe oči, uporabljati previdno. Uporaba kontaktnih leč je prav tako dejavnik tveganja za keratitits in ulceracijo. Med uporabo zdravila Tarce-

va so zelo redko poročali o primerih perforacije ali ulceracije roženice. *Medsebojno delovanje z drugimi zdravili:* Močni induktorji CYP3A4 lahko zmanjšajo učinkovitost erlotiniba, močni zaviralci CYP3A4 pa lahko povečajo toksičnost. Sočasnemu zdravljenju s temi zdravili se je treba izogibati. Tablete vsebujejo laktozo in jih ne smemo dajati bolnikom z redkimi dednimi stanji: intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Erlotinib se pri ljudeh presnavlja v jetrih z jetrnimi citokromi, primarno s CYP3A4 in v manjši meri s CYP1A2. Presnova erlotiniba zunaj jeter poteka s CYP3A4 v črevesju, CYP1A1 v pljučih in CYP1B1 v tumorskih tkivih. Z zdravilnimi učinkovinami, ki se presnavljajo s temi encimi, jih zavirajo ali pa so njihovi induktorji, lahko pride do interakcij. Erlotinib je srednje močan zaviralec CYP3A4 in CYP2C8, kot tudi močan zaviralec glukuronidacije z UGT1A1 *in vitro.* Pri kombinaciji ciprofloksacina ali močnega *zaviralca CYP1A2* (npr. fluvoksamina) z erlotinibom je potrebna previdnost. V primeru pojava neželenih učinkov, povezanih z erlotinibom, lahko odmerek erlotiniba zmanjšamo. Predhodno ali sočasno zdravljenje z zdravilom Tarceva ni spremenilo očistka prototipov *substratov CYP3A4*, midazolama in eritromicina. Inhibicija glukoronidacije lahko povzroči interakcije z zdravili, ki so *substrati UGT1A1* in se izločajo samo po tej poti. Močni *zaviralci aktivnosti CYP3A4* zmanjšajo presnovo erlotiniba in zvečajo koncentracije erlotiniba v plazmi. Pri sočasnem jemanju erlotiniba in močnih zaviralcev CYP3A4 je zato potrebna previdnost. Če je treba, odmerek erlotiniba zmanjšamo, še posebno pri pojavu toksičnosti. Močni *induktorji aktivnosti CYP3A4* zvečajo presnovo erlotiniba in pomembno zmanjšajo plazemske koncentracije erlotiniba. Sočasnemu dajanju zdravila Tarceva in induktorjev CYP3A4 se je treba izogibati. Pri bolnikih, ki potrebujejo sočasno zdravljenje z zdravilom Tarceva in močnim induktorjem CYP3A4, je treba premisliti o povečanju odmerka do 300 mg ob skrbnem spremljanju njihove varnosti. Zmanjšana izpostavljenost se lahko pojavi tudi z drugimi induktorji, kot so fenitoin, karbamazepin, barbiturati ali šentjanževka. Če te zdravilne učinkovine kombiniramo z erlotinibom, je potrebna previdnost. Kadar je mogoče, je treba razmisliti o drugih načinih zdravljenja, ki ne vključujejo močnega spodbujanja aktivnosti CYP3A4. Bolnikom, ki jemljejo *kumarinske antikoagulante*, je treba redno kontrolirati protrombinski čas ali INR. Sočasno zdravljenje z zdravilom Tarceva in *statinom* lahko poveča tveganje za miopatijo, povzročeno s statini, vključno z rabdomiolizo; to so opazili redko. Sočasna uporaba *zaviralcev P-glikoproteina*, kot sta ciklosporin in verapamil, lahko vodi v spremenjeno porazdelitev in/ali spremenjeno izločanje erlotiniba. Za erlotinib je značilno zmanjšanje topnosti pri pH nad 5. *Zdravila, ki spremenijo pH v zgornjem delu prebavil,* lahko spremenijo topnost erlotiniba in posledično njegovo biološko uporabnost. Učinka antacidov na absorpcijo erlotiniba niso proučevali, vendar je ta lahko zmanjšana, kar vodi v nižje plazemske koncentracije. Kombinaciji erlotiniba in zaviralca protonske črpalke se je treba izogibati. Če menimo, da je uporaba antacidov med zdravljenjem z zdravilom Tarceva potrebna, jih je treba jemati najmanj 4 ure pred ali 2 uri po dnevnem odmerku zdravila Tarceva. Če razmišljamo o uporabi ranitidina, moramo zdravili jemati ločeno: zdravilo Tarceva je treba vzeti najmanj 2 uri pred ali 10 ur po odmerku ranitidina. V študiji faze Ib ni bilo pomembnih učinkov *gemcitabina* na farmakokinetiko erlotiniba, prav tako ni bilo pomembnih učinkov erlotiniba na farmakokinetiko gemcitabina. Erlotinib poveča koncentracijo platine. Pomembnih učinkov *karboplatina* ali paklitaksela na farmakokinetiko erlotiniba ni bilo. *Kapecitabin* lahko poveča koncentracijo erlotiniba. Pomembnih učinkov erlotiniba na farmakokinetiko kapecitabina ni bilo. Zaradi mehanizma delovanja lahko od *zaviralcev proteasomov*, vključno z bortezomibom, pričakujemo, da vplivajo na učinek zaviralcev EGFR, vključno z erlotinibom. **Neželeni učinki:** *Zelo pogosti neželeni učinki* so kožni izpuščaj in driska, kot tudi utrujenost, anoreksija, dispneja, kašelj, okužba, navzea, bruhanje, stomatitis, bolečina v trebuhu, pruritus, suha koža, suhi keratokonjunktivitis, konjunktivitis, zmanjšanje telesne mase, depresija, glavobol, nevropatija, dispepsija, flatulenca, alopecija, okorelost, pireksija, nenormalnosti testov jetrne funkcije. *Pogosti neželeni učinki* so krvavitve v prebavilih, epistaksa, resna intersticijska bolezen pljuč, keratitis, paronihija, folikulitis, akne/akneiformni dermatitis, fisure na koži in ledvična insuficienca. *Občasno* so poročali o perforacijah v prebavilih, hirzutizmu, spremembah obrvi, krhkih nohtih, odstopanju nohtov od kože, blagih reakcijah na koži (npr. hiperpigmentaciji), spremembah trepalnic, nefritisu in proteinuriji. *Redko* pa so poročali o jetrni odpovedi in sindromu palmarno-plantarne eritrodisestezije. *Zelo redko* so poročali o Stevens-Johnsonovem sindromu/toksični epidermalni nekrolizi ter o ulceracijah in perforacijah roženice. Poročanje o domnevnih neželenih učinkih: Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na: Univerzitetni klinični center Ljubljana, Interna klinika, Center za zastrupitve, Zaloška cesta 2, SI-1000 Ljubljana, Faks: + 386 (0)1 434 76 46, e-pošta: farmakovigilanca@kclj.si. **Režim izdaje zdravila:** H/Rp. **Imetnik dovoljenja za promet:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, Velika Britanija. **Verzija:** 1.0/16. **Informacija pripravljena:** september 2016.
Samo za strokovno javnost.

PG-050-0916-TAC

DODATNE INFORMACIJE SO NA VOLJO PRI: Roche farmacevtska družba d.o.o., Vodovodna cesta 109, 1000 Ljubljana.

Roche

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Zdravilo KEYTRUDA®:

MOČ ZAVIRALCA PD-1

za podaljšano preživetje[1]

Literatura: 1. Povzetek glavnih značilnosti zdravila Keytruda, julij 2016

MSD

Merck Sharp & Dohme, inovativna zdravila d.o.o.
Šmartinska cesta 140, 1000 Ljubljana, telefon: 01/ 520 42 01, faks: 01/ 520 43 49/50,
Pripravljeno v Sloveniji, avgust 2016, ONCO-1160070-0001 EXP: 08/2017

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA:

Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih ali na sedežu družbe!

KEYTRUDA 50 mg prašek za koncentrat za raztopino za infundiranje vsebuje pembrolizumab, humanizirano monoklonsko protitelo proti receptorjem programirane celične smrti 1 (PD-1). Zdravilo KEYTRUDA je **v obliki monoterapije indicirano za zdravljenje napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih. Zdravilo je indicirano tudi za zdravljenje lokalno napredovalega ali metastatskega nedrobnoceličnega pljučnega raka (NSCLC - non-small cell lung carcinoma) pri odraslih, ki imajo tumorje z ekspresijo PD-L1 in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije.** Bolniki s pozitivnimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi zdravljenje, odobreno v primeru teh mutacij.PRIPOROČENI ODMEREK ZDRAVILA JE **2 mg/kg i.v. vsake tri tedne** do napredovanja bolezni ali nesprejemljivih tksičnih učinkov. Odmerka ni potrebno prilagajati pri starejših bolnikih ali bolnikih z blago do zmerno okvaro ledvic ali blago okvaro jeter. Zdravljenje je **kontrainidicirano** ob preobčutljivosti na zdravilno učinkovino ali katerokoli od pomožnih snovi.

Povzetek posebnih opozoril previdnostnih ukrepov, interakcij in neželenih učinkov: Pri ocenjevanju statusa PD-L1 tumorja je pomembno izbrati dobro validirano in robustno metodlogijo, da bi čim bol zmanjšali možnost lažno negativnih ali lažno pozitivnih določitev.Ob zdravljenju z zdravilom KEYTRUDA so bili poročani imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, nefritis, endokronopatije, hepatitis) od katerih je večina bila reverzibilna in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije, ter glede na izrazitost neželenega učinka zadržati uporabo pembrolizumaba oz uporabiti kortikosteroide. Pembrolizumab se lahko začne znova uporabljati v 12 tednih po zadnjem odmerku zdravila KEYTRUDA, če neželeni učinek ostane na ≤ 1. stopnji in je bil odmerek kortikosteroida znižan na ≤ 10 mg prednizona ali ekvivalenta na dan, drugače je treba zdravljenje trajno ukiniti. Zdravljenje je treba ukiniti tudi, če se kateri koli imunsko pogojeni neželeni učinek 3. stopnje znova pojavi ali se pojavi toksičen imunsko pogojeni neželeni učinke 4 stopnje razen v primeru endokrinopatij, ki so obvladljive z nadomeščanjem hormonov. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti po uvedbi zdravljenja s pembrolizumabom za zdravljenje imunsko pogojenih neželenih učinkov. Zaradi mehanizma delovanja je možno pričakovati okvaro ploda in več splavov ali mrtvorojenosti zato uporebo med nosečnostjo odsvetujemo razen ko klinično stanje ženske zahteva.Ženske v rodni dobi morajo med zdravljenjem in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo. Ker se protitelesa lahko izločajo v materino mleko, tveganja za novorojence/otroke ne moremo izključiti . Varnost pembrolizumaba so v kliničnih študijah ocenili pri 2.799 bolnikih s tremi odmerki (2 mg/kg na 3 tedne in 10 mg/kg na 2 ali 3 tedne) kjer so najpogosteje poročali o naslednjih neželenih učinkih: utrujenosti, izpuščajih , pruritusus, diareji, navzei in arthralgijah. Večina poročanih neželenih učinkov je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Večina, vključno s hudimi učinki, je po uvedbi ustreznega zdravljenja ali ukinitvi zdravljenja s pembrolizumabom izzvenela. Za popolniseznam neželenih učinkov prosimo preberite Povzetek glavnih značilnosti zdravila.

Način in režim izdaje zdravila: Zdravilo se izdaja le v bolnišnicah.

Imetnik dovoljenja za promet z zdravilom: Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU Velika Britanija

Datum zadnje revizije besedila: 22.8.2016

KEYTRUDA®

(pembrolizumab, MSD)

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

Foster 200 mikrogramov/6 mikrogramov na sprožitev inhalacijska raztopina pod tlakom

Sestava zdravila: En odmerek (iz ventila) vsebuje: 200 mikrogramov beklometazondipropionata in 6 mikrogramov formoterolfumarata dihidrata. To ustreza apliciranemu odmerku (iz sprožilca) 177,7 mikrogramom beklometazondipropionata in 5,1 mikrogramom formoterolfumarata dihidrata. **Indikacije:** Zdravilo Foster je indicirano za redno zdravljenje astme, kadar je primerna uporaba kombiniranega zdravila (inhaliranega kortikosteroida in dolgodelujočega agonista adrenergičnih receptorjev beta$_2$) pri bolnikih, neustrezno urejenih z inhaliranimi kortikosteroidi in inhaliranim hitrodelujočim agonistom adrenergičnih receptorjev beta$_2$, uporabljenim "po potrebi" ali pri bolnikih, ki so že ustrezno urejeni z inhaliranimi kortikosteroidi in dolgodelujočimi agonisti adrenergičnih receptorjev beta$_2$. Zdravilo Foster je indicirano pri odraslih. **Odmerjanje:** Zdravilo Foster ni namenjeno za začetno vodenje astme. Odmerjanje zdravila Foster je individualno in ga je treba prilagoditi resnosti bolezni, kar je treba upoštevati pri uvedbi zdravljenja s kombiniranim zdravilom in pri prilagajanju odmerka. Če bolnik potrebuje kombinacijo odmerkov, ki je drugačna od tiste v kombiniranem inhalatorju, je treba predpisati ustrezne odmerke agonistov adrenergičnih receptorjev beta$_2$ in/ali kortikosteroidov v ločenih inhalatorjih. Beklometazondipropionat je v zdravilu Foster v obliki izredno majhnih delcev, zato je njegov učinek močnejši kot učinek formulacij beklometazondipropionata, v katerih le-ta ni porazdeljen v izredno majhnih delcih (100 mikrogramov beklometazondipropionata v izredno majhnih delcih v zdravilu Foster ustreza 250 mikrogramom beklometazondipropionata v formulacijah, v katerih le-ta ni v izredno majhnih delcih), zato mora biti celotni dnevni odmerek beklometazondipropionata, apliciranega v obliki zdravila Foster, manjši kot celotni dnevni odmerek beklometazondipropionata, apliciranega v formulacijah, ki beklometazondipropionata ne vsebuje v izredno majhnih delcih. To je treba upoštevati, kadar bolnik preide iz formulacije beklometazondipropionata, ki ni v izredno majhnih delcih, na zdravilo Foster – odmerek beklometazondipropionata mora biti v takšnem primeru manjši in ga boste morali prilagoditi individualnim potrebam bolnikov. Priporočila za odmerjanje pri odraslih, starih 18 let in več: Dve inhalaciji dvakrat na dan. Največji dnevni odmerek so 4 inhalacije. Zdravilo Foster 200/6 se sme uporabljati le za vzdrževalno zdravljenje. Za vzdrževalno in olajševalno zdravljenje je na voljo manjša jakost (zdravilo Foster 100/6). Bolnikom je treba svetovati, naj imajo za primer rešilnega zdravljenja vedno pri sebi ločen kratkodelujoči bronhodilatator. Zdravnik mora zaradi zagotavljanja optimalnega odmerjanja zdravila Foster bolnika redno spremljati. Odmerjanje se lahko spremeni le na podlagi zdravniškega nasveta. Odmerek je treba titrirati do najmanjšega odmerka, ki učinkovito obvladuje simptome. Ko so simptomi dolgoročno urejeni z najmanjšim priporočenim odmerkom, lahko naslednji korak vključuje poskus zdravljenja samo z inhaliranim kortikosteroidom. Zdravila Foster 200/6 se ne sme uporabljati za stopenjsko zmanjševanje zdravljenja; za takšno zmanjševanje je na voljo zdravilo z manjšo vsebnostjo beklometazondipropionata v istem inhalatorju (zdravilo Foster 100/6 mikrogramov). Bolnikom je treba svetovati, da morajo zdravilo Foster uporabljati vsak dan, tudi če nimajo simptomov. *Posebne skupine bolnikov:* Pri starejših bolnikih odmerka ni treba prilagoditi. Podatkov o uporabi zdravila Foster pri bolnikih z okvaro jeter ali ledvic ni. Priporočila za odmerjanje pri otrocih in mladostnikih, mlajših od 18 let: Zdravila Foster 200/6 se ne sme uporabljati pri otrocih in mladostnikih, mlajših od 18 let. **Način uporabe:** Zdravilo Foster je namenjeno samo za inhaliranje. Da bo aplikacija zdravila ustrezna, mora zdravnik ali drugi zdravstveni delavec bolniku pokazati pravilno uporabo inhalatorja. Pravilna uporaba inhalatorja z določenim odmerkom pod tlakom je nujna za uspešno zdravljenje. Bolniku je treba svetovati, naj natančno prebere Navodilo za uporabo in upošteva vse smernice za uporabo v navodilu. **Kontraindikacije:** Preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov. **Opozorila in previdnostni ukrepi:** Zdravilo Foster je treba uporabljati previdno (to lahko vključuje spremljanje) pri bolnikih s/z: boleznimi srca in ožilja, tirotoksikozo, sladkorno boleznijo, feokromocitomom, nezdravljeno hipokaliemijo, hudo ali nestabilno astmo, anestezijo s halogeniranimi anestetiki, aktivno ali mirujočo pljučno tuberkulozo, glivičnimi ali virusnimi okužbami dihal. Priporočljivo je, da zdravljenja z zdravilom Foster ne končate nenadoma. Če bolnik ugotovi, da zdravljenje ni učinkovito, mora poiskati zdravniško pomoč. Povečanje uporabe rešilnih bronhodilatatorjev kaže na slabšanje osnovne bolezni in zahteva ponovno oceno zdravljenja astme. Nenadno in napredujoče slabšanje urejenosti astme je lahko smrtno nevarno in bolnik mora nujno poiskati zdravniško pomoč. Upoštevati je treba možnost povečanja odmerjanja inhaliranih ali peroralnih kortikosteroidov ali uvedbo antibiotičnega zdravljenja, če obstaja sum na okužbo. Zdravila Foster bolnikom ne smete uvesti med eksacerbacijo, v primeru značilnega poslabšanja ali akutnega slabšanja astme. Med zdravljenjem z zdravilom Foster se lahko pojavijo resni, z astmo povezani neželeni učinki in poslabšanja. Bolnikom je treba svetovati, naj zdravljenje nadaljujejo tudi v primeru, če simptomi astme niso obvladani ali se po uvedbi zdravila Foster poslabšajo, a naj hkrati poiščejo zdravniško pomoč. Tako kot pri zdravljenju z drugimi inhalacijskimi zdravili se lahko po uporabi zdravila Foster pojavi paradoksni bronhospazem s takojšnjim poslabšanjem kratke sape in piskajočega dihanja. To stanje je treba nemudoma zdraviti s hitrodelujočim inhalacijskim bronhodilatatorjem. Uporabo zdravila Foster je v tem primeru treba takoj prekiniti, bolnika pregledati in uvesti drugo zdravljenje, če je potrebno. Zdravila Foster ne smete uporabiti kot prvo terapijo obvladovanja astme. Bolnikom je treba svetovati, da morajo imeti za zdravljenje akutnih napadov astme vedno pri sebi hitrodelujoči bronhodilatator. Bolnike opozorite, da morajo zdravilo Foster uporabljati vsak dan, kot je predpisano, tudi če nimajo simptomov. Ko so simptomi astme obvladani, pride v poštev postopno zmanjšanje odmerka zdravila Foster. Pomembno je, da bolnike med zmanjševanjem odmerka redno spremljate. Uporabljati je treba najmanjši učinkoviti odmerek zdravila Foster (na voljo je zdravilo Foster z nižjim odmerkom 100/6). Pri vseh inhaliranih kortikosteroidih se lahko pojavijo sistemski učinki, zlasti ob dolgotrajni uporabi velikih odmerkov. Ti učinki so veliko manj verjetni med uporabo inhaliranih kortikosteroidov kot med uporabo peroralnih kortikosteroidov. Med možnimi sistemskimi učinki so: Cushingov sindrom, cushingoidne značilnosti, supresija nadledvičnih žlez, zmanjšanje mineralne gostote kosti, upočasnitev rasti pri otrocih in mladostnikih, katarakta in glavkom ter redkeje vrsta psiholoških in vedenjskih učinkov, vključno s psihomotorično hiperaktivnostjo, motnjami spanja, anksioznostjo, depresijo ali agresijo (zlasti pri otrocih). Bolnike morate zato redno spremljati in odmerek inhaliranega kortikosteroida zmanjšati do najmanjšega odmerka, s katerim je mogoče astmo učinkovito obvladovati. Dolgotrajno zdravljenje z velikimi odmerki inhaliranih kortikosteroidov lahko povzroči supresijo nadledvičnih žlez in povzroči akutno adrenalno krizo. Posebej ogroženi so lahko otroci, mlajši od 16 let, ki jemljejo/inhalirajo odmerke beklometazondipropionata, večje od priporočenih. Med okoliščinami, ki lahko sprožijo akutno adrenalno krizo, so poškodbe, operacije, okužbe in vsako hitro zmanjšanje odmerka. Simptomi so običajno nejasni – med njimi so lahko anoreksija, bolečine v trebuhu, zmanjšanje telesne mase, utrujenost, glavobol, navzeja, bruhanje, hipotenzija, motnje zavesti, hipoglikemija in konvulzije. Med obdobji stresa ali ob elektivni operaciji pride v poštev dodatna zaščita s sistemskimi kortikosteroidi. Pri prehodu bolnikov na zdravljenje z zdravilom Foster je potrebna previdnost, zlasti če je mogoče domnevati, da je delovanje nadledvičnih žlez zaradi predhodnega sistemskega zdravljenja s steroidi prizadeto. Bolnike, ki s peroralnih kortikosteroidov preidejo na inhalirane, lahko še dolgo ogroža zmanjšanje adrenalne rezerve. Ogroženi so lahko tudi bolniki, ki so v preteklosti potrebovali velike odmerke nujnega zdravljenja s kortikosteroidi ali so dolgo časa dobivali velike odmerke inhaliranih kortikosteroidov. V nujnih primerih in v elektivnih okoliščinah, pri katerih je verjeten stres, je vedno treba upoštevati možnost rezidualne okvare in poskrbeti za ustrezno zdravljenje s kortikosteroidi. Zaradi izrazitosti adrenalne prizadetosti utegne biti pred elektivnimi postopki potreben posvet s specialistom. Da bo tveganje za orofaringealne okužbe s kandido manjše, bolnikom svetujte, naj po inhalaciji predpisanega odmerka usta splaknejo ali grgrajo vodo ali si umijejo zobe. Zdravilo Foster vsebuje majhno količino etanola (alkohola), manj kot 100 mg na sprožitev. Ob normalnih odmerkih je ta količina etanola zanemarljiva in ne pomeni tveganja za bolnike. **Interakcije:** blokatorji adrenergičnih receptorjev beta (vključno s kapljicami za oči), beta-adrenergiki (npr. teofilin), kinidin, dizopiramid, prokainamid, fenotiazini, antihistaminiki, zaviralci MAO, triciklični antidepresivi, L-dopa, L-tiroksin, oksitocin, alkohol, zdravila, ki imajo podobne lastnosti kot furazolidon in prokarbazin, anestetiki s halogeniranimi ogljikovodiki, ksantinski derivati, steroidi, diuretiki, digitalisovi glikozidi, disulfiram ali metronidazol. **Povzetek neželenih učinkov:** Pogosti: faringitis, kandidoza ust, glavobol, disfonija. Občasni: gripa, glivična okužba v ustih, orofaringealna kandidoza, ezofagealna kandidoza, vulvovaginalna kandidoza, gastroenteritis, sinuzitis, rinitis, pljučnica, granulocitopenija, alergijski dermatitis, hipokaliemija, hiperglikemija, nemir, tremor, omotica, otosalpingitis, palpitacije, podaljšanje korigiranega intervala QT na elektrokardiogramu, spremembe elektrokardiograma, tahikardija, tahiaritmija, atrijska fibrilacija, hiperemija, zardevanje, kašelj, produktiven kašelj, draženje žrela, astmatična kriza, pordelost žrela, driska, suhost ust, dispepsija, disfagija, pekoč občutek na ustnicah, navzeja, dizgevzija, srbenje, osip, hiperhidroza, urtikarija, mišični spazmi, mialgija, zvečanje vrednosti C-reaktivnega proteina, prostih maščobnih kislin, insulina in ketonskih teles v krvi, povečano število trombocitov, znižanje vrednosti kortizola v krvi, zvišanje krvnega tlaka. **Način in režim izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** Chiesi Pharmaceuticals GmbH, Gonzagagasse 16/16, 1010 Dunaj, Avstrija. **Datum zadnje revizije besedila:** 15.07.2015.

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Podrobnejše informacije so na voljo pri predstavniku imetnika dovoljenja za promet z zdravilom v Sloveniji: **Chiesi Slovenija, d.o.o.**, Trdinova 4, Ljubljana, info.si@chiesi.com
www.chiesi.si, www.moja-astma.si

SAMO ZA STROKOVNO JAVNOST
Datum priprave informacije: september 2016
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