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Content

End stage pulmonary diseases

Challenges and evidence for better quality palliative care for patients with end stage pulmonary diseases

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Palliative care has developed around the specific needs of cancer patients. But there is much evidence that different trajectories of different groups of chronic diseases are leading to different needs. There are models known of the trajectory of cancer (Figure 1) or chronic disease of organ failure such as COPD, emphysema and cystic fibrosis (Figure 2) (1). Trajectory in COPD is characterized by acute exacerbation, and for lung cancer it is significant, that once treatments don't have any effect, deterioration is steady and rapid. Comparison between patients with end stage COPD and lung cancer indicated that patients with COPD had significantly worse activities of daily living and physical, social and emotional functioning than patients with lung cancer (2). They experience these difficulties for a much longer period. COPD patients suffer more often different co-morbidities with their COPD during longer period of time, such as heart failure, cardiac arrhythmia, pulmonary embolism, pulmonary infection and lung cancer. But lung cancer patients receive palliative care much more often (3).

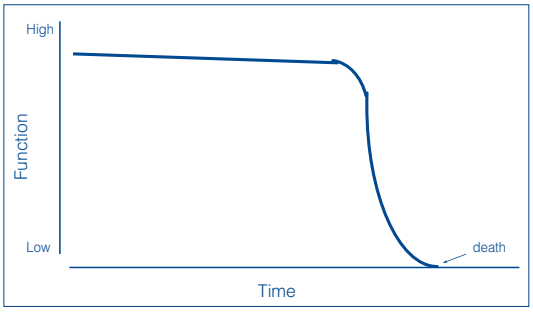

Figure 1 - Model of typical trajectory of an illness due to cancer

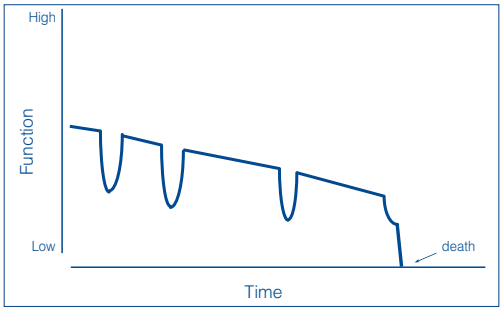

Figure 2 – Model of typical trajectory of an illness due to organ failure

Palliative care for non-malignant patients is still in its early development. COPD patients experience extensive end of life needs during their prolonged functional decline which is associated with a heavy symptom load, emotional distress and social isolation. There is growing number of research that existing service provision is unable to meet these needs. The emphasis of palliative care in COPD pa-

tients in their advanced stage appears to be given on reactive crisis intervention during the episodes of acute exacerbations, rather than continual supportive measures (4).
The American College of Chest Physicians support the position that good palliative care is an integral part of cardiopulmonary medicine only in 2005, earlier recommendations on end-of-life care don't mention palliative care the Global initiative on chronic obstructive pulmonary disease guidelines (National Heart, Lung and Blood Institute and the World Health Organization) (5).
The most prominent physical problems for patients with advanced pulmonary chronic disease (chronic obstructive pulmonary disease, emphysema, lung cancer, cystic fibrosis) in the end stage of the disease is dyspnea. It is defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary intensity (6). Dyspnea is experienced by patients and also by their families as a very distressing and frightening symptom, which is very difficult to alleviate, because its mechanism is poorly understood. Patients with increasing and fluctuating trajectories may suffer more than patients with stable or slowly increased courses (7). Fluctuating trajectories may be associated with more uncertainty for patients planning their everyday lives, and more difficult to develop coping strategies. There is evidence for judicious use of opiates and oxygen in the treatment of dyspnea. Along with dyspnea patients with pulmonary chronic disease in its advanced stage have also several other physical symptoms: fatigue, caught, pain, anxiety, panic, depression, anorexia and cachexia, constipation, poor sleep. Regular assessment and excellent symptom control are crucial, but there are several barriers and challenges for these patients to receive appropriate care at the end of life.

Challenges of palliative care in COPD

Poor symptom control in the advanced stage, difficulty in determining prognosis and lack of communication are the most problematic barriers in palliative care in COPD (8).
Patients' understanding of COPD as a life-limiting disease is poor and it seems that the importance of an adequate diagnosis and prognosis on the way patients cope with the illness and their quality of life in not recognized enough (9).
Most patients with COPD want end-of-life conversations with their health care professionals; only a substantial minority of patients does not want such a conversation. Health care professionals need to respect wishes of those not wanting to discuss end-of-life care. Patients who don't want to discuss their illness and end-of-life care are often those who estimate their prognosis to be excellent, and do not want active involvement in decision making. Patients often see COPD "not so much as an illness, more a way of life" with attitude to death comparable to those in a normal elderly population.
Giles and Higginson (4) found three most important needs in communication with COPD patients lacking in clinical practice. First, prognosis needed to be given much earlier in the illness, as part of diagnosis. Second, a step-wise approach in active decisions regarding treatment and future care, and third, the focus on the length of survival should be considered, given the uncertainty of the time of death. Careful assessment of possible supportive and palliative care needs should be triggered at key disease milestones along with life time journey with COPD, in particular after hospital admission for an acute exacerbation (10). Health care professionals find it difficult to start these conversations, and many prefer patients to initiate them. The uncertainty of prognosis creates difficulty in providing patients with information of the course of their illness. Discussions may sensitively cover explanation of functional decline, the possibility of acute exacerbation and potential for cardiovascular and other causes of death, including sudden death. All these take more time and when possible, involvement of different professions
The implications of avoidance of conversations are several. Avoidance of discussions may give false hope. Patients don't get the opportunity to prepare and plan their life. The conversation is suggested as the most balanced, when guided by the statement suggested by Back (11): "I encourage you to hope for and expect the best, but it is also wise to prepare for the worst."
Advanced care planning (ACP) is very rarely initiated in patients with COPD (12). It is "a process of discussion about future care between an individual and their care providers, irrespective of discipline" (13). Also cardiopulmonary resuscitation and in hospital ventilation should be discussed with patients in order to give them an opportunity to actively plan and cooperate in decision-making for times

of advanced disease. It is recognized that the involvement of nurses in these conversations can be provided without an additional stress for patients (14).

Summary

Patients with advanced chronic lung disease have common difficult symptoms of dispend, fatigue, pain, poor sleep, depression and other disturbing symptoms, emotional and social problems. Patients who are at the end stage of their chronic pulmonary disease may be comforted by sensitive and precise symptom control and psychological and social support. Optimal palliative care is possible by preventing most expected events; therefore advanced care planning is of significant importance.
Good communication practices are fundamental in the care of advanced chronic pulmonary disease: integration of diagnosis and prognosis as early as possible, a step-wise approach throughout the illness trajectory, a holistic and patient centered approach, recognition of uncertainty, and focus on quality of life. Health care professionals often lack education to be comfortable with skills and knowledge needed in communication challenges in end-of-life care.
Patient education is particularly important in COPD patients and therefore also wider public education about end of life issues.
Significant service improvement is needed in COPD patients, not only in clinical measures for better palliation of disturbing symptoms, but particularly also patient participation in end-of-life decision-making.

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How coordinated discharge process for patients with advanced pulmonary disease may avoid unnecessary re- hospitalizations

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Majority of patients with advanced cancer would like to be able to die in the familiar surroundings of a home environment, cared for by family members and health care professionals (1). Although more than half patients with advanced chronic disease die institutions, it is the least favorite choice for preferred place of care (2). Palliative care may with contribute largely to this change (3).
In, 40% of patients who die in hospital did not have medical needs that required hospital stay (4). Abel et al. performed a descriptive study in a general hospital in South west of to see the proportion of patients that could be recognized as being in the last year of life and to assess the appropriateness of accessing community services for home palliative care. They found that a maximum of one third of all hospital deaths could have receive palliative care at home if excellent end-of-life care services were in place (5).
Preventing hospital admissions for final illness seems to be a priority in strategic planning of palliative care.
The following components are needed to change this trend of majority of patients with advanced chronic illness dying in hospitals (5):

- The patient is recognized as being in the last year of life – the surprise question: "Would I be surprised, if my patient dies in the next 6-12 months?", with clinical and functional indicators for this criteria
- Advance care planning concerning place of death and priorities for care are documented and available for relevant health care organizations (6)
- Home palliative care is available at short notice 24 h per day
- Nursing care for the final stages of life is available

In pulmonary diseases it is usually a case as with this example:
Patient with COPD made his wish to stay at home for care to the last day of life, does not want cardiopulmonary resuscitation, and home care with appropriate palliative care expertise is available. Effective implementation of home palliative care is possible only, if on the timely discharge from a hospital advanced care plan is documented and coordinated discharge is performed to connect with primary care and patient's family.
Use of a structure of specialized palliative care was highly significantly associated with a return and dying at home without re-hospitalization needed at the deterioration stages (7).
Potentially these activities and processes could even reduce inappropriate health care services utilization at the closure of one's life (8). Family members could learn beneficial procedures in the care

giving in the dying phase, and health care settings could change their practices towards much more appropriate processes for patients in their most vulnerable phase of life.

Advance care planning and coordinated discharge

From the discharge from the hospital physical, psychological and spiritual/existential vulnerability factors contribute to the feelings of safety at home. Additionally patients and family members need accurate information about the probable trajectory of the advanced disease, possible professional help and advice, practical solutions and social aids. On the basis of all the structured framework of home care with a possibility of 24 h telephone advice of primary or palliative care team patients may decide for their advance care plan. It includes not only preferred location of care, but also chosen medical procedures not desired anymore, for example: cardiopulmonary resuscitation, transfusion, dialysis, mechanical ventilation, intubation, etc. Patient and family receive not only the information on the likelihood of the advanced disease trajectory, but also education on the drugs to be used for common symptoms that may develop basic nursing skills and information on network of home help for nursing and social aids. They are sensitively introduced in the process of progression of the diseases and its implication on the function and most common problems.

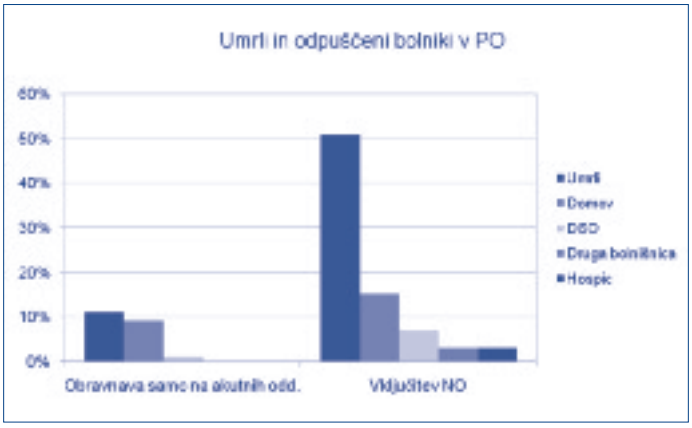
Process of advance care planning is usually performed at the family meeting when together with patient and family members also team of physician, nurse and social worker is helping negotiating goals of care and advance care planning to realistic frame in accordance with patient's values and wishes (9). Making these conversations sensitive to patient's needs there are special skills needed and reasonable empathy and sensitivity (10).

Nurses are taking the role of coordinator, informing the primary care team, community nurse and other necessary services; palliative care physician informs patient's family physician. Therefore a continuation of care is guaranteed and primary care team can easily use the opportunity to ask for advice when needed.

The challenge of implementing this cultural change is large. Studies are suggesting that patients with advanced cancer could receive palliative care more easily than patients with organ failure (9) and slow deterioration as frailty.

Experiences at the University Clinic Golnik

All these findings are proved also in practice of University Clinic Golnik. From June 2009 to July 2012, 379 patients have received specialist palliative care. Cancer was the most frequent first diagnosis (74%), organ failure in 16% and frailty in 10%. Most common cancer was lung cancer (208 patients). 58% patients in palliative care died in hospital, 24% were discharged to their home, nearly 10% in nursing home, 4% to hospice and 4% to another hospital. For all patients at least goals of care were clearly defined and basic advance care plan. Patients, who were discharged, have received also coordinated process of transition to home care, nursing home, hospice or another hospital.



In home care our coordinator from palliative care unit is available on telephone for advice 24 h a day. When needed palliative medicine specialist from our team is asked for advice. Mostly advices are needed in symptom control, (most often pain and delirium), advice how to perform change of route of drug application (syringe driver) and advice in the dying phase.

Patients with cancer were more likely dying at home and patients with heart failure, chronic obstructive pulmonary disease or other organ failure have more often returned to hospital at the end of life. It is necessary for this process of advanced care planning and coordinated discharge to be more successful to establish a wide range of basic knowledge of palliative care for all professionals in primary care and also organizational processes to support patients and their families to be able to remain at home.

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Patients' and population safety

Respiratory diseases and outdoor air pollution in Zasavje: no association or insufficient data?

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Introduction

The detrimental effects of outdoor air pollution on human health came to public prominence in the mid-1900s, as a result of high pollution episodes in , and . Since then, a large number of studies found consistent associations between outdoor air pollutants (e.g. sulphur dioxide (SO_2), ozone (O_3), and particulate matter with aerodynamic diameter < 10 μm - PM_{10}), and different measures of ill health.

Concentrations of outdoor air pollutants change daily or even hourly, primarily due to the strong influence of weather conditions. This variability provides an opportunity to investigate the acute effects of air pollution on short-term changes in health. The most frequently used method to statistically explore short-term associations between daily outdoor air pollution data and frequencies of events (e.g. primary health care visits, hospital admissions, death) are ecological time series analyses. These studies mostly rely on routinely available outdoor air pollution and health registry data.

Recent epidemiological research focuses on the health effects of outdoor air pollution on potentially sensitive population subgroups such as children. Potential determinants of children's susceptibility include the continuing process of lung growth and development, incomplete metabolic systems, immature host defenses, high rates of infection with respiratory pathogens and activity patterns that increase exposure to outdoor air pollution and to volume of inhaled pollutants.

Zasavje is considered as one of the most polluted regions of . The most important pollutants in the past were SO_2 and PM_{10}. According to the newest report of the Environmental Agency of the Republic of Slovenia (EARS) the SO_2-associated pollution has greatly improved; from 2000 to 2010 the average annual concentration of SO_2 decreased from 22 μg/m^3 to 6 μg/m^3. However, PM_{10} and O_3 concentrations constantly exceed the nationally defined maximum values.

Following these research lines, we aimed to investigate the short-term effects of outdoor air pollution (SO_2, O_3 and PM_{10}) on primary health care visits due to respiratory diseases among children in Zasavje.

Methods

Study design and study population

This study used an ecological time series design. The unit of observation was a single day. Our study population was children, aged 1-11 years, residing permanently in Zasavje, who visited the Com-

munity Health Centers Zagorje ob Savi, Trbovlje or Hrastnik due to selected respiratory diseases between January 1st, 2006 and December 31st, 2011.

Health and environmental data collection

Daily numbers of primary health care visits due to following diagnoses according to the World Health Organization International Classification of Diseases, version 10 (ICD-10) were obtained: J00-J06 (acute upper respiratory tract infection), J10-J18 (influenza and pneumonia), J20-J22 (other acute lower respiratory tract infection), J30-J32 (other diseases of upper respiratory tract) and J40-J46 (chronic lower respiratory tract disease). Community Health Centers Zagorje ob Savi and Hrastnik were able to provide health data for the whole study period, while Community Health Centre Trbovlje provided health data only for the period between June 21st, 2010 and December 31st, 2011, respectively.

Daily concentrations of outdoor air pollutants (SO_2, O_3 and PM_{10}) were obtained from three fixed monitoring stations in Zasavje (located in Zagorje ob Savi municipality, Trbovlje municipality and Hrastnik municipality), which are part of the National automated network for monitoring air quality operated by EARS. Monitoring station in Hrastnik municipality started with PM_{10} concentration measurement as late as January 1st, 2010, therefore previous data were not available. Additionally, daily data on air temperature, relative humidity and wind direction were obtained from all three monitoring stations.

Statistical analysis

We used daily time series data provided by three Community Health Centers and three fixed monitoring stations. The associations were investigated using Poisson regression models. The modeling procedure was performed in two stages. In the first stage, single-pollutant models were built by adding the single exposure variable (SO_2, O_3, PM_{10}) to a core covariate model that included all covariates considered in the study (year of data collection, day of the week, holiday effects, air temperature and relative humidity). In the second stage, models that included best lags of all pollutants (SO_2, O_3 and PM_{10}) as well as all covariates were defined (multi-pollutant models).

All statistical analyses were carried out by using SPSS 18.0 software (SPSS Inc.,). The study protocol was approved by the National Medical Ethics Committee of the .

Results

Complete health data were available for 2.191 days in Zagorje ob Savi municipality, 2.191 days in Hrastnik municipality and 559 days in Trbovlje municipality. Table 1 presents daily respiratory disease related visits among children in all three Community Health Centers in Zasavje during the study period.

Table 1. Daily respiratory disease related visits in Community Health Centers Zagorje ob Savi, Trbovlje and Hrastnik between January 1st, 2006 and December 31st, 2011.

Year	Visits due to respiratory diseases among children in Community Health Centers:		
	Zagorje ob Savi	Trbovlje	Hrastnik
2006	2.177	No data	1.348
2007	1.948	No data	869
2008	1.736	No data	674
2009	1.592	No data	679
2010	1.372	273*	638
2011	1.263	1.056	804
ICD 10 codes			
J00-J06 and J20-J22	9.472	1.072	4.727
J10-J18	233	109	39
J30-J32	162	25	162
J40-J46	221	122	84
Total	10.088	1.329	5.012

Legend: * – data were collected between June 21st, 2010 and December 31st, 2010.

The number of daily primary health care visits due to respiratory diseases was the highest in winter months (from December to February) and the most frequent complaints were acute respiratory tract infections. Figure 1 shows temporal pattern of daily primary health care visits due to respiratory diseases among children in Community Health Centre Zagorje ob Savi. The similar temporal pattern was also observed in Community Health Centre Hrastnik.

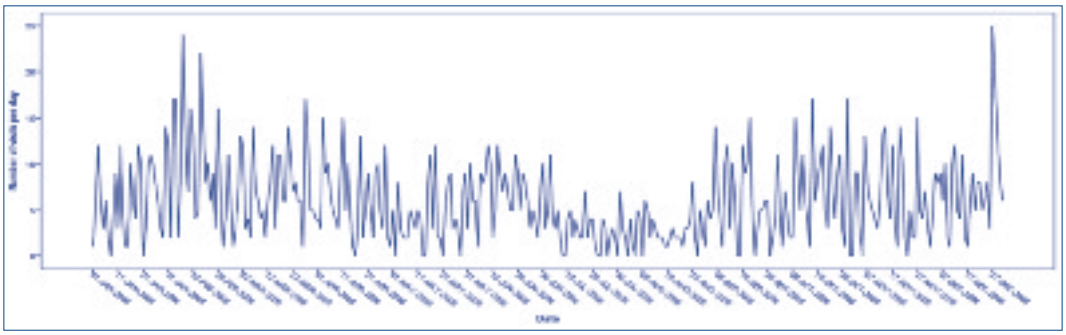

Figure 1. Temporal pattern of daily primary health care visits due to respiratory diseases among children in Community Health Centers Zagorje ob Savi between January 1st, 2006 and December 31st, 2011.

Complete environmental data were available for 2.003 days in Zagorje ob Savi municipality, 703 days in Hrastnik municipality and 1.937 days in Trbovlje municipality. On all three monitoring stations in Zasavje the highest concentrations of PM_{10} were observed in the months of December and January. Figure 2 presents temporal pattern of daily PM_{10} concentration in Zagorje ob Savi municipality monitoring station. The overall trend of daily O_3 concentrations was upward from April to July, and then downward from August to October. The highest daily SO_2 concentrations were observed in the months from November to February (both apply for all three monitoring stations). Over the study period, the results of daily PM_{10} concentration measurements show decreasing trend on both Zagorje ob Savi municipality and Trbovlje municipality monitoring stations. However, the number of days per year when the daily target value of PM_{10} concentration was exceeded is far from being consistent with Slovenian air quality legislation (not to be exceeded more than 35 days per year).

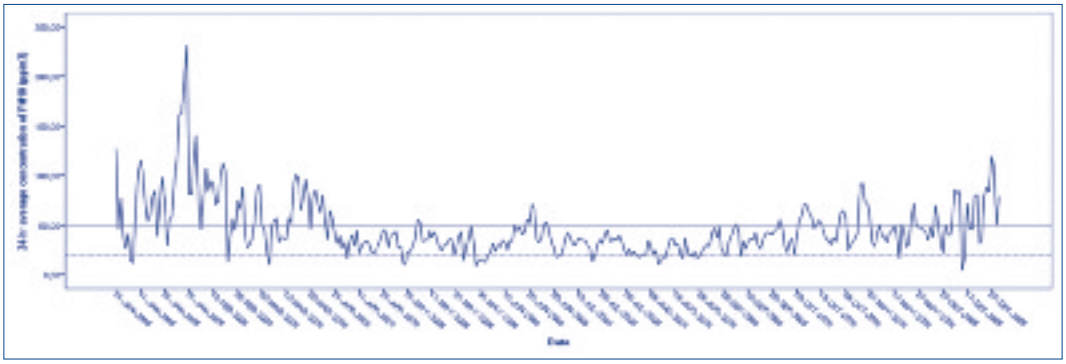

Figure 2. Temporal pattern of daily PM_{10} average concentration (µg/m^3) in Zagorje ob Savi municipality monitoring station between January 1st, 2006 and December 31st, 2011. Legend: — daily target value for 24-h average concentration (50 µg/m^3); --- annual target value for 24-h average concentration (20 µg/m^3).

Results of Poisson regression analysis with multi-pollutant model adjusted on selected covariates show that the number of primary health care visits due to respiratory diseases among children in Zagorje ob Savi municipality was significantly associated with PM_{10} concentrations (incidence rate

ratio (IRR) 1.001, 95% confidence interval (CI) 1.000-1.002, p=0.044), but not with O_3 (IRR 1.000, 95% CI 0.998-1.002, p=0.842) and SO_2 concentrations (IRR 0.998, 95% CI 0.992-1.004, p=0.470). We did not find significant associations between primary health care utilization and pollution exposure in other two municipalities in Zasavje.

Discussion

Our study demonstrated that the primary health care visits due to respiratory diseases among children were positively correlated with the concentrations of PM_{10} in Zagorje ob Savi municipality. For other two municipalities in Zasavje no such association has been found.

During the last decade epidemiologic research on the adverse health effects of air pollution has especially focused on susceptible population subgroups. With respect to children, many recent time series and panel studies have indicated the adverse health effects of exposure to PM_{10}, while the results regarding exposure to gaseous pollutants have been less conclusive. Among children in Zasavje, we did not find positive correlations between health care utilization due to respiratory problems and concentrations of SO_2 and O_3.

The choice of ecological time series design for this study was based on two reasons: comparability with other existing research, and the routine availability of the required data. The latter is likely to be one of the major reasons why time series designs make up the largest proportion of air pollution and health studies, because they are fast and inexpensive to conduct. As outdoor air pollution consists of a complex mixture of compounds, we strive to obtain data on wide range of pollutants. However, for the whole study period daily concentrations of pollutants (SO_2, O_3 and PM_{10}) were available on two monitoring stations (in Zagorje ob Savi municipality and Trbovlje municipality). In Hrastnik municipality air pollution monitoring was relatively sparse, as PM_{10} concentrations were not measured until January 1st, 2010. We faced similar problem in availability of health data as well. Community Health Centre Trbovlje used traditional method of health data collection which did not allow for a display of information needed for the analysis in our study. Consequently, we were not able to investigate the short-term effects of outdoor air pollution on primary health care visits due to respiratory diseases among children in Hrastnik municipality and Trbovlje municipality for the periods before the data necessary for our study became available. Therefore, long series of complete health and environmental data (over a period of 6 years) to study those associations were possible only in Zagorje ob Savi municipality.

An inherent disadvantage of ecological time series studies is exposure misclassification. The use of three fixed monitoring stations may not be sufficient to accurately characterize the spatial pattern in pollutants concentrations across Zasavje and true exposure of the children, thus potentially leading to errors. Nevertheless, there is some evidence that exposure misclassification in time series analysis tends to bias the estimates downwards and in that sense it does not limit the public health importance of the findings. Another drawback of a time series design is the possible presence of unmeasured confounders. However, the ecological time series studies of short-term effects which use long series of small units (days), like our in Zagorje ob Savi municipality, often downplays such errors. An important feature of such studies is that the population followed up serves as its own control over time, and thus possible confounders can only be factors varying according to small time units (from day to day). Such factors can conceivably be meteorological and chronological factors, which usually are accurately measured and easily recorded.

Conclusions

In conclusion, we found positive correlation between concentrations of PM_{10} and primary health care visits due to respiratory diseases among children in Zagorje ob Savi municipality. In the future, alternative study designs may be required to accurately estimate the effects of air pollution on children's health. One possibility to overcome those issues would be to conduct a cohort study, which requires individual level measurements of health and pollution exposure.

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Discharge coordinator intervention prevents hospitalisations in COPD patients: results of a randomised controlled clinical trial

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Introduction
Hospitalisations are a key feature of many chronic diseases, including chronic obstructive pulmonary disease (COPD). Along with decrease in lung function and health-related quality of life, hospitalisations are associated with substantial social and economic costs. COPD should therefore be regarded as a major public health problem requiring management strategies aiming to prevent hospitalisations and achieve important benefits for patients and health care systems.
Discharge planning and comprehensive multidisciplinary management generally improves the journey of a patient with a chronic disease, yet such evidence is scarce in COPD patients. Most early studies aimed to demonstrate the benefit of assisted discharge or hospital-at-home and reported on shorter length of hospital stay and the associated economic benefit. Later studies recruited patients in an outpatient setting, mostly after hospitalisation for COPD, and aimed to reduce exacerbations with or without the necessity for hospital admissions.
It is important to consider the hospital stay as a unique opportunity for involving patients in management of their disease and for evaluating their needs in their home environment. We conceived this study to test whether coordination of discharge from hospital and post-discharge care reduces hospitalisations and use of resources in COPD patients.

Methods
For this randomized controlled clinical trial we enrolled 253 eligible patients between 2 November 2009 and 6 December 2011. Eligible patients included those admitted with acute exacerbation of COPD who had reduced pulmonary function corresponding to Global Initiative for Chronic Obstructive Lung Disease stage II to IV. The main exclusion criteria were unstable or terminal stage of disease other than COPD, patients unable to deal with phone contact when out of hospital, and death or withdrawal of written informed consent before discharge.
After randomisation of the study patients, a discharge coordinator managed those in the intervention group; the control group of patients received care as usual. The discharge coordinator assessed the patient situation and homecare needs to adjust the in-hospital intervention and visits according to prespecified objectives that included patient knowledge and self-care management, together with liaison with caregivers, social care, and others as appropriate to provide continuity of care and care coordination across different levels of healthcare. Patients were contacted by phone 48 hours after discharge

to check the process of adjustment to the home environment and to inquire about any additional needs. Thereafter, phone contacts were scheduled according to the patients' needs and objectives as described previously. Intervention was completed during a home visit 7–10 days after discharge. Patients were followed-up for 180 days after discharge: healthcare utilisation and survival status were assessed during phone contact at 30 days and 90 days or during a direct patient contact at 7–10 days and 180 days. Mortality data were verified with the Central Population Registry.
The primary endpoint of the study was the number of patients hospitalised (an unplanned overnight stay in hospital) because of worsening COPD. Key secondary endpoints were time-to-COPD hospitalisation, all-cause mortality, all-cause hospitalisation, days alive and out of hospital, and health-related quality of life. Data were analysed using Student's *t*-test, chi-squared test, Mann–Whitney U-test, paired *t*-test, Kaplan–Meier analysis, and log-rank test. A Cox model of proportional hazards was built for a multivariate analysis.

Results

A total of 253 patients (118 to the intervention and 135 to the control group) were enrolled during the recruitment period and were followed-up for at least 180 days after discharge from hospital or until death. Enrolled patients were mostly elderly men (72%) with an average age of 71±9 years, with significant smoking exposure and mostly with severe pulmonary obstruction.
Overall, 59 of the 253 patients (23%) had a primary outcome (i.e. COPD hospitalisation) during the 180 days of follow-up, with significantly fewer patients from the intervention group being hospitalised for COPD when compared with the control group: 17 (14%) vs. 42 (31%) patients (p=0.002) – Table 1. The rates of primary outcome were significantly different: 0.29 per patient-year in the intervention group and 0.68 per patient-year in the control group (p=0.001) – Figure 1. Intervention was also associated with better outcome in terms of all-cause hospitalisation (31% vs. 44%, p=0.033), but not in terms of mortality.
The adjusted Cox model of proportional hazards was built to investigate an independent effect of group allocation. Intervention was associated with lower risk of COPD hospitalisation (hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.24–0.77, p=0.002) and all-cause hospitalisation (HR 0.64, 95% CI 0.42–0.98, p=0.039), whereas there was no effect on patient mortality (HR 0.54, 95% CI 0.23–1.28, p=0.164).

Table 1. Primary and secondary outcomes among COPD patients.

Outcome	Discharge coordinator	Usual care	p
COPD hospitalisation	17 (14%)	42 (31%)	0.002
All-cause hospitalisation	37 (31%)	60 (44%)	0.033
All-cause death	11 (9%)	13 (10%)	0.934
Days alive and out of hospital	166±33	161±42	0.252

Data are presented as mean±standard deviation, N (%), or median with interquartile range.
COPD: chronic obstructive pulmonary disease.

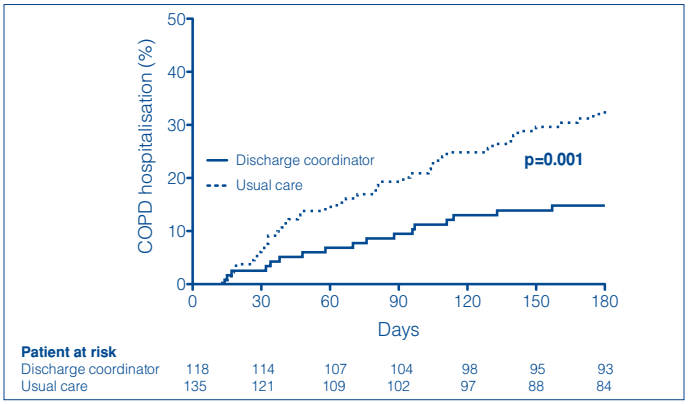

Figure 1. Cumulative incidence of COPD hospitalisation.

Discussion

Among our hospitalised COPD patients, discharge coordinator intervention significantly reduced both COPD hospitalisations and all-cause hospitalisations during the 180 days after discharge. We observed no reduction of all-cause mortality.

Over the past decade there has been growing interest in the use of interventions that allow patients with relatively mild exacerbations of COPD to be cared for at home. Such an approach is largely applicable to selected patients who are receiving care at home either after initial assessment in hospital and immediate discharge (hospital at home) or after several days of in-patient care (early or assisted discharge). Over time, the field developed and moved towards patients with advanced disease in whom the intervention would have greater clinical benefit.

Our findings differ from some recent reports in patients with COPD. There are several potential reasons that could contribute to different patient outcome. Firstly, the setting where the patients were enrolled may play a particularly important role. In most of studies, patients were recruited after hospitalisation (up to 12 months afterwards) during regular or scheduled outpatient visits or from the hospital-based pulmonary rehabilitation programme; in only one study patients were recruited during or shortly after hospital admission. This has important clinical implications since the risk of rehospitalisation in patients with COPD is greatest during the first 3–6 months after discharge. It may well be that researchers have missed eligible patients because they have already been hospitalised or have died before being assessed. In other words, populations in those studies are probably not the ones with the highest risk of short-term hospitalisation and thus much larger sample sizes might be needed to show intervention benefit. A second reason for different patient outcomes is that some patient populations were younger or had better pulmonary function. Thirdly, the particular study outcome under investigation and patient follow-up were different across the studies and could also affect the findings.

Care coordination, active patient engagement and self-management support are vital components for improvement of patient outcomes in COPD. Ultimately, we should transform COPD patients (and their caregivers) from passive recipients into active participants in disease management. In this context, discharge planning appears a promising element in the healthcare continuum, seeking to bridge the gap between the hospital and home environments.

Conclusions

Among patients hospitalised for COPD exacerbation, discharge coordinator intervention significantly reduced both COPD hospitalisations and all-cause hospitalisations. Hospital management programmes should consider discharge planning to improve outcome in COPD patients.

Acknowledgement

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Quality and safety control in bronchoscopy unit

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Introduction

Rapid developments in interventional pulmonology (IP) in recent years have additionally stratified professional community, where bronchoscopy and other interventional procedures are performed. There is a growing gap between low and high-income countries and even between centers in the same country. A lot of time on professional meetings is devoted to new technologies, which are usually in reach of minority and are rarely tested enough to be recommended as a standard treatment. Thus the pressure of the industry redirects our attention from more basic questions, which should be more central to our daily practice.

We probably all agree, that providing the best possible patient care is our most important goal, but at the moment we don't have solid criteria what is for example still acceptable quality of care and what is optimal quality of care. For majority of IP centers is therefore difficult to assess the quality of their services, since there are no widely accepted practical outcomes and no defined criteria for measurement of these outcomes. The excuse that "We do the best, what we can in certain conditions" is certainly the indicator of good will, but not the tool of quality improvement. It is often difficult to accept, that there are two (or even more) institutions on a small area that perform IP procedures on a completely different levels and that patient referral to institution with higher level of performance follows only patient's protests or several unsuccessful procedures.

There is also an increasing demand to define, track and improve quality of care / patient outcomes in recent years. In some branches of medicine they already made first steps by identifying quality and performance indicators and in certain environments full payment for procedure depends on correct performance and report (for example colonoscopies in national screening program in). Probably in near future there will be more pressure by insurance companies and government structures to satisfy performance and quality measures and report them to receive full reimbursement for IP procedures. The need to identify and recognize quality measures (preferable evidence-based) is on the side of bronchoscopy practitioners, since the other possibility is that they are going to be developed by insurance / governmental administrators without insight and experience from IP procedures.

For practical reasons we propose a list of hot spots, where quality criteria can be built around:

1. Establishment and maintenance of bronchoscopy unit
2. Patient care and safety
3. Personnel competency and safety
4. Planning and completition of the procedure
5. Processing of samples

Analysis of outcomes / implementation of audit cycles.

1. Establishment and maintenance of bronchoscopy unit
The basic items here are:
- The needs of background population / health center,
- The economic (affordable) level of equipment and personnel,
- The appropriate reprocessing, storage and handling of instruments.

The unit should define its range of activity and equipment according to the needs of the background population, existence/availability of referring center and economic capabilities.
Very important item under this topic is also microbiological safety of the bronchoscopy room: for patients and for personnel. Strict standards of equipment disinfection and maintenance should be implemented and evaluated. Traceability of equipment, personnel and microbiological samples should be established for effective prevention of infective disease transmition.

2. Patient care and safety
The basic items here are:
- Availability of IP procedure in reasonable time,
- Informing of the patient about the proposed procedure (including written information and informed consent) by treating physician, discussing alternatives and risks,
- Instructions about preparation for the procedure and for period after procedure,
- Information about results of the procedure in reasonable time.

3. Personnel competency and safety
We need to establish criteria for training and maintenance of competence in bronchoscopy personnel in doctors and nurses. Number and type of procedures performed are probably not adequate criteria. Even adverse events are fortunately too rare to be a meaningful indicator of quality. Observation of each procedure by an evaluator with formal training is impractical. Only complete statistical evaluation of procedures of each member of the team could give answers about adequate performance and ways to improve outcomes.

4. Planning and completition of the procedure
Procedures should be planned in advance, according to indications and risks at individual basis. Goals of the procedure should be set in advance (for example: bronchoscopy for lung cancer should include staging of mediastinum, where non-invasive pre-procedural assessment suggests option or radical treatment; biopsy specimens should be adequate for firm diagnosis and biological markers assessment where they influence the choice of treatment).
Possible complications during the procedure should be evaluated and their impact assessed. We propose the following evaluation of adverse events:
- Severity: death / permanent consequences for patient / no permanent consequences for patient, but procedure prematurely terminated / no consequences for patient and procedure completition,
- Preventability: expected but risk not properly assessed / expected at acceptable risk rate, unexpected,
- Sort of complication: bronchoscopy related / sedation related / equipment related / personnel related.

5. Acquiring and processing of samples
Biological samples are often in the center of bronchoscopic procedure. It is therefore of greatest importance, that they are acquired safely and that they represent the basis for patient's diagnosis and treatment decisions. This field requires multidisciplinary approach and close cooperation between IP unit and specialized laboratories (pathology, microbiology, biochemistry etc.) Important issues are:
- Adequacy of samples (number of biopsies and their size, volume of lavage fluid, etc.),
- Quality of samples (diagnostic elements, contamination, etc.),

- Rapid on site evaluation,
- Appropriate processing of the samples (optimal staining, growth media, etc.),
- Conditions of transport and sample preservation before final evaluation in specialized laboratories,
- Competency and quality of specialized laboratories,
- Time from sampling to pathologist's / microbiologist's report.

6. Analysis of outcomes / implementation of audit cycles.
Any unit in the chain from indication of interventional procedure till final report should collect and analyze data according to accepted standards for quality surveillance and plan improvements of their performance.

Conclusions

The aim of establishing quality criteria and performance measures is not only quality improvement but also the way to distinguish high-quality endoscopic procedure from inadequate. Proposed measures are not perfect and perhaps not applicable in all cases but they are the first step to an objective way to grade the performance of IP units. Bronchoscopists and heads of IP departments should use them to assess and improve their performance and economical effectiveness. Patient care will be improved that way and comparative information will be at hand for distinction of high quality from poorly performed bronchoscopy unit (bronchoscopist). This could be the basis for patient's decision, which center to choose and for more rational reimbursement of IP procedures.

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COPD and asthma

COPD and Asthma treatment is not the same

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Introduction
The most common chronic lung diseases - COPD and asthma - are well controlled with regular maintenance treatment with inhaled medications. Since asthma is primarily inflammatory disorder of airways the mainstay of treatment is alleviation of airway inflammation. Airway obstruction is only periodically linked to exacerbations and reversible in most cases. In COPD structural changes on level of airways, lung parenchyma and lung vessels present a permanent damage to the lung tissue that is manifested mainly with airway obstruction, inflammation, altered apoptosis and systemic involvement. Both asthma and COPD phenotyping is necessary since clinical phenotypes and patients' characteristics vary and personalized therapy is needed. Increasing knowledge of molecular biology of both diseases is leading to target specific drugs that will differ for both conditions in future even more than today.

Asthma
Traditionally 2 phenotypes of asthma have been described - atopic and non-atopic asthma. Both phenotypes do not differ regarding the airway inflammation that is present. Suppression of that inflammation alleviates symptoms, normalizes lung function and in at least some extent prevents long terms airways modeling, probably through indirect mechanisms. Inhaled glucocorticoids are the mainstay of treatment and careful stepwise dose - finding approach in individual patients if needed. Due to variable nature of the disease most patients do not need constant dosing of anti-inflammatory medications over their lifetime. Inhaled glucocorticoids are more potent than oral LTE4 receptor antagonists and long acting bronchodilators are added if the doses of inhaled glucocorticoids increase to moderate and high levels. Long acting bronchodilators are used to alleviate acute symptoms and the use of these drugs more than twice a week clearly points to uncontrolled disease. Patients with high doses of inhaled corticosteroids that are not controlled despite of that treatment and the patients depending on oral steroid treatment should be assessed for the treatment with IgE antibody – omalizumab. Moderate to severe asthma that could be controlled only with a combination of bronchodilating and anti-inflammatory drug should prefer be treated with fixed combination (ICS/LABA)). Acute exacerbations of asthma require high doses of inhaled short acting bronchodilators preferably in combination of SAMA and . At the same time it is necessary to increase the dosage of anti-inflammatory treatment.

COPD
COPD is both a disease of respiratory system as well as a systemic disease. There is usually a neutrophilic inflammation present in the airways of COPD patients but has little impact on the level and

nature of bronchial obstruction (emphysema vs., bronchitis). Bronchodilator drugs are the main treatment and reduce the symptoms, improve quality of life, have impact on lung function decline and influence the time to the next exacerbation. Many phenotypes of COPD patients are recognized and the therapy should be aimed both to prevent the risk of exacerbations and improve control of symptoms of disease (GOLD Guidelines 2011). Frequent exacerbator phenotype of COPD – the patients, that have at least 2 documented exacerbations requiring treatment with oral corticosteroid or antibiotics in the previous year, indicate high risk patients, that should be treated with combination with both long acting bronchodilators and inhaled corticosteroids. Principle of treatment during progression of the disease is adding the medications rather than increasing the dosage. Oral treatments with PDE4 inhibitors are available for the patients with bronchitic phenotype and frequent exacerbations with a loss of at least half of normal lung function.

Table1: *Summary of therapeutic interventions in asthma in COPD*

Intervention	ASTHMA	COPD
Education of a patient	+++	+++
Rehabilitation	?	+++
Avoidance to triggers	+++	++
Drug treatment		
ICS	+++	++ (phenotype specific)
SABA	+++ (PRN only; reliever)	++ (reliever)
SAMA	++ (in acute exacerbations as odd-on to SABA; PRN)	++ (reliever)
LAMA	+ (Severe GK dependent, uncontrolled; regular treatment)	+++ (mainstay of treatment)
LABA	++ (in combination with IGK only; regular treatment)	+++ (mainstay of treatment)
LTRA	+ (as add-on for uncontrolled asthma; single treatment for mild asthma only)	/
Fixed combination ICS/LABA	+++ (uncontrolled on medium to high ICS dose)	++ (as add-on to LAMA in high risk and frequent exacerbator phenotype)
Teophylline	+ (short term – severe exacerbations)	++ (acute exacerbations – respiratory muscles fatigue)
Roflumilast	/	+ (as add-on in bronchitic phenotype, high risk)
Systemic GK	+ (acute asthma; rarely permanent)	+ (AE COPD, never as maintenance treatment)

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Rehabilitacija bolnika s KOPB, kako izbrati primerne kandidate?

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V zadnjih letih se je znanje o KOPB (kronična obstruktivna pljučna bolezen), njenem nastanku in poteku, pomembno izboljšalo. Kljub vsemu pa so orodja za diagnostiko in zdravljenje ostala enaka. Večina navodil je zelo splošnih in izhajajo iz statističnih analiz večjih skupin bolnikov. V vsakdanji praksi se zato srečujemo s številnimi dilemami, kako posamezniku najbolje pomagati, da bo s svojo boleznijo živel čim bolj kvalitetno dlje časa.
V zadnji izdaji priporočil GOLD je vloga rehabilitacije še bolj izpostavljena in njen pomen posebej poudarjen. Kako naj rehabilitacija zgleda, koga vključiti, kako dolgo naj traja, kako pogosto jo ponavljati in podobna vprašanja pa ostajajo odprta. Ob številnih raziskavah, s tega področja, v zadnjih letih, v katerih je vloga rehabilitacije nedvoumno dokazana, se odpirajo nova vprašanja, jasnih odgovorov na stara pa ne dobimo. Vemo, da se, skoraj vsako intenzivnejše posvečanje tej skupini bolnikov kaže v izboljšanju nekaterih kazalcev kvalitete življenja ali parametrov telesne zmogljivosti, odvisno od orodja, ki smo ga uporabili. To vnaša še dodatno zmedo na področje priprave kompleksnejših programov, ki vključujejo delovanje na različnih področjih rehabilitacije (telesna aktivnost, telesna sestava, mentalno zdravje, poznavanje bolezni, uporaba zdravil,….). Ob podrobni preučitvi, se za ključni element pokaže izbira bolnika, ki ga v posamezno aktivnost vključimo (bolniki s slabšo telesno zmogljivostjo več pridobijo s treningom, bolniki z manjšo mišično maso s prehranskimi intervencijami, slabo osveščeni bolniki z različnimi šolami, kadilci s prenehanjem kajenja,…). Zato je, verjetno, potreben skrben pregled bolnikov pred vključitvijo v rehabilitacijo, izvedba različnih testov s pomočjo strokovnjakov različni področji, ter nato izbira kandidatov, glede na program, ki se v določenem centru izvaja. Katere teste in na kakšen način nato izbrati kandidata pa nam, obstoječa, literatura ne pove. Večina programov vsebuje nekatere splošne vključitvene in izključitvene kriterije, kot so:starost, hudost bolezni(stadij GOLD), SGRQ, telesna zmogljivost, telesna sestava, motiviranost,…

STAROST: podatki se zelo razlikujejo in se gibljejo ob 18let za spodnjo mejo, do povsem odprtega območja za zgornjo mejo.

HUDOST BOLEZNI (stadij GOLD): glede na zadnja priporočila GOLD je rehabilitacija namenjena vsem bolnikom z diagnozo KOPB. Različni centri bolnike običajno razdelijo glede na MRC vprašalnik. Običajno v skupine z MRC do MRC nad 5.

SGRQ: se kot merilo za vključitev v rehabilitacijo ne uporablja, je pa pomemben kazalec uspeha obravnave

TELESNA ZMOGLJIVOST: telesno zmogljivost merimo z različnimi orodji in nam, tako kot SGRQ, običajno služi zgolj kot merilo uspeha obravnave in zelo redko kot merilom za vključitev v program.

TELESNA SESTAVA: ponovno zgolj merilo za uspeh obravnave

MOTIVIRANOST: omenjena v vseh priporočilih, kako jo meriti ni jasno

NAŠI REZULTATI:

V Bolnišnici Topolšica smo decembra 2011 pričeli z vodenim programom rehabilitacije. V prvem mesecu smo, po pregledu obstoječe medicinske dokumentacije, izbrali 50 potencialnih kandidatov in jih poklicali na dodatne preiskave. V januarju smo nato pričeli izvajati 4 tedenski program rehabilitacije s poudarkom na izboljšanju telesne zmogljivosti, ki naj bi vodila v izboljšanje kvalitete življenja, zmanjšanje števila hospitalizacij zaradi KOPB in manjši porabi zdravil.

Značilnosti skupine:
M:Ž = 44:6

starost	64,5 +/- 8,9 let
FEV1	48,7% +/- 16%
Leta kajenja	33 let +/- 8 let
6 minutni test hoje	408 m +/- 98 m
BMI	27,4 kg/m^2 +/- 5,3
SGRQ	34,5 +/- 13,3
MMRC	2,8 +/- 0,8
BODE	3,4 +/- 1,8

Vsi bolniki so opravili tudi razgovor s psihologom, dietetičarko, socialno delavko in diplomirano medicinsko sestro. Na osnovi opravljenega testiranja smo v mesecu januarju pričeli z izvajanjem programa rehabilitacije. V prvi skupini z dvema kandidatoma, nato s po šestimi kandidati hkrati. Program je potekal 4 tedne od ponedeljka do petka z dodatnima dvema dnevoma za dodatna testiranja pred in po programu. Do julija je tako program uspešno zaključilo 20 bolnikov, nekaj pa jih je program predhodno zaključilo zaradi poslabšanja stanja(pljučnica1x, cistitis 1x, viroza 1x) ali drugih bolezenskih stanj (novo odkrit ca. Črevesja, novoodkrita IBS, novoodkrit ca. Prostate).
Z začetnimi rezultati smo lahko zadovoljni, saj se je prehojena razdalja pri 6 minutnem testu hoje, povečala v povprečju, za 158m, čas vožnje na ergometru ob konstantni obremenitvi za 71%, delež puste mišične mase se je povečal za 2,7kg, MMRC se je izboljšal za 1,2 točki. Neprijetno pa nas je presenetil podatek, da se je kvaliteta življenja, merjena s pomočjo SGRQ poslabšala kar za slabih 9 točk. Zaradi tega podatka smo se odločili natančneje pregledati rezultate in bolnike ob kontroli 3 mesece po odpustu povprašati o njihovih občutkih in mnenju.
Primerjava posameznih parametrov po skupinah odgovora ne da. Po analizi rezultatov psihološkega testiranja ugotovimo zmanjšanje stopnje anksioznosti in depresije. Analiza posameznih podenot SGRQ posebnosti ne pokaže. Pri skupini bolnikov pa izstopa zelo nizko število točk doseženih na SGRQ pred vključitvijo v rehabilitacijo, ki ni skladno z rezultati v MMRC vprašalniku. Po pogovoru z bolniki izvemo, da so namenoma ocenjevali svojo kvaliteto življenja za boljšo, v upanju po čimprejšnji vključitvi v proces rehabilitacije. Zaradi teh ugotovitev, smo se odločili, da za oceno bolnikovega stanja pred pričetkom rehabilitacije ponovimo teste, tudi če ti niso starejši od treh mesecev.

ZAKLJUČEK:

Rehabilitacija ostaja eden najpomembnejših elementov pri obravnavi bolnikov s KOPB. Izbira bolnikov za vključitev v posamezni program naj temelji na orientiranosti programa samega oziroma naj bodo programi zelo individualni in usmerjeni k bolnikovim potrebam. Zdi se, da najpomembnejši dejavnik pri uspehu rehabilitacije, igra sama motiviranost bolnika, ki pa je zelo težko ocenljiva. Pri tem nam v veliki meri lahko pomaga psihološka ocena bolnika in vključevanje psihologa v proces rehabilitacije

za povečevanje motiviranosti bolnika med samo rehabilitacijo. Prav tako naj vsi, ki v procesu rehabilitacije sodelujejo delujejo pozitivno v smislu motivacije bolnika znotraj posameznih procesov, ga spodbujajo in mu stojijo ob strani v telesno in duševno napornih dnevih, zlasti uvodne faze rehabilitacije. V našem okolju je eden najpomembnejših motivator ravno zdravnik, saj bolniki veliko pričakujejo od njega, si želijo pogovora in tolažbe, zato se delo z njimi izplača in pokaže v dobrih končnih rezultatih.

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COPD and asthma treatment is the same

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Chronic obstructive pulmonary disease (COPD) and asthma are mostly viewed as different diseases. Their treatments should consequently differ also.
In fact we treat patients with asthma or COPD with nearly identical drugs. Why?
Is it important, that COPD and asthma share many clinical, patho-physiological and immunological features? (1, 2)

1. Symptoms. Dyspnea is a cardinal symptom of both diseases. Asthma and COPD even share the most important trigger for dyspnea-which is physical exercise. Even more pathophysiological base for exercise induced dyspnea is very similar in both diseases. Bronchoconstriction and/or dyspnea is caused by bronchial hyper responsiveness (which is a feature of both diseases) or by dynamic hyperinflation, which is not only present in COPD but also in asthma, even in mild forms of this disease.
2. Circadian variability. Patents with mild asthma sometimes suffer from very large daily fluctuations of symptoms or bronchial obstruction. Those features are much less prominent in patients with advanced asthma with important remodeling and probably do not significantly differ from such variability of symptoms or bronchial obstruction in COPD (3).
3. Reversibility of obstruction. In mild asthma there is complete reversibility of obstruction but after all in mild COPD there is present only mild obstruction. Even more in many recent studies it was found, that many COPD patients had clinically importantly positive bronchodilatation test. Not much different as seen in asthmatics with prominent airway remodeling. (4, 5)
4. The small airways are involved in important yet poorly understood immunological processes of asthma, but small airways are as well profoundly involved in pathogenesis of COPD (6,7).
5. There is no known drug by which we could cure or at least slow down the progression of damage to small airways caused by asthma or COPD.
6. Asthma is traditionally viewed as “eosinophilic” disease. But not rare asthmatics have persistent sputum neutrophilia and many patients with COPD have significant sputum eosinophilia, especially at exacerbations of disease (8, 9).
7. The most potent anti-inflammatory drugs –glucocorticoids- prevent exacerbations of asthma as well as of COPD. Also withdrawal of inhaled glucocorticoids leads to worsening of asthma and also of COPD (10, 11).
8. Asthma and COPD share many biomarkers. (12, 13)
9. Overlap with simultaneously presence ob both diseases are probably much more frequent than is commonly believed (14-16).

10. Exacerbations of asthma or COPD are commonly caused by viruses with very similar pathogenesis of this event in both diseases (17).
11. COPD and asthma have features of endothelial dysfunction (18).
12. Both asthma and COPD are characterized by systemic inflammation (19).
13. Not so rarely we can not differentiate asthma from COPD. This is - according to cited common features - not at all surprising (20-22).

So is it surprising, that different bronchodilators and glucocortioids are effective treatments for asthma and COPD? (Table 1)

Table 1 Drugs used in asthma and COPD.

Drug	asthma	COPD
Short acting bronchodilators	+	+
Long acting bronchodilators	+	+
Inhaled glucocorticoids	+	+
Systemic glucocorticoids	+	+
Theophyllin	+	+

Conclusion

Do we treat asthmatics or COPD patients in the same way? Yes, we do.

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Diagnostic procedures in lung cancer

Endobronchial ultrasound - guided biopsy in the diagnosis of peripheral lung lesions

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The aim of our retrospective study was to determine the diagnostic yield of endobronchial ultrasound (EBUS) - guided transbronchial biopsy, its sensitivity in malignant and benign diseases and its sensitivity according to the position of the probe in relation to peripheral lung lesion (PLL).
One hundred thirty-six consecutive patients with 147 PLLs underwent EBUS-guided transbronchial biopsy (TBB). Patients in whom biopsies were not diagnostic underwent more invasive procedures to obtain a final diagnosis (fluoroscopy or computer tomography-guided transthoracic needle aspiration, surgery). One patient was lost from follow-up.
A definitive diagnosis was established in 111 PPLs (75,5%) by EBUS-guided TBB. The mean diameter of the lesion was 42 ± . Sensitivity for lung malignancy was 80,0% and 59,4% for specific benign diagnosis. Overall diagnostic yield was 75,5%: it was 60% for lesions smaller than , and 86% for lesions larger than . PPLs in which the probe was positioned within the PPL on the endobronchial ultrasonography (EBUS) image had a higher diagnostic yield (92,2%) than PPLs in which the probe went through the lesion (80,0%), or where PPLs in which the probe was positioned adjacent to the PPL (77,8%) or outside the PPL (43,2%). In the latest group additional fluoroscopic guidance was used.
EBUS-guided TBB is an important option in the diagnosis of peripheral pulmonary lesions. The position of the probe (i.e., within or adjacent to the PPL) is a significant factor in predicting the diagnostic yield of TBB using EBUS-guided TBB.

Management of patients with lung cancer

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Introduction
Lung cancer is a major public health problem and the killer number one in the world. In Slovenia with 2 millions populations more than 1200 new cases of lung cancer are diagnosed per year. Five year survival rate is only 13% (1).
Fortunately, significant advances in the management of non small cell lung cancer (NSCLC) have been made since 2000. NSCLC accounts about 85% of lung cancers and includes mostly adenocarcinomas and squamous cell carcinomas. Incidence of small cell lung cancer (SCLC) is decreasing but there have been no major advances in therapy since the development of platinum and etoposid in 1990.
Today, postoperative adjuvant therapy became standard of care for many patients with operable stage of NSCLC. Combined treatment approaches are adopted for patients in good medical status with locally advanced disease. Patients with metastatic disease might receive not only first-, but also second- and third- line systemic therapy. Histological differentiation has become more and more important in treatment selection. Although cytotoxic chemotherapy remains an important part of treatment, the discovery of oncogenes (EGFR, ALK) leads to specific targeted treatment.

Specialized lung cancer diagnostic clinics
Early lung cancer diagnosis is associated with better prognosis. At the moment we are facing with the fact that more than one half of lung cancer patients have locally advanced or metastatic disease at presentation; in Slovenia 84% of such lung cancer patients (1).
Delays in completing diagnosis are multiple. One of the reasons is the fact that tests are ordered by multiple specialists.
The implementation of specialized lung diagnostic clinics could reduce delays (2, 3, 4) in diagnosis with the possibility to access diagnostic procedures and multidisciplinary approach in a single location. The next role of specialized lung cancer diagnostic clinics will be also screening of lung cancer. Data from National Lung Screening Trial published in NEJM demonstrated that screening with low dose computed tomography can reduce the relative risk of death from lung cancer by 20% (5).
Specialized diagnostic clinics reduce the time to diagnosis, decrease patient anxiety and increase patients satisfaction. Multiple team members are required for successful work: pulmonologists, radiologists, thoracic surgeons, pathologists, nursing team. Bronchoscopist, interventional radiologists or thoracic surgeon are those who should be trained to obtain adequate tissue samples, not only from primary tumor but also from mediastinal lymph nodes and from lesions suspicious for metas-

tases, especially in those patients with a solitary distant metastasis (brain, adrenal glands). Mediastinal lymph nodes involvement is critical in the management of patients with NSCLC. Less invasive approaches to sample mediastinal lymph nodes have been developed including ultrasound guided transbronchial (EBUS-TBNA) and trans-esophageal (EUS-FNA) needle biopsy.
Adequate tissue samples and in lung cancer specialized pathologists are crucial in establishing diagnosis of lung cancer.

Treatment of lung cancer

Treatment decisions for NSCLC nowadays strongly depend on histological subtype, molecular testing and staging.
The last staging system for lung cancer was implemented in 2009 after been validated using a large prospective clinical trial database and is based on the recommendation of IASLC (international association for the study of lung cancer (7, 8).
Surgical resection is the gold standard treatment for fit patients with early stage disease. The quality of surgery resection strongly depend on optimal mediastinal lymph nodes excision after accurate non-invasive (computed tomography-CT, positron emission tomography-PET-CT) and invasive lymph node staging.
Neoadjuvant chemotherapy in early-stage disease lung cancer has been evaluated in many clinical trials with variable results and the current standard of care for early-stage lung cancer is surgery followed by adjuvant chemotherapy and/or radiotherapy (completely resected II and IIIA) (9).
The optimal treatment of patients with locally advanced NSCLC has not been clearly defined. Many treatment options are available; patients are usually treated with combined chemo-radiotherapy.
Treatment of metastatic NSCLC includes platinum-based doublet chemotherapy in fit patients. Recent advances in our knowledge of tumor biology and development of markers predictive of response to small-molecule epidermal growth factor receptor (*EGFR*) inhibitors have encouraged an interest in “personalized therapy” for these patients. Agent such as pemetrexed is a treatment of choice for patients with non-squamous histology, molecular testing help us in planning targeted treatment (9, 10) with gefitinib, erlotinib, crizotinib…

Multidisciplinary case conference

Multidisciplinary case conferences (11, 12, 13) include different specialists: pulmonologists, medical and radiation oncologist, radiologist, thoracic surgeons, pathologists, palliative care specialists and others (social workers, nurses…). The board of specialists is responsible to make a decision for the best possible treatment for individual patient with lung cancer based on guideline-recommended treatment. The board should discus all treatment options, also the possibility to include patient to clinical trial. Patients and their relatives should be involved in decision making (14).

Early palliative care

Lung cancer patients with metastatic disease have usually a lot of symptoms. Some studies demonstrated that up to 75% of patients with metastatic disease use hospital emergency departments in last three months of life (15). Introduction of palliative care early in the course of illness improve quality of care. Patients included to early palliative care survived longer than patients with usual oncologic care (16).

Conclusions

The management of patients with lung cancer has become complex. The implementation of specialized lung diagnostic clinics could reduce delays in diagnosis with the possibility to access diagnostic procedures and multidisciplinary approach in a single location. New treatment options depend on histology and molecular testing are expanding. Multidisciplinary care offer benefits for patients and also for the team, including education and promotion of evidence-based care. Early palliative care improves quality of life and prolongs survival. The best care for the patients could be achieved only with the involvement of patients and there relatives in decision making.

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Bronchiolitis

Progress in functional testing in patients with bronchiolitis

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Introduction
Bronchiolitis in adult is a rare condition and should be suspected in a patient with persistent fixed obstructive lung function deficit, particularly in non-smokers. Most often the disease is linked to either known exposition to inhalation substances, that can cause small airway damage, or to connective tissue diseases and infections (Table 1.). Symptoms of a patient include dry cough, dyspnea (particularly on exertion), crackles are heard non-uniformly over the lung bases (velcro - type) and chest is hyperinflated. Both constrictive and proliferative types can be found with different functional abnormalities.

Lung function testing
Spirometry is a mainstay of diagnostic procedures also in bronchiolitis. Obstructive defect is more common in constrictive bronchiolitis, although the lung function tests can be normal at some early stage of a disease. Obstruction is due to air trapping and hyperinflation and therefore lung volume measurements (body plethysmography) are indicated. Bronchodilator test in those patients is mostly negative; but increases in FVC in parallel to increase in FEV1 may indicate that the BD relieved air trapping. Among indexes of small airway function MEF50% is the one that could be monitored as a marker of disease progression in the same patient and he same equipment.
Diffusion capacity of the lungs is usually reduced and can diminish further if disease progresses. Blood gas abnormalities are common, particularly during exertion. Rise in pCO2 and decrease on pO2 point to decrease in alveolar ventilation. At CPET there is a large Vd/Vt ratio and raised ventilatory equivalents for CO2. Hypoxemia is common and degree of dyspnea is associated with the amount of lung hyperinflation.
In proliferative bronchiolitis restrictive pattern could be found that is in contrast with high lung volumes in chest radiograph. Both restriction and obstruction can be due to air trapping with_-_without larger airway pathology. Intraluminal polyp obliteration can cause loss of functional units as seen in decrease in Va in DICO measurement (Example 1.)

Table 1. CLINICAL SYNROMES ASSOCIATED WITH HISTOLOGIC BRONCHIOLITIS, WITH OR WITHOUT OBLITERANS
Inhalation injury
- Toxic fume inhalation
- Irritant gases
- Mineral dusts

- Organic dusts
- Volatile flavoring agents

Postinfectious
- Diffuse lesions
- Localized lesions

Drug – induced reactions

Idiopathic
- No associated diseases
- Cryptogenic bronchiolitis
- Respiratory bronchiolitis – associated interstitial lung disease
- Cryptogenic organizing pneumonia

Associated with other diseases
- Associated with organ transplantation
- Associated with connective tissue disease
  - De novo process
  - Drug reaction
- Idiopathic pulmonary fibrosis
- Hypersensitivity pneumonitis
- Malignant histiocytosis
- Chronic eosinophilic pneumonia
- Adult respiratory distress syndrome
- Vasculitis, especially Wegener's granulomatosis
- Chronic thyroiditis
- Primary billiary cirrhosis
- Ulcerative colitis
- Irradiation pneumonitis
- Aspiration pneumonitis
- Diffuse panbronchiolitis
- Lysinuric protein intolerance
- Ataxia-teleangiectasia
- Kartagener's syndrome
- Pulmonary capillaritis
- Paraneoplasic pemphigus

INHALATIONAL EXPOSURES ASSOCIATED WITH DEVELOPMENT OF BRNOCHIOLITIS

Toxic gases

Grain dusts

Irritant gases (e.g., chlorine)

Mineral dusts

Organic dusts (hypersensitivity pneumonitis)

Cigarette smoke

Free-base cocaine

Fire smoke

TOXIC EXPOSURES ASSOCIATED WITH BRONCHIOLITIS, WITH OR WITHOUT OBLITERANS

Nitrogen dioxide (nitrous fume)
- Spillage of nitric acid (component of jet and missile fuels)
- Metal pickling
- Silo gas
- Chemical manufacturing (explosives, dyes, lacquers, celluloid)
- Detonation of explosives
- Electric arc or acetylene gas welding
- Contamination of anesthetic gases (nitrous oxide gas cylinder)

Nitrocellulose combustion
Tobacco smoke
Fire smoke (firemen, astronauts, others exposed to burning materials)
Sulfur dioxide
Burning of sulfur-containing fossil fuels
Bleaching of wool, straw, wood pulp
Sugar refining, fruit preserving
Fungicides
Refrigerants
Ore smelting
Acid production
Ammonia
Fertilizer and explosives, production, refrigeration
Chlorine
Bleaching, disinfectant and plastic making
Chloramine gas
Phosgene
Chemical industry, dye and insecticide manufacturing
Chloropicrin
Trichloroethylene
Ozone
Arc welding and air, sewage and water treatment
Cadmium oxide
Ore: smelting, alloying, welding
Methyl sulfate
Hydrogen sulfide
Natural gas making, paper pulp, sewage treatment, tannery work
Hydrogen fluoride
Etching, petroleum industry, silk-working
Talcum powder (hydrous magnesium silicate)
Stearate of zinc powder
Oxygen toxicity
Asbestos (chrysotile and amphibole)
Iron oxide
Aluminum oxide
Silica
Sheet silicates (talc, mica, etc.)
Coal
Activated charcoal
Talc
Free-base cocaine
Incinerator fly ash

Lung function tests are not conclusive or specific for diagnosis of bronchiolitis, but can be used as a guide to impairment due to the disease. As many forms of bronchiolitis caused by acute lung injury do not deteriorate during time, it is feasible to repeat lung function measurement in three month period, and if no change is detected, repeated test is done in one year period. Since the mainstay of treatment is influencing obstruction, it is feasible to perform bronchodilator tests repeatedly and with the drugs and modes of administration that have high small airway deposition. High doses of those drugs are usually used. Ergospirometry (CPET) is a tool to objectively determine the degree of dyspnea during exertion and its relation to lung ventilation. It is feasible to be performed at the time of follow up when the lung function is stable and the deficit irreversible. The test is necessary in evaluation of working disability and prescription of patient's exercise levels for everyday life activities.

New tests of peripheral lung function include impulse oscillometry (IOS). The method is more than 2 decades old, but has never been fully validated in clinical setting. It measures resistance and reactance of respiratory system by applying a sound wave through the mouthpiece. Resistance at 20 Hz wave and 5Hz wave is specific for either central or peripheral obstruction respectively and corresponds to pathologic changes on that level. Reactance is also calculated and corresponds to compliance of the lungs. The advantage of the method is that it requires only tidal breathing without any forced maneuvers. No publications of IOS results in patients with bronchiolitis are available.

Bronchiolitis in asthma

Small airway disease is present in some asthmatic patients. It can be either reversible or irreversible. Patterns in lung function, which point to small airway involvement, are:

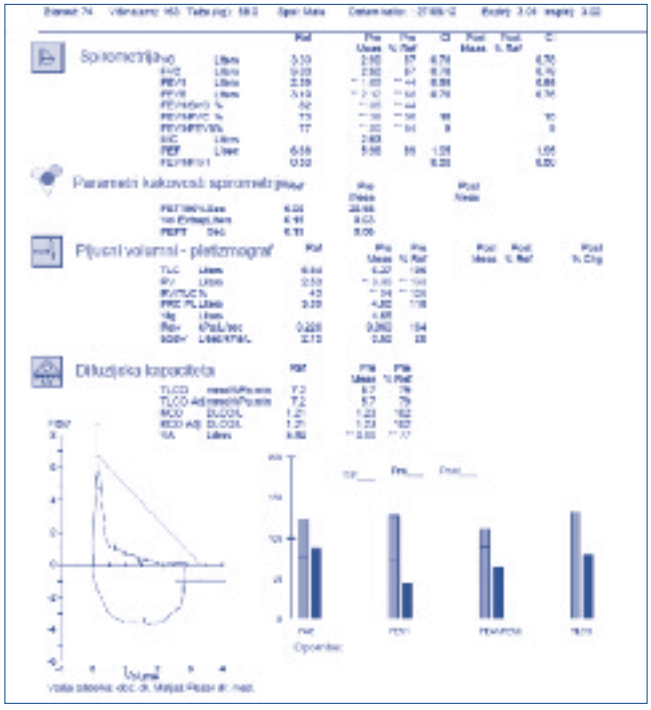
- Negative bronchodilator test before the treatment with anti-inflammatory drugs, that becomes positive after certain period of treatment
- Fall in FVC as well as FEV1 during bronchial provocation test indicating air trapping induced by bronchioloconstriction (only in high-quality-assessed spirometry maneuvers)
- Increased air trapping (RV / TLC) in plethysmographic measurements
- Increase in R5 in IOS measurements

The area of small airway involvement in asthma is under intense research and new data will be available shortly

Conclusions

Irreversible obstructive defect in a non-smoking individual should always raise suspicion of underlying disease of small airways. Numerous substances can cause inhalation injury and over time induce irreversible changes in the airways. Specific lung function tests of small airways are not jet available, but patterns of existing lung function tests can add supporting information to detect the disease.

Example 1. *Lung function tests of a patient with constrictive bronchiolitis*



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Graft-versus-host-disease bronchiolitis – bronchiolitis obliterans

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Hematopoietic stem cell transplantation (HSCT) is a widely used treatment for many mostly malignant blood disorders. Unfortunately, HSCT has many potentially fatal complications. Infectious and non-infectious pulmonary complications are important causes of morbidity and mortality in these patients. Bronchiolitis obliterans (BO) is the most common and the most important late noninfectious complication of allogeneic HSCT (alloHSCT).

BO develops only in patients after allogenic transplantation and it is assumed that is a form of chronic graft versus host disease (cGVHD) of the lung. There is no standard definition of BO, and no specific tests exist to confirm the diagnosis. So, the incidence of this complication varies from 0 to 48% of alloHSCT patients. In a large IBMTR study, the reported incidence of BO was 1.7 %. However, it seems that BO is under-diagnosed, as up to 30% of patients with cGVHD developed signs of airflow obstruction.

The pathogenesis of BO is not well explained. The most important mechanism is probably alloreactive immune process of donor's lymphocytes against patient's epithelial cells of bronchioles with subsequent inflammatory reaction.

There are several risk factors for BO. The most important risk factor is cGVHD. BO is very rare in patients without this complication. The other risk factors are patients age (> 20 years), air flow obstruction before transplantation (FEV1/FVC < 0.7), viral lung infection after HSCT, conditioning regimen with high dose busulfan, and myeloablative conditioning regimen.

BO usually presents itself after the first 100 days after alloHSCT. The beginning is usually insidious, with upper respiratory tract symptoms such as dry cough, wheezing, and dyspnea. Fever is not a sign of BO and means concomitant infection. The disease usually has a slow progressive course and ends with a severe obstructive lung disease, which demands a home oxygen therapy. Concomitant respiratory infections, which are frequent because of intensive immunosuppression, aggravate the course of BO and are most common cause of death.

As mentioned above, there are no specific laboratory tests to confirm the diagnosis of BO. Conventional chest X-ray is usually normal or with signs of lung hyper inflation only. Pulmonary functional test are abnormal, consistent with an onset of an airflow obstruction with FEV1 < 75% of predicted and FEV1/FVC < 0.7 of predicted, unresponsive to bronchodilators and residual volume > 120% predicted. FEV1 of < 45% predicts poor outcome. Diffusion test is normal. Beside pulmonary function tests, HRCT of chest with inspiratory and expiratory views is mandatory to confirm the diagnosis. The most common and specific sign is the presence of an air trapping during the expiratory phase with typical mosaic appearance and bronchiectasis in the advanced stage of the disease. Bronchoscopy

is usually not necessary, except to exclude a respiratory tract infection (CMV, RSV, influenza, parainfluenza, herpes simplex virus, and pneumocystis jirovecii). Transbronchial biopsy is not indicated, as specimens are usually too small. If histological confirmation is necessary, open lung biopsy is recommended.

Therapy of BO is difficult because it usually only slows down the course of airflow obstruction, though sometimes an improvement or even complete remission is observed. The treatment approach is similar as in cGVHD. The first line consists of reinstitution or augmentation of systemic immunosuppression. The cornerstone is systemic glucocorticoid – methylprednisolone 1–1.5 mg/kg BW for 2 to 6 weeks and with very slow tapering over 6 to 12 months. An alternative option is intermittent pulse dose regimen with methylprednisolone 10 mg/kg BW for three days monthly. Beside systemic therapy, high dose inhaled glucocorticoids are indicated, such as fluticasone 500–1000 mcg twice daily. Cyclosporine A or tacrolimus is added for 3 to 12 months in the dose to achieve therapeutic range between 250 and 350 ng/L if the patient is without calcineurin inhibitor already. Mycophenolate mofetil may be added for steroid resistant disease. Some studies report beneficial effect of azithromycin, which decreases the inflammatory response. The usual regimen is 250 mg of azithromycin three times a week for three months. Leukotriene inhibitor montelukast 10 mg daily may have a beneficial effect on BO, too. Extracorporeal phototherapy with psoralen (ECP) is efficient in patients with resistant cGVHD, especially with predominant skin and liver involvement, but it may be useful in BO too. Unfortunately, we have no ECP facility in Slovenia yet, and patients with extensive cGVHD or BO have to be referred abroad.

The use of anti TNF- monoclonal antibodies such as infliximab may be efficient, but there is no sufficient data to support this claim.

Imatinib (target drug for chronic myelocytic leukaemia) has been shown to reduce fibrosis and may be efficient in patients with mild forms of BO.

Beside immunosuppressive treatment, supportive measures are essential. During intensive immunosuppressive therapy, the patient must receive antimicrobial prophylaxis against pneumocystis jirovecii, viral and fungal infections. The usual vaccination programme against most common infectious diseases is recommended, especially against influenza and pneumococci.

Prompt treatment of respiratory infections is essential. Intravenous immunoglobulins may be helpful, especially in patients with low level immunoglobulin concentration.

However, beside all treatment approaches, the lung function is usually slowly declining over several month or years and patients need oxygen home therapy in the advanced phase. Prognosis of progressive BO (>10% FEV 1 decline per year is poor). Two year overall survival is about 45% and 5 year survival only 13%. Only for a minority of patients – less than 20% – the treatment results in an improvement of pulmonary function.

An experienced team consisting of a hematologist, a pulmonologist, and an infectious disease specialist is essential for the optimal treatment of BO and related complications.

University Medical Centre Ljubljana is the only transplantation centre in Slovenia for adult and pediatric patients. Between 2007 and 2011, 120 alloHSCT in adult patients were performed at the Department of Hematology. In 4 patients (3.3%) BO developed between 2 and 24 months after HSCT. All patients were treated with immunosuppressive therapy according to the guidelines, but pulmonary function tests improved and stabilized in only one patient. Other three patients had progressive course Mycophenolate mofetil may be added for steroid resistant disease. As in other reports, the incidence of BO in our patients is underestimated and regular pulmonary function test are recommended in asymptomatic patients.

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Small airways in asthma

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Small airways are usually defined as airways <2 mm in internal diameter without cartilage. Although small airways contribute little to airway resistance in healthy subjects, studies using invasive measurement of airway resistance have shown that small airways are the major site of airflow limitation in both asthma and COPD. Despite their importance, small airways have proven difficult to study.

Pathology of small airways in asthma

In healthy subjects, small conducting airways have a thin wall and offer little resistance to airflow that is laminar. Importantly, resistance to airflow varies inversely with the fourth power of the airway radius. A decrease in airway radius may be the result of increased amount of mucus and inflammatory cells obstructing the airway lumen, increased thickness of the sub mucosa related to inflammation, fibrosis or increase in smooth muscle mass, and distortion and narrowing of the lumen by the loss of alveolar attachments.

Most pathological studies performed in asthmatic subjects were performed using autopsy tissue collected in patients with acute fatal asthma. These studies have shown extensive luminal plugging by muco-inflammatory exudates and goblet cell hyperplasia in airway epithelium in both large and small airways. Airway wall thickening with increase in smooth muscle mass and inflammatory cell infiltration by T lymphocytes and eosinophils were also present in large and small airways. Inflammation in fatal asthma extended to the adjacent alveoli and to the perivascular area. There is also a loss of alveolar attachments in fatal asthma.

But an important point is that data obtained in patients with fatal asthma, which probably represented acute exacerbations of poorly controlled asthma, cannot be extrapolated to patients with chronic, severe asthma. Unfortunately, very little data exist on small airways pathology in living asthmatics. Data obtained in surgical specimens of asthmatic subjects undergoing lung resection indicated increased eosinophils and CD4+ T lymphocytes. Although it is clear that inflammation and remodeling are increased in small airways in acute fatal asthma and in severe and poorly controlled asthma , no pathological data exist on small airways in milder and/or in well controlled asthmatics. Importantly it remains unknown whether all subjects with asthma have small airways involvement or whether a »small airways phenotype« exists.

Physiological measurement of small airways function

The characteristics of small airways obstruction include premature airway closure and air trapping, regional heterogeneity and exaggerated volume dependence of airflow limitation. RV is elevated in

the presence of premature airways closure and air trapping. Because TLC is commonly increased in obstructive disease, the RV/TLC ratio is the best measure of elevation of RV and is also considered the first step of hyperinflation. Some studies have showed that RV/TLC (% predicted) was markedly increased in severe asthmatics compared to non-severe asthmatics. The authors showed RV/TLC inversely correlated reasonably well with FVC, indicating, that in the absence of volume measurements, reduction in FVC can be considered as a marker of air trapping. RV/TLC remains the most interesting marker of small airways closure in clinical practice or in large multicentre trials.

Imaging techniques in the evaluation of small airways

High resolution CT (HRCT) allows direct assessment of large and medium airways (diameter >2-2.5 mm), but also indirect assessment of mosaic lung attenuation (on inspiratory CT) and air trapping (on expiratory CT) have been studied as markers of small airways disease in both asthma and COPD. There are several limitations to the use of CT scans to monitor small airways disease. First, the technique uses ionizing radiations, which may be important to take into account due to the potential increase in malignancy especially in younger females. Secondly, there is a need for standardization of measurements of lung attenuation and air trapping.

Magnetic resonance imaging (MRI) following inhalation hyperpolarized helium has the advantage to the absence of ionizing radiation and it offers additional functional information, whereas HRCT offers better morphological information. Hyperpolarized ^{3}He and ^{129}Xe are inert nontoxic, inhaled contrast agents that can be detected by MRI to provide a high resolution image of ventilated lung airspaces. In healthy lung inhaled gasses are distributed rapidly and evenly throughout the lung, which results in a uniform signal. In patients with COPD, cystic fibrosis and asthma, focal ventilation defects appear as dark areas on MRI.The disorder behind these ventilation defects could be associated with mucus plugging, structural defects or airway narrowing. Ventilation defects are common in asthma, and the degree of these defects has been positively correlated with the disease severity.

Forced oscillation and impulse oscillometry are simple noninvasive techniques, although not widely available at present. Impulse oscilometry provides data with respect to separate measurements for both large and small airway function.

Therapeutic intervention in small airways disease

Anti-inflammatory treatment with ICS (inhaled glucocorticoides) with or without long acting b2-agonists (LABA) is the corner stone of asthma management. Nevertheless, some asthmatic patients do not gain optimal asthma control even with LABA/ICS combination. Inhaled therapies delivered via dry powder inhaler (DPI) or chlorofluorocarbon (CFC)-metered dose inhaler (MDI) generate large particles with a median mass aerodynamic diameter (MMAD) between 2-4 m lead to deposition in large airways. An HFA (hydrofluoroalkane) pressurized-MDI can deliver compounds with an MMAD that is significantly smaller than other available devices. These devices are able to deliver particles to both large and small airways, resulting in significant increase in peripheral airways drug deposition. A major question is whether targeting all airways (both large and small) can lead to further clinical benefit. In 2010 Hoshino has published that ciclesonid (HFA pressurized MDI) significantly improved IOS measured resistance of small airways and decreased late phase sputum eosinophils level compared with fluticasone propionate. At the same time there were no significant changes in spirometry in either group during the study.

Studies were also performed using fixed combinations. Papi and coworkers have shown that extra fine combination of BDP/formeterol was not inferior to nonextrafine combination ob budesonide/formoterol. But the combination with extra fine BDP/formeterol leads to greater improvement in FVC compared to fluticasone/salmeterol, suggesting effect on small airways.

Current data indicate that inhaled therapies with extra fine particles are at least as effective compared to larger particles in asthmatic subjects. To date there is no definitive answer to the question: »can we achieve any additional clinical benefit more by targeting small airways in asthmatics? «. It is probable, that patients with specific phenotypes may benefit more from the treatment with extra fine particles: asthmatic patients with fixed airflow limitation, those who show higher rates of FEV1 decline and higher rates of exacerbations. These groups of patients would be interesting to study.

In our study (Kopač, Fležar, Škrgat,) air trapping was confirmed in 25% patients with mild asthma and in 42% patients with severe asthma. Only 30% patients with air-trapping had clinical symptoms.

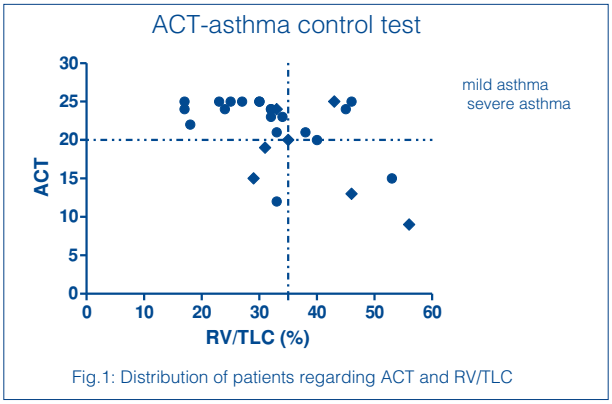

Fig.1: Distribution of patients regarding ACT and RV/TLC

For the pulmonologist the practical questions are still as follows:

1. Should small airways be systematically assessed in poorly controlled or severe asthma and, if the answer is yes, by which clinically relevant and available method?
2. In patients with demonstrated small-airway dysfunction (»small airway phenotype«), what is the additional benefit of small particle ICS or systemic treatments on specific parameters and usual clinical outcomes.

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Respiratory infections

Use of influenza and pneumococcal vaccine in adults in Slovenia

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Background
Vaccinations have been historically proven to be effective and safe preventive measure for prevention of infectious disease. Not only prevention of disease and even epidemics for the diseases with no specific treatment, but also significant decrease of hospitalization rate, complications and mortality has been proved for most vaccines in use. In spite of evidence based results, some vaccination skeptics have always voiced their own views and doubts. Development of new vaccines stirs controversy in professional and lay audience. The scientific discussions, the threat of new epidemics and the ageing population may yet reflect in the vaccines uptake. Among the variety of vaccines, the influenza and pneumococcal vaccine are probably the most globally and frequently used. In, both vaccines belong into the optional program, which stipulates the patients to pay or at least co-pay for the flu and pneumococcal vaccination. The flu and vaccines must be ordered through the Institute of public health of, which is the official distributer of these vaccines. The Institute also collects the yearly reports on vaccinations as well as the reports on incidents and side effects of the vaccinations. Typically in, the regional public health institutions, primary level doctors, public as well as private, would vaccinate majority of the patients (family/general medicine physicians, pediatric specialists, pulmologists). In some environments, the occupational medicine has taken over the flu and pneumococcal vaccination. All vaccinating doctors must be specially licensed for vaccination by the Institut of public health.

Vaccination against influenza in Slovenia
Vaccination in is conducted yearly in accordance with the WHO recommendations and guidelines. Regardless of the proven efficacy of flu vaccination, is not reaching the recommended threshold of the vaccinated population (5,6). In the season 2000/2001, 168.000 individuals were vaccinated representing 8,4% of all population, and 100.000 individuals older than 65 years, representing 34,7% of the population in this age group.(1,2). In the same season, 74% of the age group 65 and above were vaccinated in (3). The aim of the government of was to vaccinate 90% of the population in the age group 65 and above, while in the season of 2000/2001 it was varying among the different member states between 34,9 and 80,3% (4). In order to explore the reasons behind insufficient flu vaccine uptake, different research has been conducted. The results of one of them, carried out in 2001/2002 are presented in this abstract (5,6). A random sample of 300 individuals was drawn from the registry of 1000 Slovene practicing medical doctors, licensed for vaccinating by the Institute of public health.

A self-applied, anonymous questionnaire was mailed to each of them. Out of 175 responders with average age 46,65 years, only 45,7% stated, that they vaccinate regularly against influenza. Surprisingly, only one of all the participating doctors had influenza in the period of observation (i.e.2000/2001). Among other specialties of the participating doctors, significantly few pediatricians vaccinated themselves against influenza (p = 0,043). The general/family physicians vaccinated significantly more patients then other specialties (p = 0,028). In spite of more curative orientation, 70,3% participating physicians answered that the role of the eneral/family physicians in the preventive activities should be more pronounced. Between the answers to questions concerning general preventive attitude and those concerning vaccination no significant statistical correlation was detected- with two exceptions. Physicians who vaccinated themselves against influenza in the observed season, regarded mammography as a more reliable preventive screening than others; and those, who vaccinated more patients in the observed season, thought that more importance in preventive activities should be afforded to general/family practitioners. The greatest barrier in doctors against vaccinating more individuals was overburdening with other work, and they characterized their patients as not interested in vaccination. The majority of participating doctors were sufficiently informed about the vaccination (78,9%), although there is hardly any access to the specific data on vaccination and its effect in.

The outcome of this study was that vaccination against influenza is not considered by the participating doctors as one of the preventive measures, routinely carried out in practices. The underlying cause is most probably the lack of interest of public health offices for the vaccination against influenza. The results of our study could serve as the starting point for planning educational activities for physicians as well as adequate strategy against the threatening health problem of our times.

Vaccination with Pneumococcal vaccine in Slovenia

Two types of pneumococcal vaccine are used in: the polysaccharide vaccine and the conjugated vaccine. The national guidelines are freely available and reedited yearly on the website of Slovene institute of public health.(7).

Vaccination should be recommended and carried out by the respective treating physician, regardless of specialty. Therefore, this task is not exclusively entrusted into the hand of the primary care physician. Should vaccination be recommended due to medical indication, it is financed by the health insurance. After bone marrow transplantation, the polysaccharide vaccine is recommended regardless of age.

Vaccination is recommended for the adults with chronic kidney disease, anatomical or functional asplenia. helix implants, neuro-muscular disease with the risk of aspiration, for those with suspicion of liquor fistula, some malignant neoplasms, some of the neoplasm of the haemopoetic system, some of the internal disease.

Vaccination is also recommended for the individuals with chronic cardiovascular disease, liver disease, respiratory disease and for all individuals 65 years of age and older. These vaccinations should be financed by the vaccine recipients. The role of general/family practitioners in this subgroup of vaccine recipient is essential. Recognizing vulnerable individuals, informing them about the possible protection against possibly fatal pneumonia, motivating them and carrying out the vaccination demands according knowledge, standpoints, skills and-above all-time. The homes for elderly are definitely an environment where the vaccination should afford group immunity. According to our experience, when frailty, non-fatal chronic disease and age are the only indications for vaccination, the financial burden often prevents the agreement of the subject of the individual or his family. However, a debate has been raised in the scientific environment concerning the efficacy of the 23-valent polysaccharide vaccine. The most vulnerable groups, the ill and the elderly, Immunogenicity of the 7-valent conjugated vaccine in adults seems to be higher in comparison with 23-valent polycaccharide vaccine for some serotypes, the immunogenic response may last longer and the response to repeated vaccination is greater (8). Also, better immunogenicity was shown in trials with13-valent conjugated vaccine. The Slovene guidelines may yet undergo a revision, base on the clinical studies still underway.

Conclusions

The Slovenian recommendation for the use flu and pneumococcal vaccination are in accordance with international recommendations. Insufficient uptake of both vaccines has been observed in the past seasons. The standpoint of the treating/chosen physician has been proven in our research to be essential for the vaccine uptake by the patients. Although the research has pointed to severe overburdening of the primary care physicians, the time/cost benefit of vaccination, the prevention of epi- and pandemic, the general importance of preventive vaccines, better organization of vaccination and improved motivation of the medical professionals should overcome these difficulties. Slovenian physicians are aware of the scientific controversy concerning some of the vaccines and will follow up on the outcomes of undergoing research.

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Antimicrobial therapy of pneumococcal pneumonia - short presentation of our study results

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Introduction

The efficacy of antibiotics is under threat because their indiscriminate use has triggered antibiotic resistance, resulting in the bacterial treatment failure. Antibiotic resistance is a major European and global public health problem and is, for a large part, driven by misuse of antibiotics. As a result, patients are suffering from infections caused by bacteria that are resistant to multiple antibiotics (1). Community acquired pneumonia (CAP) is a form of an acute respiratory infection that affects the lungs of the adults either in an environment outside the hospital or up to 48 hours after the hospitalization (2). CAP remains a very serious respiratory infection of a high risk for fatal outcome (3).The most common bacterial cause of CAP is *Streptococcus pneumoniae*. In December 2005, the Slovenian guidelines for community acquired pneumonia were introduced and updated in 2010 (3).
We aimed to evaluate the appropriateness of treatment of CAP at the University Clinic Golnik in 2011 according to the Slovenian guidelines for treating CAP by analyzing the quality indicators. Our study is the first research about the antibiotic usage for a specific disease at the University Clinic Golnik.

Methods

We conducted a retrospective cohort study by reviewing medical records of patients, who have been hospitalized at the University Clinic Golnik from 01.01.2011 until 31.12.2011. Patients were identified by two means. Firstly, we searched patients with discharge diagnose of pneumonia caused by *Streptococcus pneumoniae* (J13). These patients' files were further evaluated and were included only if clinical data indicated CAP caused by *Streptococcus pneumoniae*. Secondly, the laboratory data of patients was screened. We identified patients with the laboratory data of isolated *Streptococcus pneumoniae* from patients' blood, sputum, tracheal aspirates or other samples in 2011. These patients' files were further evaluated and only patients that had clinical manifestation of CAP were included. The decision whether patients fulfill the inclusion criteria was made by the panel of experts, which comprised a clinical microbiologist, a pneumologist and a pharmacist. The project was approved by the institutional review board. Data analysis was performed by SPSS 20.0 statistical package.
Different parameters were analyzed, where the vast majority represents the quality indicators for treating CAP listed in the guidelines. We extracted the following data: patients' age and gender; smoking status; the pneumonia severity index (PORT) when determined on admission, if not, an estimation was done retrospectively (groups from I-V); information about the empiric treatment (choice,

dose and duration of empiric treatment)if the blood culture samples were taken;; if the *Streptococcus pneumoniae* was isolated and the type of specimen; if the susceptibility testing was performed ; time lapse between susceptibility results (antibiogram) acquisition and therapy; the choice of antibiotic, dose and dosing interval, patient's renal and liver function; co-morbidities (selected by the importance of Charlson co-morbidity index). Following outcomes were included: the length of stay, duration of antibiotic treatment and clinical outcome, concomitant therapy.

Results

In the study period, 122 admitted patients fulfilled the predefined criteria. Forty-seven of them were included by the discharge diagnose of pneumonia caused by *Streptococcus pneumoniae* (J13). Seventy five patients had the laboratory data of isolated S. pneumonia from patients' blood, sputum, tracheal aspirates or other samples in 2011; none of them had the expected discharge diagnose J13. All identified patients' files were further evaluated. According to the first criteria 40 of 47 patients were included and 18 of 75 patients according to the second criteria were included in the study. A total of 64 patients were excluded from the study: 55 with S. pneumonia isolate but no CAP, 6 with hospital-acquired pneumonia, 3 had a positive PCR result later determined as false positive and with no CAP. The final study sample included 58 patients.

The median age was 73 (Q1=63, Q3=80); 74,1 % of patients were older than 65 years which means that almost three-quarters of patients had at least one risk factor for CAP according to the guidelines; 46,6% of patients were smokers with 62,96% being former smokers while 27,6% of the whole group of patients had not been asked about this epidemiological status which also represents a risk factor for CAP.

Quality indicators listed in Slovenian guidelines for treating CAP are: determination of PSI/PORT, determination of oxygen saturation, collection of blood cultures, empiric choice of antibiotic, administration of antibiotic within 4 hours after diagnose of CAP. In our study no patient had PSI/PORT determined, all patients had oxygen saturation determined on admission and for 75,9% of patients blood cultures were collected. The choice of empiric antibiotic treatment was adequate in 89,5%. Antibiotics were administered within 4 hours after the diagnose of CAP to 86,2% of patients. Patients were treated empirically with amoxicillin/clavulanate potassium (AMC) alone in 53,4%, 8,6% of AMC was used in combination with azithromycin and in one case (1,7%) with ciprofloxacin. In one case (1,7%) ciprofloxacin was used as monotherapy. Moxifloxacin (MXF) was used in 22,7% of patients (Figure 1). Median duration of empiric treatment was 3,5 days.

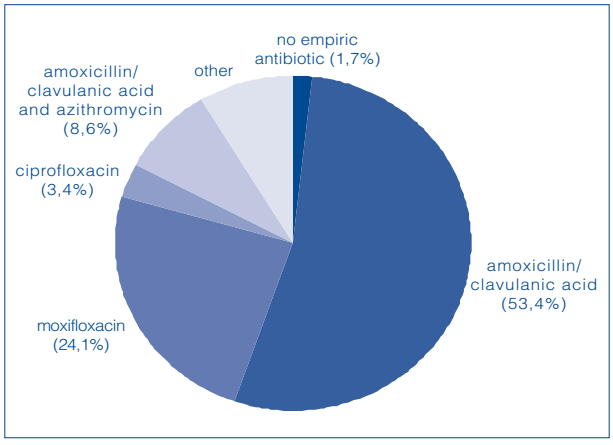

Figure 1: Choice of antibiotics for empiric treatment

Antibiogram was done in 94,8% of cases. Surprisingly, just 15,5% of therapies were changed based on the antibiogram results. In 62,1 % of cases, physicians considered empiric treatment as an adequate empiric therapy choice and did not change the therapy to narrower bacterial spectrum. Only

8,4% of all antibiotic changes represented a step down to the antibiotic with a narrower spectrum of activity (e.g. penicillin V or G). Median time from the results of antibiogram until the therapy change was 22 hours (Q1=4, Q3=61). Figure 2 shows the choice of antibiotic after the antibiogram results.

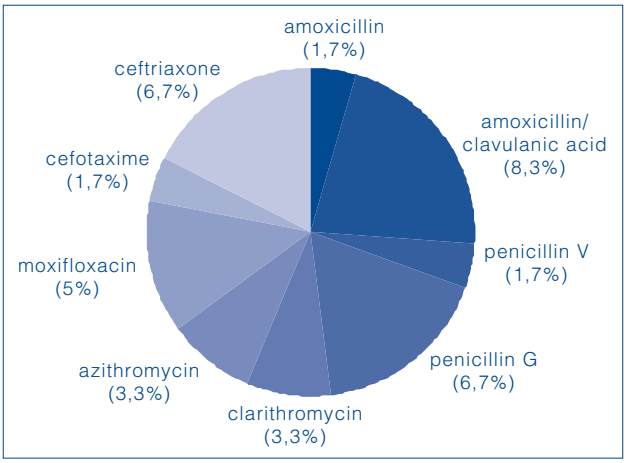

Figure 2: Choice of antibiotic after acquisition of antibiogram.

To 46 patients (79,3%) empiric antibiotic was administrated parenterally (others had either oral antibiotic from the beginning or this data was missing). In 15,2% of 46 patients administration of antibiotic wasn't switched to oral during hospital stay. Following comorbidities were recorded: 43,1% of patients had arterial hypertension; 36,2% had chronic obstructive pulmonary disease (COPD); 24,1% had asthma; 12,1% had chronic heart failure and the same percentage had carcinoma.
When looking at clinical outcome, 67,2% of patients were successfully treated and left the hospital cured with almost complete regression of the infiltrate and a small incidence of recurrence of pneumonia. On the other hand, 24,1% of patients completed treatment in the hospital with a higher incidence of pneumonia recurrence, scheduled regular reviews and advises on immunization with the pneumococcal vaccine. Overall,8,6 % of patients died.
Median total time of antibiotic treatment was 12 days and median length of hospital stay was 10,5 days which was in correlation with age of patients (0,561; $p<0,001$).

Discussion

Measured quality indicators showed fairly good compliance (above 75%) with the guidelines, with the exception of PSI/PORT determination, which was totally absent in patients' files. Despite this absence, the correct empiric choice of antibiotics, which is determined by PSI, was seen in 89,5% of cases. Possible explanation for this finding is either PSI/PORT was determined but not evidenced in the patients' files or clinicians made a good estimation of pneumonia severity in individuals, although the PSI was not calculated. However, there were some unusual choices of empirical treatment - for instance, combination of ceftriaxon and moxifloxacin for a patient with estimated PSI II or ciprofloxacin as a monotherapy. Due to the retrospective design of our study, we could not find any logical explanation for such cases, although clinicians at the point of care might have had the reason for such choice.
The most important finding of this study is that clinicians rarely (8,4%) changed the empiric treatment of CAP, although susceptibility testing for *Streptococcus pneumoniae* was performed in almost 95% of cases. We can only speculate why clinicians did not change the therapy to an antibiotic with a narrower bacterial spectrum. The most plausible explanation why clinicians did not change the therapy is the positive clinical effect of empiric treatment and awareness that susceptibility of isolated pathogen *Streptococcus pneumoniae* is also good to the empiric-broad spectrum antibiotic. This attitude of clinicians would need to be changed in order to prevent or reduce occurrence of bacterial

resistance. Nevertheless, it must be pointed out that the retrospective design of our study could not identify the real reason of such low rate of changing empiric antibiotic to pathogen specific one.

Conclusions

Our preliminary results indicate that there is still room for improvement in treating CAP at our hospital setting. Prospective study would be beneficial to further evaluate the clinicians' choice of antibiotics, especially pathogen specific antibiotic treatment.

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Diagnostic approach to lower respiratory tract infection

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Respiratory infections remain the most common illness in humans, the most prevalent reason why patients seek acute medical care. Lower respiratory tract infections, mainly pneumonia, are the most frequent and prevalent source of sepsis. Mortality is attributable primarily to bacterial pneumonia and severe influenza infections. Identifying a true "gold standard" for the diagnosis of respiratory infections is often problematic. The use of blood and sputum cultures has significant limitations because of the duration of time required to obtain positive cultures and issues of colonization and contamination. We are not able to grow certain bacteria in standard cultures, as evidenced by the fact that causative microorganisms can be detected in only 10% to 20% of patients with respiratory infections (1). In diagnostic procedure clinicians emphasized the importance of auscultation, fever, discolored sputum and breathlessness, general impression of the illness course, familiarity with the patient, comorbidity, and age in informing their antibiotic prescribing decisions for LRTI (2). Some of these factors may be overemphasized. Standardization of assessment and integration of findings (national guidelines) may help reduce variation in management (3).

We retrospectively examined data from 735 patients hospitalized in University Clinic of Respiratory and Allergic Diseases, Golnik in year 2011 with diagnosis of pneumonia. Causal organisms were determined using blood and sputum cultures, PCR from respiratory samples (pharyngeal smear, sputum), antigen tests for *Legionella pneumophila* and *Streptococus pneumoniae* in urine and serology tests for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila.*

206 (28%) of them had known etiology. In group of patients with known etiology, 11,6% had atypical pneumonia (*Mycoplasma pneumoniae* 54%, *Chlamydophila pneumoniae* 4,5% and *Legionella pneumophila* 41,5% patients). In 39% of patients *Streptococcus pneumoniae*, 9% *Haemophilus influenzae*, 8% *Staphylococcus*, 7% *Pseudomonas spp*, and in 13% other G- bacteriae (*Klebsiella pn*, *E. colli*), were diagnosed as causative agents.

We also retrospectively examined data of serological tests for atypical infections in 2011 in University Clinic of Respiratory and Allergic Diseases, Golnik. Serology for *Mycoplasma pneumoniae* was done in 180 patients. 8,3% of tested patients had positive IgM and 23,8% had positive IgG. Serology for *Chlamydophila pneumoniae* was done in 66 patients. 2,4% of tested patients had positive IgM and 32% had positive IgG. Serology for *Legionella pneumophila* was done in 137 patients. 2,1% of tested patients had positive IgM and 2,1% had positive IgG.

We retrospectively examined data from 2011 for antigen *Legionella pneumophila* test in urine. 189 tests were done: 9 (4,7%) were positive. PCR test from respiratory samples (pharyngeal smear, sputum) for *Legionella pneumophila* was done in 340 cases. 4 (1,1%) were positive. 340 PCR tests from

respiratory samples (pharyngeal smear, sputum) for *Chlamydophila pneumoniae* were done. 1 (0,2%) was positive.
342PCR tests from respiratory samples (pharyngeal smear, sputum) for *Mycoplasma pneumoniae* were done. 19 (5,5%) were positive.
Serology for infections caused by *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila* is more useful in epidemiological studies than in the routine management of the individual patient. If etiological diagnosis of the atypical agents is considered in the management of the individual patient, serological tests should not be performed as the only routine diagnostic test. A combination of IgM antibody detection and PCR may be the most sensitive approach (4). Application of molecular tests for the detection of atypical pathogens (*Mycoplasma pneumoniae*) is useful, provided the tests are validated and the results can be obtained sufficiently rapidly to be therapeutically relevant (4).
Compared to patients with other definite and unknown etiologies, patients with atypical pneumonia were younger and had less co-morbidity. Patients with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were presented with a less severe disease and had better outcomes, including a shorter length of hospitalization, nobody requiring mechanical ventilation and nobody had died. In opposite, patients with legionelosis in 40% required intensive care, mechanical ventilation and longer hospitalization. Combination of PCR test with urinary antigen test for *Legionella pneumophila* is useful in patients with suspected legionelosis and might allow the early detection (5). Antigen detection in urine is the most rapid method to diagnose or exclude the infection. A negative test makes legionella unlikely, but does not exclude legionella infection (4).
Classical microbiological methods for detection of respiratory tract pathogens can be slow, are often not sensitive, could not distinguish infection from colonization and are influenced by previous antibiotic therapy. Molecular diagnostic tests have the potential to increase the diagnostic yield and to make the tests faster. Unfortunately, these tests are usually not widely available.
Antibiotic management of low respiratory tract infections is still initially empirical and based on guidelines and knowledge of local microbial patterns and resistance rates.
Sputum cultures or endotracheal aspirates (in mechanically ventilated patients)
should be obtained in hospitalized patient with COPD exacerbation. They are a good alternative to bronchoscopic procedures for evaluation of the bacterial burden by
potential pathogenic microorganisms (4). In patients with exacerbations of bronchiectasis colonization should be considered Antibiotic treatment should be given after obtaining a sputum sample for culture. For empirical antibiotic treatment, patients should be stratified according to the potential risk of *Pseudomonas spp* infection. Empirical antibiotic therapy should be adjusted to sputum culture results in all patients.

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Doctors' knowledge and perception of antimicrobial resistance and antibiotic prescribing

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Introduction
Increasing resistance of bacteria to antimicrobial agents is a major public health problem. If our efforts to curb the growing rates of resistance should fail it is possible we may see the emergence of post-antibiotic era (1). To avoid this it is imperative to make the best and most prudent use of currently available antimicrobials which would also buy us some time needed to develop new antimicrobials. The importance of prudent use of antibiotics in an era of growing antimicrobial resistance has been addressed already in 1998 by World Health Organization (WHO) as well as European Council (EC) issuing several recommendations in the past decade (2). In 2008 European Centre for Disease Control (ECDC) initiated the annual European Antibiotic Awareness Day (EAAD) to take place on November 18 in order to highlight the utmost importance of prudent antibiotic prescribing.
Through several studies we learnt that 20% to 50% of antibiotic use is either unnecessary or inappropriate and decreasing it is the most important step to curb antibiotic resistance (3, 4). National recommendations and guidelines are useful but education has a central role in helping to improve the quality of antibiotic prescribing although it's quite challenging to develop and implement effective educational strategies which would cause the change of physicians' behavior and attitudes (5). Few studies on physicians' attitudes towards and knowledge of antibiotic resistance and antibiotic prescribing have been published on both sides of the Atlantic. Our aim was to gain some understanding of this process among a subset of Slovene physicians dealing mainly with patients with lung diseases.

Setting and Participants
We conducted an internet-based survey of members of Slovenian Respiratory Society and fellows on rotation at University Clinic for Respiratory and Allergic Diseases Golnik. An invitation to fill the online questionnaire was sent in May 2012. The questionnaire was based on a questions previously used by Pulcini et al. who conducted a survey among junior doctors in Dundee, Scotland, UK and Nice, France. Through the questionnaire we collected the information on attitudes about antibiotic prescribing, their perception of importance of antibiotic resistance, their beliefs about the causes of antibiotic resistance, their knowledge of the national prevalence of antibiotic resistance in two common pathogens (MRSA, *Escherichia coli*). All physicians were assigned to 2 groups (junior doctors and senior doctors) according to the years of experience (fellows and young specialists with less than 5 years experience after becoming specialist and senior specialist with more than 5 years experience after becoming specialist).

Results

Of the 150 members of the Slovenian Respiratory Society and fellows on rotation at our hospital who were invited to participate in the online survey, 61 (40,6%) filled the online questionnaire. There were 22 junior doctors (14 fellows, 8 junior specialists) and 39 senior doctors. Most respondents (86,9%) perceived antibiotic resistance as a national problem, but only 43,3% believed that it was a problem in their clinical practice. Three factors were perceived as being important causes of antibiotic resistance: prescription of too many antibiotics, prescription of too many broad-spectrum antibiotics and not removing the focus of infection. Factors most frequently identified as unimportant or neutral were: paying too much attention to pharmaceutical representative/advertizing, poor hand hygiene and too long durations of antibiotic treatment.

When asked questions about MRSA in hospitals and trimethoprim/sulfamethoxasol (SXT) resistant *E. coli* in the community in Slovenia any prevalence of MRSA between 5% and 20% and of *E.* coli between 25% and 35% was considered to be a correct answer. Correct answers were given for MRSA in 81,8% and 71,1% by junior and senior doctors, respectively. For resistant *E. coli* the correct answers were given in 36,6% and 41% by junior and senior doctors, respectively.

All but two of the responding doctors (2 junior doctors) had prescribed an antibiotic within past 6 months. Thirty-five per cent of doctors had prescribed antibiotics to two or fewer patients in the last week, 40,7% to three to five patients, and 23,7% to more than 5 patients. The five measures rated as the most helpful interventions for improving antibiotic prescribing were availability of guidelines, educational sessions, availability of local/national resistance data and availability of clinical microbiologist and infectious disease specialist's advice. Five scenarios doctors feel most confident when prescribing antibiotics are: making accurate diagnosis of infection/sepsis, choosing the correct dose and interval of administration, choosing between IV and PO administration (only senior doctors), planning the duration of antibiotic treatment (only senior doctors) and planning to streamline/stop the antibiotic treatment according to clinical evolution and investigations. Both groups felt most insecure when prescribing a combination antibiotic treatment, 54,5% junior doctors and 23,7% senior doctors.

Conclusions

This is the first study of doctors' attitudes towards and knowledge and perception of antibiotic resistance and prescribing in a subset of Slovene physicians. Although 86,9% of respondents perceived antibiotic resistance as a national problem, only half of them (43,3%) thought it was a problem in their practice. Although three factors perceived as being important causes of antibiotic resistance are not to be argued about it's fascinating that poor hand hygiene and too long duration of antibiotic treatment were not perceived as such. Good knowledge of MRSA prevalence is probably a consequence of much talk about it among healthcare workers for past ten years but the knowledge of SXT resistance of *E. coli* is poor although *E. coli* is the most prevalent cause of urinary tract infections. Through the answers we learnt that education, availability of comprehensive local/national guidelines and ready available advice from clinical microbiologists and infectious disease specialists were desired by majority respondents and should be able to plan our future quality improvement interventions.

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Abstracts

Setting up a noninvasive ventilation service

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Noninvasive mechanical ventilation (NIMV) refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal intubation. Delivery of NIMV in a respiratory ward, outside intensive care unit, is feasible. A non-invasive mechanical ventilation service in our Clinic has been established in 2005. The aim of our presentation is to review our work since then. In the present study we summarize the number of patients treated with acute and chronic NIMV, their clinical characteristics and outcome of NIMV.
The activity is integrated on the respiratory ward (outside the intensive care unit) with special interest in obstructive pulmonary disease and hypercapnic respiratory insufficiency. The primary point or our work at the beginning of NIMV was integrated care of hypercapnic respiratory insufficiency due to acute exacerbation of chronic obstructive pulmonary disease (COPD). Later on patients with non COPD hypercapnic respiratory insufficiency also become candidates for NIMV.
We use pressure support ventilation and pressure assisted controlled ventilation and mostly oronasal (full face) masks. During acute NIMV the monitoring of patients is performed according to guidelines. Arterial blood gases analyze is taken before and after 1-2 hours after beginning of NIMV.
At the beginning the number of patients treated with NIMV was low: 3 patients in 2005, 9 patients in 2006 and 6 patients in 2007. After additional training and improving the cooperation with sleep laboratory and intensive care unit, the number of patients has increased.
We have analyzed patients data, treated with NIMV from June 2008 to July 2011. Their clinical characteristics are presented in table 1 and 2.
Acute NIMV was performed in 78 patients, with mean age of 65 years (min 41 years, max 81 years). Their mean pH value at the beginning of NIMV was 7.32 (min 7.16, max 7.39), achieved mean pH value was 7.41 (min 7.23, max 7.50). Mean pCO2 baseline value was 9.03 kPa (min 6.2, max 14.3); achieved mean pCO2 value was 6.3 kPa (min 4.9, max 11.1). According to clinical outcome and the blood gas analyze results, acute NIMV was successful in 87% of patients.
Chronic NIMV was performed in 141 patients. It was successful in 92% of patients. Their clinical characteristics are presented in Table 2. No serious adverse effects or complications were recorded during acute or chronic NIMV settings.
We have established our non invasive ventilation service on respiratory ward. According to our results the delivery of acute and chronic NIMV on respiratory ward in selected patients is safe and successful.

Table 1: Clinical characteristics of patients with acute NIMV.
*COPD: chronic obstructive pulmonary disease
**ALS: amyotrophic lateral sclerosis

No. of patients	Disease	Result of NIMV	
		Successful (No. of patients)	Unsuccessful (No. of patients)
53	Obesity hypoventilation syndrome	50	3
14	COPD*	9	5
4	Thorax deformation (kyphoscoliosis)	4	0
3	Diaphragmatic paresis	3	0
2	Muscular dystrophy	0	2
1	ALS**	0	1
3	Cystic fibrosis	2	1

Table 2: Clinical characteristics of patients, treated with chronic NIMV.

No. of patients	Disease	Result of NIMV	
		Successful (No. of patients)	Unsuccessful (No. of patients)
76	Obesity hypoventilation syndrome	74	2
2	COPD	1	1
22	COPD/obesity hypoventilation.	21	1
16	Thorax deformation	16	0
17	Diaphragmatic paresis	15	2
1	Polyneuropathy	1	0
1	Periodic breathing in heart failure	1	0

How to genotype Mycobacterium tuberculosis directly from clinical samples – first insight into preliminary results

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Ability of genotyping *Mycobacterium (M.) tuberculosis is* of great importance since it improves and helps epidemiological data to gain some genetic value and helps to understand transmission of tuberculosis (TB). In some cases timeline is very important and fast results of genotyping are needed. With this prospective study started in January 2012 we tried to establish the ability of typing *M. tuberculosis* directly from samples (sputum) and not as usually from *M. tuberculosis* cultures. In agreement with Ward for tuberculosis at our Clinic Golnik samples of all patients with smear positive pulmonary TB were taken. The aim of our work was to evaluate first results of this prospective study. In this prospective study a total of 44 sputum samples from 14 patients with pulmonary TB were exposed to standard procedures in Laboratory for Mycobacteria. Procedures of decontamination, homogenization, culturing on solid and liquid media, smear microscopy were done as daily routine with all technicians involved. Pre-treated samples were centrifuged, supernatant discharged, 1xTE buffer added and samples were prepared for extraction of DNA. Extraction was performed by the protocol for extraction from bacterial culture. Extracted DNA was amplified with MIRU-VNTR Genotyping Kit (GenoScreen, Lille, France) and subjected to fragment analysis. Twenty-four-locus-based MIRU-VNTR typing was routinely applied using a four-capillary-based ABI 3130 genetic analyzer (Applied Biosystems, USA). When 24 digit results were not obtained at first, PCR and fragment analysis was performed again. Second result was final for analysis. Analysis of typing results was performed with BioNumerics program ver. 5.1 (Applied Maths, Belgium).
Samples were ranged according to daily routine smear microscopy result into positive+++ (POS+++), positive++ (POS++), positive+ (POS+), positive 2ARB (2ARB), positive 1ARB (1ARB) and negative (NEG). According to microscopy result among 44 sputum samples 10 were POS+++, 4 POS++, 13 POS+, 6 2ARB, 4 1ARB and 7 NEG. In first trial 18 (40.9%) samples were successfully typed completely with all 24 loci. Analysis showed success in 7 (38.9%) POS+++, 4 (22.2%) POS++, 4 (22.2%) POS+, 1 (5.5%) 2ARB, equally for 1ARB and NEG samples. When some loci were missing at first trial PCR and fragment analysis were repeated. Additional 6 (13.6%) samples were typed successfully with second trial. Altogether 24 (54.5%) samples were successfully typed directly from sputum samples. The highest successful rate was observed with samples having microscopy result POS+++, 9 (20.5%). Also 1 (2.3%) sample was successfully typed for all 24 loci although microscopy showed rare and damaged acid-resistant bacilli in smear.
Additionally 14 (31.8%) samples were typed partially missing from 1 to 13 loci out of 24 and 6 (13.6%) samples were not typable, 3 of them were smear NEG, 2 were POS+ and 1 was 2ARB according to

microscopy. With detailed analysis of all errors in missing loci we observed that out of all loci 4156 has the highest rate of missing and being the hardest loci to type. In 40 PCR results loci 4156 was missing in 29 (72.5%) cases. For samples that were typed partially 28 PCR results showed 4 different loci to be the most problematic ones. First three loci (960, 1644, 3192) are all belonging to 2nd triplex and were all having very high rate of missing: 20 (71.4%), 26 (92.8%) and 22 (78.6%) respectively. The fourth locus is 4156 missing in 25 (89.3%) cases. This locus is part of 4th triplex.

To the best of our knowledge, our study represents the first insight into direct genotyping *M. tuberculosis* from clinical samples not only in Slovenia, but also worldwide. Our preliminary study proved that genotyping of *M. tuberculosis* is possible from clinical samples (sputum) with standard procedures established for bacterial culture. We observed that some samples and corresponding genotypes are more difficult to type than others, because the quality and quantity of sputa are influencing on result as well. Therefore, further study of sampling, determination of sputa and extracting method are needed, to optimize the protocol for direct genotyping *M. tuberculosis* from clinical samples.

Drug interactions in tuberculosis treatment - the role of pharmacists

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Tuberculosis as a disease demands long-term multidrug treatment. Most first-line antituberculotic drugs induce or inhibit cytochrome P450 isoenzymes or P-glycoprotein. This can result in clinically significant interactions with numerous drugs. Aim of study was to screen for drug interactions in patients with first-line antituberculotic drugs.
Data collected from June 2011 to February 2012. 54 hospitalized patients receiving antituberculotic therapy reviewed. Clinical pharmacists performed regular reviews of interactions with first-line antituberculotic therapy. Clinically significant drug interactions were recorded and appropriate interventions were suggested according to drug indication and patient status. Drugs per needed were not included in the analysis.
Patients were mostly men (72%, 39/54) with an average age of 59 years (24-89 years). Drug interactions assumed to be clinically significant were identified in 33,3% (18/54) of patients. The average number of drug interactions per patients was 1,4 (25/18).
Most interactions (92%, 23/25) were with rifampicin, only few (8%, 2/25) were with isoniazide.
Table 1. Interactions of antituberculotics with drugs in chronic therapy and interventions suggested by pharmacists.

INTERACTING DRUG (No. of interactions recorded)	EFFECT OF ANTITUBERCULOTIC ON DRUG / INTERVENTION SUGGESTED
WITH RIFAMPICIN	
Bisoprolol (5)	Decreased effect. Monitor heart rate and increase dose if needed.
Esomeprazole (3)	Decreased effect. Increase dose.
Methadone (3)	Decreased effect. Monitor for withdrawal symptoms and increase dose appropriately. 2 to 3 times higher doses may be needed.
Clopidogrel (2)	Decreased effect. Increase dose or change therapy.
Simvastatin (2)	Decreased effect. Increase dose or switch to rosuvastatin.
Warfarin (1)	Decreased effect. Monitor INR and increase dose appropriately. 2 to 5 times higher doses may be needed.
Omeprazole (1)	Decreased effect. Increase dose.
Methyldigoxin (1)	Decreased effect up to 50%. Monitor drug serum concentration and increase dose appropriately.
Methylprednisolone (1)	Decreased effect. Increase dose if needed.
Citalopram (1)	Decreased effect. Monitor CNS effect and increase dose if needed.

INTERACTING DRUG (No. of interactions recorded)	EFFECT OF ANTITUBERCULOTIC ON DRUG / INTERVENTION SUGGESTED
Carvedilol (1)	Decreased effect. Monitor heart rate and increase dose if needed.
Fentanyl (1)	Decreased effect. Monitor pain control and increase dose appropriately.
Lercadipine (1)	Decreased effect. Monitor blood pressure and increase dose or change therapy if needed.
WITH ISONIAZID	
Carbamazepin (1)	Increased effect. Decrease dose to ½ or 1/3 of starting dose.
Risperidon (1)	Increased effect. Monitor CNS effect and decrease dose if needed.

The detected interactions did not alter the effect of selected antituberculotic drugs.
Every third patient receiving first-line antituberculotic therapy is at risk of experiencing a presumably clinically significant interaction with drugs in chronic therapy. These drugs belong to various different drug groups. Clinical pharmacists can detect these interactions and suggest interventions to assure safe and effective therapy. The actual clinical significance of these interactions is yet to be analyzed. The project was supported by a grant of the Health Insurance Institute of Slovenia.

Velocity of resolution of radiographic abnormalities in elderly patients hospitalized for community acquired pneumonia

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To recommend short-term, in hospital chest radiograph follow-up, resolution of chest radiograph abnormalities in relation to clinical cure were studied, predictors for delayed resolution were evaluated and influence of deterioration of radiographic findings during follow-up on prognosis were determined.
One hundred twenty patients aged 65 and older, consecutively admitted to a hospital for community acquired pneumonia (CAP) followed up for 28 days in prospective study. Clinical data and scores for clinical improvement at day 7 and clinical cure at day 28 were obtained. Chest radiographs were obtained at hospital admission and at days 7 and 28. Resolution and deterioration of chest radiograph findings were determined.
At day 7, 23 (19.2%) of the patients had resolution of chest radiograph abnormalities, whereas 59 (49.2%) had clinical improvement ($p<0.001$; odds ratio (OR): 0.60; 95%CI: 0.35-1.00). At day 28, 59 (49.2%) of the patients had resolution of chest radiograph abnormalities and 74 (61.6%) had clinical cure ($p<0.069$; OR: 0.60; 95%CI: 0.35-1.00). Delayed resolution of radiograph abnormalities was independently associated with multilobar disease ($p<0.001$; OR: 0.06; 95%CI: 0.02-0.14); altered mental status on admission ($p<0.001$; OR: 27.1; 95%CI: 7.8-94.2) and high respiratory rate at admision, defined as > 23 breath/min ($p<0.001$; OR: 5.94; 95%CI: 2.05-17.19). There were no significant difference in outcome at day 28 between patients with and patients without deterioration of chest radiograph findings during the follow-up period ($p=0.63$).
The resolution of radiographic abnormalities in the elderly patients with CAP should take into account the extent of lobar disease, mental status and respiratory rate at admission. In the hospitalized elderly patients with CAP routine short-term follow-up chest radiographs (obtained < 28 days after hospital admission) provide no additional clinical value. Follow-up chest radiography to exclude noninfectious abnormalities should not be performed within 4 weeks after the initial diagnosis. A delay of at list 8-12 weeks after an episode of community acquired pneumonia is reasonable.

Quality indicators of adult community acquired pneumonia at University Clinic Golnik

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Community acquired pneumonia (CAP) is pneumonia acquired at home or other environment outside the hospital or up to 48 hours after admission in hospital.
We have checked documentation of 100 patients who have been treated from March to June 2011 in our hospital with diagnosis of bacterial pneumonia.
Severity of CAP and mortality risk evaluated according to the PSI and PORT system is shown in Table 1.

Table 1.

PSI-class	PORT points	Severity CRB+PSI	Mortality risk	%	Mortality
I	<50	Mild (CRB 0)	low	4	
II	<70	Mild (CRB 0)	low	12	
III	71-90	Mild (CRB 0)	low	17	
IV	91-130	Moderate (CRB 1-2)	increased	49	2%
V	>130	Severe (CRB 3-4)	high	18	3%

In order to determinate etiology of CAP blood cultures were taken in 89% of patients (in 11% they were not taken, for 1,5% there is no information). Etiology of CAP was undefined in 80% patients. In the rest of the patients treated for CAP *Pseudomonas aeruginosa* was isolated in 4%, *Streptoccocus pneumoniae* in 3%, *Staphyloccocus spp.* in 3%, *Haemophilus influenzae* in 2%, *Enterobacter spp.* in 2%, *Moraxella catharralis* in 1%, *Serratia marcensens* in 1%, *Klebsiella pneumoniae* in 1%, E. coli in 1%, *Mycoplasma pneumoniae* in 1%, *Proteus mirabilis* in 1%. Indicators of treatment quality are presented in Table 2.

Table 2.

Severity of pneumonia has been evaluated	100%
Oxygenation has been measured	100%
Blood cultures have been taken before the administration of antibiotic	Blood cultures have been taken in 56% of patient with moderate and severe pneumonia, sputum was taken in more than 95% of patients.
Administration of antibiotics 2 to 4 hours after admission in hospital	89% - yes 11% - no
Choice of empirical antibiotic therapy according to current guidelines	90%

Following antibiotics have been used for treatment of CAP as first line treatment: penicillin in 42%, respiratory quinolones in 12%, cephalosporin in 10% and macrolides in 5% of patients. In 31 % of patients two kinds of antibiotics have been given or antibiotic therapy has been changed: patients with severe community-acquired pneumonia and patients with risk factors for *P. aeruginosa* 11% were treated initially with two or more antibiotics. Antibiotic therapy has been changed in 15% of patients who didn't respond to initial treatment.

We conclude that 67% of our patients treated for CAP in our hospital had moderate and severe pneumonia. In 20% of our patients etiology was established. Indicators of treatment quality were not perfect (blood cultures have not been taken in all patients with moderate pneumonia, antibiotics haven't been administrated within to 4 hours to all patients), but mainly in accordance with guidelines. Antibiotic therapy prescribed as first line was in accordance with the guidelines.

Evaluation of the BD MGITTM TBc identification test for the detection of M. tuberculosis complex in a routine laboratory setting

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A rapid, accurate and simple method for differentiation of Mycobacterium tuberculosis complex (MTBC) isolates from nontuberculous mycobacteria (NTM) is greatly needed for successful control of tuberculosis. Recently, a simple immunochromatographic assay was developed by BD () – the BD MGIT™ TBc identification test (TBc ID test) for differentiation between MTBC and NTM in as little as 15 minutes. It is based on the detection of the antigen MPT64, a mycobacterial protein that is secreted by MTBC cells during culture. This study was designed to evaluate the performance of the TBc ID test for detection and identification of MTBC in positive BACTEC MGIT 960 cultures.
A total of 187 positive BACTEC MGIT cultures were tested using the TBc ID test according to the manufacturer's instructions within 10 days after MGIT tube positivity. The results were compared with those obtained with the GenoType MTBC and GenoType Mycobacterium CM/AS line probe assays (Hain Lifescience Gmbh, Nehren, Germany) as described by the manufacturer.
Out of 168 GenoType MTBC positive samples, 157 samples (93.4%) were correctly identified as MTBC by the TBc ID test and 11 samples (6.6%) failed to detect MTBC. 19 samples were identified as NTM by GenoType CM/AS assay and all of these samples were TBc ID test negative. The most prominent NTM species identified by GenoType CM/AS were *M. kansasii* (31.6%), *M. avium ssp.* (21.1%) and *M. abscessus* (15.8%). The sensitivity, specificity, positive and negative predictive value of the TBc ID test for identifying MTBC were 93.9%, 100%, 100% and 63.3% respectively.
Among the 11 false negative samples, two were identified as *M. bovis* BCG with GenoType MTBC, which explains the negative TBc ID results since some substrains of M. *bovis* BCG produce no MPT64 antigen. Four false negative samples were not pure MTBC cultures (contaminated with other bacteria) and this was the reason for false negative results. When we repeated TBc ID test from another clinical specimens from the same patients the results were positive in all four cases. For the remaining five false negative results the possible explanation could be that there was not enough amount of detectable MPT64 antigen due to a low amount of tubercle bacilli in the liquid medium.
However, the results of our study show that the TBc ID test is a reliable, useful and specific tool for rapid identification of MTBC from positive BACTEC MGIT 960 cultures. Test is extremely simple, provides results in just 15 minutes and it requires no complex equipment or specialized personnel. Thus it can be easily implemented in clinical laboratories as a first step for differentiation of MTBC isolates from NTM.

The outcome of Slovenian lung transplantation patients

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Lung transplantation has become an established therapy for carefully selected patients with end-stage lung disease. Although medical management of transplanted patients is steadily improving, long term survival is still limited with chronic rejection syndrome (BOS) and therapy side effects. Since the year 1997, 30 Slovenian patients received lung transplantation (29 at AKH Wien and 1 and UMC Ljubljana). Number of referred patients is still increasing. In this observational study we analyzed survival of Slovenian lung transplant patients and the frequency of significant complications.
The cohort comprised of 30 patients (20 female, median age at transplantation 32 years) who received lung transplantation between July 1997 and January 2012. Data was collected continuously in this period. The observed parameters were survival, acute rejection, chronic rejection, infection (sepsis, tuberculosis, pneumonia, CMV) and some therapy-related complications (diabetes, arterial hypertension, osteoporosis and chronic kidney failure).
The median observation period was 2.0 years (3.7 years in the surviving patients). In the observed cohort 30% of patients died (cause of death was: sepsis in 4, vascular complications in 2, perioperative complications in 2 and rejection in 1). Survival estimated with Kaplan-Meier analysis was: 1 year – 79.7%, 3 years – 70.5% and 5-years - 70.5%. Acute rejection was observed in 20% and chronic rejection in 13.3% of patients (BOS 0p - 6.67%, BOS 3 – 6.67%). Sepsis was observed in 23.3%, tuberculosis in 6.67%, at least one episode of pneumonia in 43.3% and CMV infection in 20.0% of patients. Diabetes was observed in 36.7%, arterial hypertension in 36.7%, osteoporosis in 53.3% and chronic kidney failure in 53.3% of patients (one patient received kidney transplant). Compared to data from ISHLT registry, our patients were younger (median age 32 vs. 53 years) and had better 5-year survival (70.5% vs. 55%).
The outcome of Slovenian patients with lung transplantation could be superior to ISHLT average but longer observation period will be required for definite answer. Immunosuppressive therapy side effects (both infectious and non-infectious) are the main cause of morbidity and mortality in our patients, but not rejection. Lowering the dosage of the immunosuppressants will have to be considered.

Cyclooxygenase-2 expression in NSCLC

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Overexpression of COX-2 correlates with aggressive disease in NSCLC.
Aim of our study was to determine the COX-2 expression levels by two methods.
Analysis was done on 24 consecutive surgical specimens of NSCLC fixed in Paxgene tissue system. Relative quantification of COX-2 mRNA expression was performed by quantitative RT-PCR using intron-spanning primer-probe set. COX-2 protein expression was assessed by immunohistochemistry (IHC) using monoclonal antibody (clone SP21). Scoring was performed using an intensity-extent system, both parameters on the scale 0-3 and multiplied to give IHC index.
There were 12 cases of adenocarcinoma, 11 cases of squamous cell carcinoma and one typical carcinoid. COX-2 mRNA expression was detectable in all specimens. The median COX-2 mRNA expression value, normalized against he internal reference gene GADPH, was 0,53 (range 0,08 -12,49). We observed cytoplasmic and membranous immunohistochemical reaction patterns. Average IHC index was 3,8. There was positive correlation between mRNA and protein COX-2 expression (R^2 = 0,31). Adenocarcinoma cases had average relative mRNA expression value 2,45 and IHC index 5,08, while squamous cell carcinoma had average relative mRNA expression value 0,67 and IHC index 2,73.
COX-2 is expressed in NSCLC with various IHC reaction patterns. Adenocarcinoma and squamous cell carcinoma have different COX-2 expression levels.

Impact of some clinical factors on probability of metastatic disease to the brain in patients with non-small cell lung carcinoma at staging

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Lung cancer is a common disease with approximately 1,3 million new cases per year worldwide. It is the most common primary tumor giving rise to brain metastases. Approximately 50% of all patients with brain metastases have a lung primary. Metastses to the brain occur in approximately 32% (25%-38%) of patients with non-small cell lung carcinoma (NSCLC). In our institution brain CT scan is performed in all patients with lung cancer. We undertook this study to retrospectively assess possible clinical predictors of metastatic disease to the brain in patients with NSCLC.
A review of 594 patients with newly diagnosed lung cancer at our institution in the year 2011 has been performed. Our aim was to determine frequency and predicted probability of metastatic disease to the brain as a function of patient gender, age, clinical symptoms, performance status, cell type, peripheral versus central location, tumor stage, and lymph node stage of the primary NSCLC.
Metastases to brain were found in 45 patients; that is 7,6% of all. 38 of them were included in the study.

1. Age: 44 – 81, mean ages 64.6
2. Gender: 17 men (45 %), 21 women (55 %)
3. Performance status (known in 30 patients): 0-1 20 (67 %), 2-3 10 (33 %)
4. Clinical appearance: without symptoms 21 (55 %), symptomatic 17 (45 %)
5. T status: T1 8 (21 %), T2 12 (31,5 %), T3 6 (16 %), T4 12 (31,5 %)
6. N status: N0 2 (5 %), N1 3 (8 %), N2 16 (42%), N3 17 (45 %)
7. Pathological type: adenocarcinoma 25 (66 %), squamous 11 (29 %) undifferentiated 2 (5 %)
8. Localisation of tumor: peripheral: 26 (68%), central: 12 (32%)

Probability of metastatic disease to the brain is greater in women with peripheral adenocarcinoma with higher lymph node stage, which have good performance status and are without suspect clinical symptoms. According to our data, CT scan of the head is warranted in all patients with newly diagnosed lung cancer.

Do patients with asthma feel air-trapping?

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Air-trapping is associated with severity of asthma, however level of asthma control is estimated only by clinical characteristics and spirometry measurement. In this study we tried to evaluate if patients with air-trapping have clinical symptoms.
27 patients (9 male, 18 female, aged 19-76 years, median 49 years), all non-smokers, were included into study. The group was heterogeneous: in 20 patients asthma was mild and controlled with inhaled therapy, while in 7 patients asthma was severe and patients were on additionally treatment with systemic steroids and omalizumab. Asthma control was assessed based on the Asthma Control Test (ACT) scoring system; if ACT was < 20 asthma was regarded as uncontrolled. For each patient plethysmography was performed and air-trapping was assessed if residual volume / total lung capacity (RV/TLC) ratio > 35 %.
Air-trapping was confirmed in 8/27 patients: in 5/20 patients with mild asthma and in 3/7 patients with severe asthma. In 3 (2 with severe asthma) of them asthma was poorly controlled (ACT< 20) while 5 (1 with severe asthma) of them had clinically controlled asthma without symptoms (ACT ≥ 20). Results are summarized in Figure 1.
In our study air trapping was confirmed in 25% patients with mild asthma and in 42% patients with severe asthma. Only 30% patients with air-trapping had clinical symptoms. Further studies are needed to explore clinical role of air-trapping in asthma.

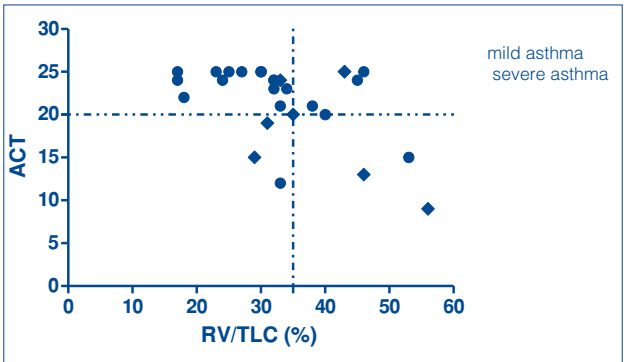

Fig.1: Distribution of patients regarding ACT and RV/TLC

Risk factors for colonization or infection with extended-spectrum beta-lactamase producing Enterobacteriaceae: an 18-month retrospective study

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Considering the growing prevalence of ESBL-producing Enterobacteriacae (ESBL-E) worldwide, in our study we tried to identify demographic and clinical patterns associated with colonization or infection with an ESBL-E.
We performed a retrospective descriptive analysis of 159 patients in whom ESBL-E strains were isolated from clinical specimens over an 18-month period. Clinical data were collected from patients' medical charts.
From 159 patients hospitalized at our clinic with ESBL-E isolated from clinical specimens, 68 were male (43%) and 91 were female (57%) with mean age 72 and 75, respectively. Eighty per cent of patients were over 65 years of age, and 35% were living in nursing homes. A high number of co-morbidities were present: cardiovascular diseases in 79% of patients, chronic respiratory diseases in 45%, neurological disorders in 38%, diabetes in 32%, malignant diseases in 26% of patients and alcoholism in 8% of patients. Chronic respiratory diseases and alcoholism were more frequently represented in males: 54% had chronic respiratory diseases as opposed to 37% of females, and 15% of males were alcoholics as opposed to 1% of females. Other risk factors commonly present in MDR-bacteria colonized patients were also found: within 5 years prior to admission to our clinic 81% of patients had been hospitalized (12% in ICU), 67% had been exposed to antibiotics and 23% had undergone a surgical procedure. *Escherichia coli* was the most common isolate (in 59% of patients), followed by *Klebsiella pneumoniae* (in 37% of patients), 4% of patients had more then one species isolated.
In our retrospective study, the demographic and clinical profiles of patients colonized or infected by ESBL-E were characterized by a high prevalence rate of several known risk factors and major co-morbidities. Advanced age, living in a nursing home, several co-morbidities (cardiovascular, chronic respiratory, neurologic, diabetes or malignant disease), multiple contacts with health care system, especially exposure to antibiotics, surgery or treatment in the ICU, are major risk factors for colonization or infection with an ESBL-E.

Interobserver Agreement in Thyroidectomy Specimens

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Distinguishing benign from malignant, but also neoplastic from non-neoplastic lesions of the thyroid may sometimes present a real challenge. As a result, we can experience disagreements that may compromise diagnostic consistency. A good way of quality control is reviewing of archived samples by two or more independent observers and evaluating the results.
This study was performed to evaluate interobserver agreement of thyroidectomy and hemithyroidectomy specimens. Two independent observers reviewed 129 thyroidectomy and hemithyroidectomy specimens from our archive. Diagnoses were compared and overall interobserver agreement was calculated as concordant diagnoses/all reviewed samples ratio. We also calculated interobserver agreements for neoplastic and non-neoplastic pathology separately and expressed as concordant neoplastic diagnoses/all neoplastic diagnoses ratio and concordant non-neoplastic diagnoses/all non-neoplastic diagnoses ratio, respectively.
Overall interobserver agreement was 0,94. For non-neoplastic specimens we had interobserver agreement of 0,98. Interobserver agreement for specimens with neoplastic lesions was 0,85.
The results of the study show good interobserver agreement, but also point out the complexity of diagnosing neoplastic lesions of the thyroid and necessity of regular quality controls.

Is it asthma? - Flexible videolaringoscopy during bicycle ergometry in children and adolescents

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Exercise-induced laryngeal obstruction is not uncommon in children and adolescents. The condition presents with abrupt distressing symptoms and is many times misdiagnosed as asthma. Our aim was to directly visualize the larynx during exercise in patients with the history of dyspnea and inspiratory stridor on exertion in order to confirm the diagnosis.
Continuous flexible transnasal laryngoscopy was combined with bicycle ergometry. The data from 37 consecutive patients were analyzed; prior medical history and functional tests, laryngeal endoscopic findings and ergometry results were assessed. Selected patients were further referred for laryngeal sensory testing.
All 37 subjects (22 female) were able to perform the test. Their median age was 13.3 years (range 9 - 21 years). Seventeen were atopic, 18 were active athletes (mostly cyclists and swimmers, 6 and 3 subjects respectively). Exercise-induced laryngeal obstruction was diagnosed in 25 (60% female). Ten among them were atopics and the same number (40%) was treated for presumed asthma. Only one had moderate to severe bronchial hyperresposivness ($p = 0.05$), none had elevated exhaled nitric oxide ($p = 0.03$). No adverse reactions were recorded.
Flexible videolaringoscopy during bicycle ergometry can be performed safely in children and adolescents. It is a valuable diagnostic tool for assessment of possible exercise-induced laryngeal obstruction.

The survival and infections of Slovenian cystic fibrosis lung transplant patients

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Cystic fibrosis (CF) is a multisystem hereditary disorder and pulmonary manifestation remains the leading cause of morbidity and mortality in these patients. Severe lung disease is a common indication for lung transplantation and outcomes are better than those of patients undergoing lung transplantation for other indications. A patient should be referred (ISHLT recommendation) to a transplant center when five-year predicted survival without transplant is less than 30 percent. All lung transplants require bilateral transplantation because of the infection risk.
Aim of our study was to determine the survival of the patients with CF who had lung transplantation and the number of lung infections with emphasis on *Pseudomonas aeruginosa* infection.
We studied the group of 13 patients who had lung transplantation between years 1999 and 2012. The data was collected from medical records. We observed the survival after lung transplantation and lung infections before and after transplantation with emphasis on *P. aeruginosa* infection within the first year after transplantation.
In our subjects there were 8 (61.5%) females and 5 (38.5%) males (average age 26.2, range 13-52 years). There were 5 urgent transplantations. To date, 2 (15.4%) patients died, both in the early postoperative period (both urgently transplanted). Before lung transplantation only 2 (15.4%) patients didn't have recurrent lung infections which would require antibiotic treatment, in 10 cases (76.9%) of infections the cause was Pseudomonas aeruginosa. In the first year after transplantation, lung infection was the cause for more than one hospitalization in 4 (36.4%) patients, for one hospitalization in 4 (36.4%) patients and for none in 3 patients. Only in 3 (37.5%) cases the causative agent was *P. aeruginosa*, all were colonized before transplantation. The patients who died were excluded in the post transplant analysis.
The survival of our transplanted CF patients is very good. In the literature, the need for urgent lung transplantation is recognized as a major risk factor for adverse outcome, which is true for our group as well. It is advisable to refer the patients for transplantation when they meet ISHLT criteria. *P. aeruginosa* infections were frequent before but not after transplantation, albeit they persisted in a subgroup of patients.

Molecular Detection of Streptococcus pneumoniae in Lower Respiratory Tract Specimens

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Aim of our study was to evaluate the usefulness of multiplex PCR assay Seeplex PneumoBacter ACE Detection Assay (Seegene, Seoul, Korea) for detection of *Streptococcus pneumoniae* in respiratory samples. During our routine work we discovered a high rate of positive results for *S. pneumoniae,* so we wanted to verify the accuracy of these results.
Molecular detection was performed on samples from patients admitted to University Clinic of Respiratory and Allergic Diseases Golnik between November 2010 and June 2011. We extracted DNA with QIAamp DNA Stool Mini and Blood kit (QIAgene, Venlo, Netherlands) from throat swabs. Extracted DNA samples were tested for *S. pneumoniae* with Seeplex PneumoBacter ACE Detection Assay and with highly specific in-house PCR for *S. pneumoniae* using lytA and cpsA gene primers. Of 209 samples tested with Seeplex Pneumobacter assay, 122 (58,4%) were positive for *S. pneumoniae*. All samples were also tested with in-house multiplex PCR specific to *S. pneumoniae*. Of all samples, only 11 (5,3%) were positive with multiplex lytA and cpsA gene PCR. Agreement between results of these two tests was just 46,9%. Results of in-house multiplex PCR specific to *S. pneumoniae* were used to calculate specificity and sensitivity of Seeplex Pneumobacter assay for *S. pneumoniae*. Calculated specificity was 0,64 and sensitivity was 1.
Seeplex PneumoBacter ACE Detection Assay is a good multiplex assay for detection of atypical pathogens but lacks appropriate specificity for *S. pneumoniae*. Rapid and accurate diagnosis of pneumococcal pneumonia is necessary for appropriate course of treatment and to avoid unnecessary use of antibiotics. An assay with such low specificity has little or no clinical relevance in diagnosis of pneumococcal disease.

Detection of Viral Respiratory Pathogens with Real-Time PCR

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To investigate the usefulness of multiplex real-time polymerase chain reaction test to detect influenza A virus (Flu A), influenza B virus (Flu B), human respiratory syncytial virus A/B (RSV A/B), human metapneumovirus (hMPV), human adenovirus (AdV), human coronavirus 229E/NL63/OC43 (CoV), human rhinovirus A/B/C (HEV), human enterovirus (HEV), human bocavirus 1/2/3/4 (HBoV) and human parainfluenza virus 1/2/3/4 (PIV) and to assess the prevalence of these viruses in respiratory samples.

We evaluated the results retrospectively. Magicplex RV Panel Real-Time Test (Seegene, S. Korea) was performed in 93 patients with suspected viral respiratory infection, admitted to University Clinic of Respiratory and Allergic Diseases Golnik between July 2011 and June 2012. Nucleic acid was extracted from 74 nasal swabs, 16 throat swabs, two bronchial lavages and from 1 aspirate with protected catheter using QIAAMP MinElute virus spin (Qiagen, Venlo, Netherlands). PCR test was performed according to manufacturer's instructions.

A viral pathogen was detected in 53 (57%) patients. Multiple viral pathogens were detected in 16 (17,2%) patients. Influenza A virus was detected in 25 (26,9%) patients, influenza B virus in 11 (11,8%), human respiratory syncytial virus A/B in 8 (8,6%), human metapneumovirus in 4 (4,3%), human adenovirus in 17 (18,3), human rhinovirus/enterovirus in 3 (3,2%), human bocavirus in 2 (2,2%) and human parainfluenza virus in 8 (8,6%) patients. Human coronavirus was not detected in any patient.

Real-time PCR test Magicplex RV Panel Real-Time rapidly detects viral pathogens in respiratory samples. Results are very clear and easy to interpret. Test is a powerful tool to help clinician to differentiate between bacterial and viral cause of the disease. Results should help clinician to avoid unnecessary use of antibiotics.

The impact of Air Quality in Ljubljana on onset of Asthma and Chronic Obstructive Lung Disease

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Pollutants such as particles occur in high concentrations along streets and roads carrying heavy traffic. And evidence is growing that living near such streets and roads may have serious health effects, particularly on the development of chronic diseases such as asthma and chronic obstructive lung disease (COPB). Until now, however, standard Health Impact Assessment (HIA) has not explicitly incorporated this factor.
For this purpose, in the frame of Aphekom Project, innovative HIA method has been applied, taking into account the additional long-term impact on the development of chronic diseases from living near busy roads.
The main objective was to assess the impact of urban air pollution in vicinity of busy road on prevalence of asthma and COPB in the area of Ljubljana.
Innovative HIA method has been developed within Aphecom project and used. We first determined that, on average, over 50 percent of the population in the Ljubljana lives within 150 metres of roads travelled by 10,000 or more vehicles per day and could thus be exposed to substantial levels of toxic pollutants.
The risk factor obtained from literature was applied to background level of asthma and COPD on the population living near busy roads.
In area of Ljubljana 47 % of inhabitants live near busy roads. In the city of Ljubljana, the HIA showed that living near these roads could be responsible for some 12 percent of all new cases of: asthma in children; and of 18 percent of COPD (chronic obstructive pulmonary disease) in adults 65 years of age and older. We further estimated that, on average 15-30 percent of exacerbations of asthma in children and acute worsening of COPD in adults are attributable to air pollution.
In the area studied, study shows that living near these roads could be responsible for onset of asthma in children age 0 – 17 and chronic obstructive lung disease of people aged > 65. All the cases are attributable to exposure to air pollution in the area, due to large number of people living near busy road where the pollution is the worst. This burden is substantially larger than previous estimates of exacerbations of chronic diseases, since it has been ignored so far that air pollution may cause the underlying chronic disease as well. There are sources of uncertainty in our models like change of pollution during the day because of very local climatological characteristics, lifestyle (e.g. ventilation systems). Used that transferred CFS`s are appropriate even for local conditions, therefore we think, that we can take the results of the HIA with high confidence and consider them as real.

Viral prevalence in acute exacerbations of COPD

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COPD exacerbations are multifactorial and heterogeneous episodes thought to be caused by complex interactions between the host, respiratory viruses, airway bacteria and environmental pollution resulting in an increase in the inflammatory burden. A one year prospective analysis of viral prevalence among patients hospitalized due to acute exacerbation of COPD is presented in this paper.
Seventy-one patients with acute exacerbation of COPD were evaluated in 1 year time period. Forty-four (62%) were men and 27 (38%) women. Collected samples were sputum, nasal and/or pharyngeal smear and/or nasal lavage. Polymerase chain reaction (PCR)–based detection of viral nucleic acids was used. Viral nucleic acids were detected in 41 (58%) of patients. In the majority of patients - 69 (97%) nasal and pharyngeal mucosa samples were obtained whereas sputum samples were obtained in 23 (32%) patients. Viral nucleic acids of influenza type B, influenza type A, parainfluenza, human rhinovirus and human enterovirus, respiratory syncytial virus, coronavirus, adenovirus, human metapneumovirus and human boca virus were isolated (Fig. 1).
Respiratory tract viral colonization and infection in COPD patients seems to play an important role in acute exacerbations of COPD. Viruses were detected in 58% of patients with AE COPD in our setting. Findings are comparable to the studies in the literature. Whether all respiratory viral infections in COPD patients are clinically relevant remains to be determined although it could be concluded influenza vaccination should be applied more aggressively in selected COPD patients as one of the factors of COPD exacerbation prevention.

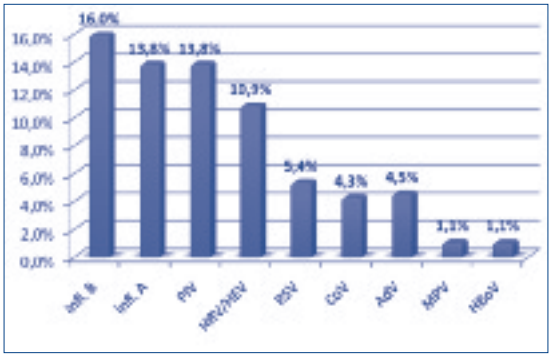

Figure 1

Comparison of ESBL-E carriage rate in newly admitted nursing home residents and patients admitted to hospital

Katja Šinkovec[1], Dane Lužnik[1], Judit Stokič[1], Vesna Špendal[1], J. Černivec[2], Vesna Tomič[1]
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Resistant bacteria are a major public health concern. Enterobacteria producing extended spectrum beta-lactamase (ESBL-E) are distributed worldwide and are of increasing prevalence. Most outbreaks of ESBL-E occur in hospitalized patients, although outbreaks have also been described in out-of-hospital locations such as nursing homes and rehabilitation units.
We wanted to determine the carriage rate of ESBL-E on admission to the largest nursing home in Slovenia (Nursing Home Danica Vogrinec, Maribor) and on admission to our hospital (University Clinic of Respiratory and Allergic Diseases Golnik).
During an 18-month period (January 1, 2011 to June 30, 2012), all newly admitted residents to a nursing home and all patients transferred to our hospital were screened for ESBL-E carriage. To assess carriage of ESBL-E rectal and wound (when present) swabs and urine samples (when catheter present) were collected. Swabs were inoculated into brain-heart infusion broth and after 24 hour incubation, broths were subcultured onto Brilliance ESBL agar plates (Oxoid, UK). Urine samples were inoculated directly onto Brilliance ESBL agar plates. Colonies of ESBL-E were identified by standard laboratory procedures.
We screened 366 newly admitted nursing home residents (424 samples collected) and 2077 patients transferred to our hospital (2661 samples collected). Of the 366 newly admitted nursing home residents 270 (73.8%) were females and 96 (26.2%) males. On admission to the nursing home we detected 58/366 new residents (15.8%) colonized with ESBL-E, 41/270 females (15,2 %) and 17/96 males (17,7%). We collected 63/424 positive samples (14,8%). Most commonly isolated ESBL-E was *E. coli*, in 28/58 (48.3%) cases (6 females, 22 males), followed by *K. pneumoniae* in 25/58 (43.1%) (10 females, 15 males), *E. cloacae* in 5/58 (8.6%) (all female), 3/58 (5.2%) *K. oxytoca* isolates (1 female, 2 males) and *C. freundii* was isolated in 2/58 (3.4%) cases (both in females). Of the 366 newly admitted residents 162 were admitted from home environment (44.3%) and 19/162 were ESBL-E positive (11.7%), 47 were transferred from other nursing homes (12.8%) and 7/47 were ESBL positive (14.9%), 125 were admitted from hospitals (34.1%) and 32/125 were ESBL positive (25.6%).
In a group of patients screened on admission to our hospital we detected 182 positive samples out of 2661 collected (6.8%). From 2077 patients screened 150 (7.2%) were colonized with ESBL-E. Also in this case most commonly isolated ESBL-E was *E.coli* in 93/150 (62%) cases (56 females, 37 males), second most commonly isolated ESBL-E was *K. pneumoniae,* in 55/150 cases (36,6%) (28 females, 27 males), *E. cloacae* in 2/150 cases (1.3%) (1 female, 1 male), *M. morgani, P. mirabilis* and *P. stuarti* isolates (1 of each) were all found in females (0.6%) and *E. aerogenes* was found in one male.

ESBL-E carriage rate in newly admitted nursing home residents was almost twice as high as carriage rate in patients admitted to our hospital with the highest carriage rate detected in patients transferred from hospitals to nursing home. Effective measures to prevent the emergence and spread of ESBL-E are urgently needed.

Clinical characteristics of hospitalized patients with atypical community acquired pneumonia

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Community acquired pneumonia (CAP) is one of the most frequent reasons for hospitalization and represents the largest part of acute hospitalization. CAP in definition is an acute illness with cough and at least one of new focal chest signs, fever >4 days or dyspnoea/tachypnoea, without other obvious cause. Agents such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila* are recognized as important causes. In this study we examined the role of these 'atypical pathogens' among hospitalized patients with CAP.

We retrospectively examined data from 24 patients hospitalized in University Clinic of Respiratory and Allergic Diseases, Golnik in year 2011 with confirmed etiology of atypical CAP. Causal organisms were determined using: PCR from respiratory samples (pharyngeal smear, sputum), antigen test for *Legionella pneumophila* in urine and serology.

In 2011, 735 patients with diagnosis CAP were treated in our hospital. 206 (28%) of them had known etiology. In group of patients with known etiology 24 (11,6%) had atypical pneumonia: *Mycoplasma pneumoniae* 13 (54%), *Chlamydophila pneumoniae* 1 (4,5%) and *Legionella pneumophila* 10 (41,5%) patients. There were 12 male patients (average 51 years old), 58% smokers, and 12 female patients (average 49,2 years old), 25% smokers. 50% of patients had no co-morbidities, 20% had asthma or COPD, 29% arterial hypertension. 16% of patients had two or more co-morbidities. Before admission 37% of patients had antibiotic therapy (all of them β-Lactam antibiotics). On admission 66% patients were hypoxemic (90% of those with *Legionella pneumophila*). Four patients admitted to intensive care (all with *Legionella pneumophila*) were from the beginning treated with combination antibiotic therapy: (β-Lactam antibiotics plus macrolide or quinolon). Averege length of hospitalization was 6 days for *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, and 12,5 days for *Legionella pneumophila*. Compared to patients with other definite and unknown etiologies, patients with atypical pneumonia were younger and had less comorbidity. Patients with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were presented with a less severe disease and had better outcomes, including a shorter length of hospitalization, nobody requiring mechanical ventilation and nobody had died. In opposite, patients with legionelosis in 40% required intensive care, mechanical ventilation and longer hospitalization. The decision for hospitalization remains a clinical decision. However, this decision should be validated against an objective tool of risk assessment (CRB-65, PORT). In this group of patients with definite atypical pneumonia, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* appear as a condition with a largely benign course.

In view of a favorable clinical outcome, recent recommendations including regular coverage of atypical pathogens in patients with mild to moderate CAP might be reconsidered.

Obesity hypoventilation syndrome: misdiagnosed or neglected disease?

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University Clinic of Respiratory and Allergic Diseases, Golnik

Obesity hypoventilation syndrome (OHS) is characterized by body mass index (BMI) ≥ 30 and daytime hypercapnia in the absence of any other cause of hypoventilation. It is often accompanied by sleep disordered breathing. Even though OHS is related to many comorbidities and it seems to become an important public health problem, scientific and clinical interest in the disease is scarce. According to American Academy of Sleep Medicine Guidelines positive airway pressure (PAP) therapy is treatment of choice in OHS patients and supplemental oxygen is added when the patients' awake supine SpO2 is less than 88%. We aimed to assess whether OHS is recognized and managed according to guidelines in our University Clinic.

Medical records of all patients discharged with diagnosis of OHS (ICD E66.2) between 2005 and 2010 from University Clinic Golnik were reviewed. Diagnosis was reevaluated and patients were divided in three groups: those that were admitted in acute hypercapnic exacerbation (aeOHS) or in stable phase (sOHS), and those who did not meet the criteria for OHS (nOHS). Management of patients in aeOHS and sOHS group was evaluated. During index hospitalization 5 patients in nOHS group died and were excluded from analysis.

Out of 380 patients (54.5% men, age 62.4+/-11.9 years) discharged with the diagnosis of OHS, 130 (34.2%) were in aeOHS, 120 (31.5%) in sOHS, and 130 (34.2%) in nOHS group. In the latter group, 52 (13.7% of all) did not have data on pCO2 or BMI, 57 (15% of all) were not hypercapnic and 21 (5.5% of all) had other diseases that cause hypercapnia: severe COPD, fibrothorax, kyphoscoliosis, diaphragm paralysis, severe bronhchiolitis or muscular dystrophy. In aeOHS 69 (53%) patients were treated with PAP and 110 (92%) in the sOHS group ($p<0.001$). Supplemental oxygen, without PAP treatment, was prescribed in 52 (40%) patients in aeOHS and in 7 (5.8%) patients in sOHS group, ($p<0.001$). Prescription of PAP treatment in sOHS was relatively stable during years (81.8%, 100.0%, 96.8%, 86.2%, 91.7%, respectively), but there was a trend of higher prescription in aeOHS group (26.7%, 56.3%, 37.9%, 44.0%, 65.0%, respectively).

In one third of cases the diagnosis of OHS was incorrect. Patients who were diagnosed with OHS during acute hypercapnic exacerbation were often not treated according to guidelines. Management of these patients was improving over the years of the study.

The success rate of pleural effusion diagnostics in a tertiary hospital

Anja Žargaj, Aleš Rozman, Izidor Kern, Mitja Košnik
University Clinic of Respiratory and Allergic Diseases, Golnik

The etiology of pleural effusion is often established by simple diagnostic procedures; however in some patients they fail to establish diagnosis. The purpose of this study was to define, how often a single thoracocenthesis establish the etiology of pleural effusion. The additional aim was to assess the diagnostic value of subsequent thoracocentheses. The study was retrograde, performed in a tertiary hospital on a sample of 100 random patients with pleural effusion.
We analyzed patient's medical records for cytological and biochemical data of their pleural effusions, blood proteins and lactate dehydrogenate (LDH) level, other diagnostic procedures and follow up data to get the clinical assessment of final diagnosis of pleural effusion. Differentiation between exudates and transudates was made according to Light's criteria.
We performed 154 thoracocentheses on 100 patients with 106 pleural effusions (6 had bilateral pleural effusion). 67 patients had single thoracocenthesis, 18 had two thoracocentheses (two of them on both sides), 11 patients had three (two of them on both sides), 2 had four (one of them on both sides) and 2 patients had five thoracocentheses (one of them on both sides). 64 effusions were defined as exudates, 40 as transudate, 1 was peripheral blood, and for 1 effusion we didn't find data. Etiological classification of pleural effusions:

Effusion (n)
heart disease (37)
parapneumonic (21)
malignancy related 11 carcinoma 3 mesothelioma 9 paramalignant 1 after radiation
undefined (7)
non-specific pleurisy (4)
fibrothorax (4)
pulmonary embolism (2)
iatrogenic (2)
ascites (3)
chylothorax (1)
drug induced (metothrexate) (1)

Five patients with pleural effusion due to carcinoma fulfilled criteria for transudate. Five patients with pleural effusion due to cardiac disease fulfilled criteria for exudates. Malignant cells found in 8 effusions. For eight pleural effusions were performed additional invasive procedures to establish etiology: thoracoscopy (2), blind needle biopsy (4) and CT guided biopsy (2). Additional thoracocenthesis established diagnosis of malignancy in only one case.
Thoracocenthesis establishes the etiology of pleural effusion in majority of patients – only 8 needed additional diagnostic procedures and additional 7 remained undefined. Subsequent thoracocenthesis rarely confirms diagnosis of malignancy if initial was negative.

Molecular methods in detection of drug-resistant tuberculosis in Slovenia and FYR Macedonia

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The rapid recognition of drug-resistant strains of *Mycobacterium tuberculosis* (MT) is crucial for the timely initiation of appropriate therapy, reduction of the transmission of tubercle bacilli, and improvement of treatment outcome. The conventional phenotypic drug susceptibility tests are routinely performed only after a pure, viable culture is obtained, and it often takes 3–5 weeks from the admission of clinical sample to the laboratory. Molecular test GenoType MTBDR*plus* (GTM; Hain Lifescience GmbH, Nehren, Germany) is PCR-based amplification and reverse blotting assay for the detection of rifampicin (RMP) and isoniazid (INH) resistance from cultures or directly from clinical samples. The assay detects mutations in the *rpoB* gene for RMP resistance, and in the *katG* and *inhA* genes for INH resistance. The purpose of our study was to evaluate the reliability of the GTM assay for the detection of INH and RMP resistance in Slovenian and Macedonian MT strains.

A total of 89 drug-resistant MT isolates (55 Slovenian and 34 Macedonian) from our strains collection were included in this retrospective study. A little more than one half of them (22 Slovenian and 26 Macedonian strains) was multi-drug resistant (MDR) strains isolated from clinical samples in the Laboratory for Mycobacteria Golnik and the Laboratory for Mycobacteria Skopje between 1996 and 2011. Fifty-one Slovenian and 33 Macedonian strains were INH-resistant, and 26 Slovenian and 27 Macedonian isolates were RMP-resistant by conventional drug susceptibility method (BACTEC MGIT 960 method (BD, Sparks, USA)).

Resistance to INH was correctly identified by the GTM molecular test in 41 of 51 Slovenian isolates (80.4%) and in 23 of 33 Macedonian isolates (69.7%). The rate of the RMP resistance detection by the GTM test was 100% for Slovenian and only 77.8% (21/27) for Macedonian strains. The most common mutation carried in RMP–resistant isolates was *rpoB* MUT3-S531L in both Slovenian and Macedonian strains. In INH-resistant isolates, mutations of the *katG* gene were responsible for resistance in 75.6% of Slovenian and 60.9% of Macedonian strains, and mutations of the *inhA* gene were responsible for resistance in 24.4% of Slovenian and 39.1% of Macedonian isolates.

Our retrospective analysis of Slovenian MT strains showed a relatively good agreement between the GTM molecular test and phenotypic drug susceptibility testing for RMP and INH. This does not apply for the Macedonian MT strains where the agreement for RMP is extremely low. Previous studies around the world have demonstrated that the GTM test identified from 91.7 to 100% of RMP resistance and from 34.6 to 96.6% of INH resistance. Therefore further analysis of Macedonian strains is required.

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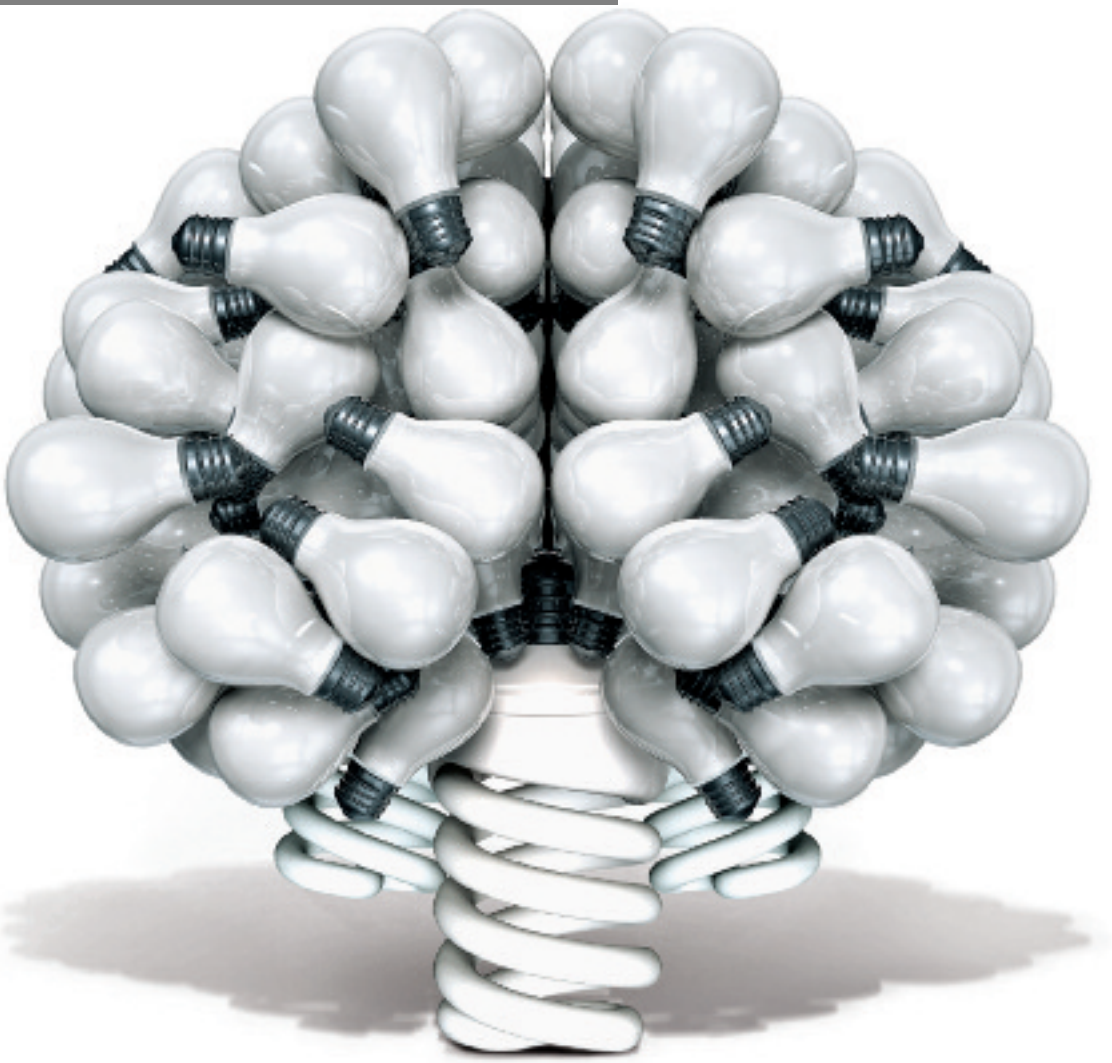

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ORALAIR 100 IR in 300 IR podjezične tablete, ORALAIR 300 IR podjezične tablete; SESTAVA: Alergenski izvleček iz cvetnega prahu naslednjih trav: pasje trave (Dactylis glomerata L.), dišeče boljke (Anthoxanthum odoratum L.), trpežne ljuljke (Lolium perenne L.), travniške latovke (Poa pratensis L.) in mačjega repa (Phleum pratense L.), 100 IR ali 300 IR na podjezično tableto. Pomožna snov je laktoza monohidrat. **FARMACEVTSKA OBLIKA**: Podjezična tableta. **INDIKACIJE**: Zdravljenje odraslih, mladostnikov in otrok (starejših od 5 let) z alergijskim rinitisom zaradi cvetnega prahu trav, s konjunktivitisom ali brez njega, s klinično pomembnimi simptomi, ki se potrdi s pozitivnim kožnim testom in/ali pozitivnim titrom specifičnih protiteles IgE proti cvetnemu prahu trav. **ODMERJANJE IN NAČIN UPORABE**: Zdravljenje z zdravilom ORALAIR lahko predpiše in začne samo ustrezno usposobljen zdravnik z izkušnjami z zdravljenjem alergijskih bolezni. Pri pediatričnem zdravljenju morajo imeti usposobljeni zdravniki ustrezne izkušnje pri otrocih. Prva tableta zdravila ORALAIR se vzame pod zdravnikovim nadzorom in se bolnika spremlja 30 minut. Odmerjanje: Zdravljenje je treba začeti približno 4 mesece pred pričakovanim začetkom sezone cvetnega prahu in ga je treba vzdrževati skozi celotno sezono cvetnega prahu. Terapijo sestavlja začetno (vključno s 3-dnevnim povečevanjem odmerka) in nadaljevalno zdravljenje. Začetno zdravljenje traja prvi mesec zdravljenja z zdravilom ORALAIR 100 IR in 300 IR podjezične tablete. Od drugega meseca naprej se nadaljuje z nadaljevalnim zdravljenjem z eno podjezično tableto ORALAIR 300 IR na dan do konca sezone cvetnega prahu. Tableto je treba položiti pod jezik, dokler se popolnoma ne raztopi (za vsaj eno minuto), potem pa pogoltniti. Drugi dan zdravljenja je treba pod jezik hkrati položiti 2 tableti 100 IR in potem pogoltniti. Priporočamo, da se tableta vzame zjutraj na prazen želodec. **KONTRAINDIKACIJE**: Preobčutljivost za katerokoli pomožno snov, sočasno zdravljenje z blokatorji beta, huda in/ali nestabilna astma (FEV1 < 70 % predvidene vrednosti), huda imunska pomanjkljivost ali avtoimunska bolezen, maligne bolezni (npr. rak), oralna vnetja (kot je oralni lichen planus, oralne ulceracije ali oralna mikoza). **POVZETEK POSEBNIH OPOZORIL, PREVIDNOSTNIH UKREPOV IN INTERAKCIJ**: Pri oralnem kirurškem posegu (tudi izruvanje zoba), je treba zdravljenje z zdravilom ORALAIR prekiniti za 7 dni. Potem se lahko zdravljenje nadaljuje s predhodnim odmerkom. Če je prekinitev daljša, se priporoča, da se zdravljenje s predhodnim odmerkom ponovno začne pod zdravnikovim nadzorom. Hude alergijske reakcije se lahko zdravijo z adrenalinom. Učinek adrenalina je lahko močnejši pri bolnikih, ki se zdravijo s tricikličnimi antidepresivi in inhibitorji monoaminoksidaze (MAO), kar lahko povzroči smrt; to je treba upoštevati pred začetkom specifične imunoterapije. Kliničnih izkušenj, povezanih s sočasnim cepljenjem in zdravljenjem z zdravilom ORALAIR, ni. Cepljenje brez prekinitve zdravljenja z zdravilom ORALAIR se lahko opravi po zdravstveni oceni splošnega stanja bolnika. Ker zdravilo vsebuje laktozo, ga bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze, ne smejo jemati. V kliničnih preskušanjih z zdravilom ORALAIR, med katerimi so lahko bolniki jemali zdravila za zdravljenje simptomov alergije (antihistaminike, steroide), niso poročali o nobenih interakcijah. O morebitnih tveganjih sočasne imunoterapije z drugimi alergeni med zdravljenjem z zdravilom ORALAIR ni podatkov. Uvajanja imunoterapije med nosečnostjo se ne priporoča. Če bolnica med zdravljenjem zanosi, se lahko zdravljenje nadaljuje, vendar je potrebno skrbno spremljanje. Ni pričakovati učinkov na otroke, ki so dojeni. Uvajanja imunoterapije med dojenjem se ne priporoča. Če pa se bolnica zdravi v času poroda, lahko doji, vendar je potrebno skrbno spremljanje. Zdravilo ORALAIR nima vpliva na sposobnost vožnje in upravljanja s stroji. **NEŽELENI UČINKI:** med zdravljenjem lahko pričakujemo blage do zmerne lokalne alergijske reakcije (tj. otekanje ali neugodje v ustih). 50 % teh reakcij se pojavi v prvih treh dneh zdravljenja (povečevanje odmerka). Če ima bolnik med zdravljenjem hude lokalne neželene reakcije, je treba razmisliti o simptomatičnem zdravljenju (npr. z antihistaminiki). V zelo redkih primerih se lahko pojavijo močnejše alergijske reakcije, ki vključujejo občutek otekanja grla, oteženo požiranje ali dihanje in spremembe glasu. V takih primerih se je treba takoj posvetovati z zdravnikom in takoj prekiniti zdravljenje. Zdravljenje se lahko ponovno začne samo po zdravnikovem nasvetu. Če bolnik vzame odmerek, ki je večji od priporočenega dnevnega odmerka, se poveča tveganje neželenih učinkov, vključno s sistemskimi neželenimi učinki ali hudimi lokalnimi neželenimi reakcijami. Če se pojavijo hudi simptomi, kot je angioedem, težave pri požiranju, težave pri dihanju, spremembe glasu ali občutek tiščanja v grlu, se je treba takoj posvetovati z zdravnikom. Pri prevelikem odmerjanju je treba neželene učinke zdraviti simptomatično. **IMETNIK DOVOLJENJA ZA PROMET:** STALLERGENES S.A., 6 rue Alexis de Tocqueville, 92160 ANTONY, Francija **DATUM ZADNJE REVIZIJE BESEDILA**: 10/2010 **REŽIM IZDAJE**: Rp/Spec **LISTA**: V*

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- zdravljenje globoke venske tromboze (GVT) in preprečevanje ponovne GVT in pljučne embolije (PE) po akutni GVT pri odraslih.

P70* – pozitivna lista z omejitvijo predpisovanja; krito iz obveznega zdravstvenega zavarovanja v 70 odstotnem deležu, v celoti le skladno s predpisi

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Zdravljenje z zdravilom Xarelto je dolgotrajno, če koristi preprečevanja možganske kapi in sistemske embolije pretehtajo tveganje za krvavitve. Izpuščeni odmerek zdravila Xarelto naj bolnik vzame takoj, ko se spomni in naslednji dan nadaljuje z jemanjem enkrat na dan, kot je priporočeno. Bolnik naj isti dan ne vzame dvojnega odmerka, da bi s tem nadomestil izpuščeni odmerek. *Zdravljenje GVT in preprečevanje ponovne GVT in PE:* Priporočeni odmerek za začetno zdravljenje akutne GVT 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. Če bolnik pozabi vzeti zdravilo Xarelto v času zdravljenja, ko jemlje tablete po 15 mg dvakrat na dan (1. do 21. dan), ga mora vzeti takoj ko se spomni, da zagotovi odmerek 30 mg zdravila Xarelto na dan. V tem primeru lahko vzame dve tableti po 15 mg hkrati. Bolnik naj naslednji dan nadaljuje z rednimi odmerki po 15 mg dvakrat na dan, kot je priporočeno. **Kontraindikacije:** Preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov; klinično pomembna aktivna krvavitev; 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:** *Uporaba zdravila Xarelto se ne priporoča:* pri bolnikih, ki sočasno jemljejo tudi azolne antimikotike za sistemsko zdravljenje (npr. ketokonazol, itrakonazol, vorikonazol in posakonazol) ali zaviralce proteaz HIV (npr. ritonavir). Te zdravilne učinkovine močno zavirajo CYP3A4 in P-gp ter lahko klinično pomembno (2,6-krat na povprečna vrednost) povečajo plazemske koncentracije rivaroksabana, kar lahko poveča tveganje za krvavitve; pri bolnikih s hudo okvaro ledvic (očistek kreatinina < 15 ml/min); za zdravljenje bolnikov z akutno pljučno embolijo; pri otrocih in mladostnikih, mlajših od 18 let; pri bolnikih z umetnimi srčnimi zaklopkami ali pri bolnikih, sočasno zdravljenih z dronedaronom, zaradi pomanjkanja podatkov. *Previdna uporaba zdravila Xarelto:* 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 ali so močni induktorji CYP3A4; pri bolnikih s povečanim tveganjem za krvavitve. Pri bolnikih, pri katerih obstaja tveganje za pojav razjed v prebavilih, je treba razmisliti tudi o ustreznem profilaktičnem zdravljenju. Ves čas zdravljenja se priporoča klinično spremljanje v skladu z običajnim vodenjem antikoagulacijskega zdravljenja. 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. Za bolnike z zmerno ali hudo okvaro ledvic veljajo posebna priporočila za odmerjanje. Zdravilo Xarelto vsebuje laktozo. **Neželeni učinki:** *Pogosti:* anemija, omotica, glavobol, sinkopa, krvavitev v očesu, tahikardija, hipotenzija, hematom, epistaksa, krvavitve v prebavilih, bolečine v prebavilih in trebuhu, dispepsija, navzea, zaprtje, driska, bruhanje, srbenje, osip, ekhimoza, bolečine v udih, krvavitve v urogenitalnem traktu, 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, hemoptiza, suha usta, moteno delovanje jeter, urtikarija, krvavitve v koži in podkožju, hemartroza, okvara ledvic, slabo počutje, lokaliziran edem, povečane vrednosti: bilirubina, alkalne fosfataze v krvi, LDH, lipaze, amilaze, GGT. *Redki:* zlatenica, krvavitve v mišicah, povečane vrednosti konjugiranega bilirubina. *Neznana pogostnost:* pseudoanevrizma pri perkutanem posegu, utesnitveni sindrom sekundarno po krvavitvi, sekundarna akutna odpoved ledvic po krvavitvi. **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/2 (06/2012)

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[1] Povzetek glavnih značilnosti zdravila TARCEVA, www.ema.europa.eu

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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 samostojno vzdrževalno zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč s stabilno boleznijo po 4 ciklih standardne kemoterapije na osnovi platine 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 klinično 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 (sočasno jemanje drugih zdravil, simptomi, bolezni ali drugi 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. *Hepatisis, 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 luščenjen 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. *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 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 Tarceva 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 *spodbujevalci 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.
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, keratitis, paronihija, folikulitis, akne/akneiformni dermatitis, fisure na koži. *Občasno* so poročali o perforacijah v prebavilih, hirzutizmu, spremembah obrvi, krhkih nohtih, odstopanju nohtov od kože, blagih reakcijah na koži (npr. hiperpigmentacija), spremembah trepalnic, hudi intersticijski bolezni pljuč (vključno s smrtnimi primeri). *Redko* pa so poročali o jetrni odpovedi. *Zelo redko* so poročali o Stevens-Johnsonovem sindromu/toksični epidermalni nekrolizi ter o ulceracijah in perforacijah roženice.
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:** 1.0/12. **Informacija pripravljena:** September 2012.

DODATNE INFORMACIJE SO NA VOLJO PRI:
Roche farmacevtska družba d.o.o., Vodovodna cesta 109, 1000 Ljubljana.
Povzetek glavnih značilnosti zdravila je dosegljiv na
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- Izboljša kakovost življenja[4,5,**]

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******SPIRIVA® 18µg z vdihovalnikom HandiHaler® ni spremenila letne stopnje upada pljučne funkcije, ki je bila soprimarni opazovani dogodek v raziskavi UPLIFT®, vendar pa je vsa 4 leta vzdrževala boljšo pljučno funkcijo v primerjavi s kontrolno skupino.

Predstavljeni klinični podatki se nanašajo na zdravilo SPIRIVA® 18µg z vdihovalnikom HandiHaler®, uporabljeno enkrat na dan.

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
SPIRIVA 18 mikrogramov prašek za inhaliranje, trde kapsule
Kakovostna in količinska sestava: 1 kapsula vsebuje 22,5 µg tiotropijevega bromida monohidrata, kar ustreza 18 µg tiotropija. **Terapevtske indikacije:** Vzdrževalno bronhodilatacijsko zdravljenje, ki zmanjša simptome pri bolnikih s kronično obstruktivno pljučno boleznijo (KOPB). **Odmerjanje in način uporabe:** Inhalacija vsebine ene kapsule 1-krat na dan ob enakem času z vdihovalnikom HandiHaler. Bolnikov mlajših od 18 let ne smemo zdraviti s Spirivo. **Kontraindikacije:** preobčutljivost za tiotropijev bromid, atropin ali njune derivate, npr. ipratropij ali oksitropij ter za pomožno snov laktozo monohidrat. **Posebna opozorila in previdnostni ukrepi:** Tiotropijev bromid je bronhodilatator za vzdrževalno zdravljenje z enim odmerkom na dan in ga ne smemo uporabljati za začetno zdravljenje akutnih epizod bronhospazma oz. kot reševalno zdravilo. Po dajanju tiotropijevega bromida v obliki praška za inhaliranje se lahko pojavijo takojšnje preobčutljivostne reakcije. Tiotropijev bromid je treba previdno uporabljati pri bolnikih z glavkomom zaprtega kota, hiperplazijo prostate ali zaporo vratu sečnega mehurja. Pri zdravilih za inhaliranje lahko inhalacija sproži bronhospazem. Pri bolnikih z zmerno do hudo ledvično okvaro smemo uporabiti tiotropijev bromid samo, kadar je pričakovana korist zdravljenja večja od morebitnega tveganja. Pri pojavu znakov in simptomov glavkoma zaprtega kota morajo bolniki tiotropijev bromid prenehati jemati in se nemudoma posvetovati s specialistom. Suha usta so lahko dolgoročno povezana z zobnim kariesom. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorbcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Interakcije:** Pri sočasni uporabi tiotropijevega bromida v obliki praška za inhaliranje in drugih zdravil niso zasledili kliničnih znakov interakcij. Ta zdravila so bila simpatikomimetični bronhodilatatorji, metilksantini ter peroralni in inhalacijski steroidi, ki jih pogosto uporabljamo v zdravljenju KOPB. Sočasnega zdravljenja s tiotropijevim bromidom in drugimi zdravili, ki vsebujejo antiholinergik, niso raziskovali, zato ga ne priporočamo. **Nosečnost in dojenje:** Študije na živalih so pokazale vpliv na sposobnost razmnoževanja, povezano s toksičnimi učinki pri samici. Možno tveganje za ljudi ni znano. Spirivo smemo med nosečnostjo uporabljati samo, kadar je jasno indicirana. Spirive med dojenjem ne priporočamo. Tiotropijev bromid je dolgodelujoča spojina. Pri odločitvi o nadaljevanju ali prenehanju dojenja oziroma nadaljevanju ali ukinitvi zdravljenja s Spirivo je treba presoditi med koristjo dojenja za otroka in koristjo zdravljenja matere. **Neželeni učinki:** Pogost neželeni učinek so suha usta. Občasni neželeni učinki so: omotica, glavobol, motnje okušanja, meglen vid, atrijska fibrilacija, faringitis, disfonija, kašelj, stomatitis, gastroezofagealna refluksna bolezen, zaprtost, siljenje na bruhanje, izpuščaj, dizurija, zastoj seča. Redki neželeni učinki so: nespečnost, glavkom, povečan očesni tlak, supraventrikularna tahikardija, tahikardija, palpitacije, bronhospazem, epistaksa, laringitis, sinusitis, črevesna zapora, tudi paralitični ileus; gingivitis, glositis, orofaringealna kandidoza, disfagija, urtikarija, pruritus, druge oblike preobčutljivosti (tudi takojšnje reakcije), okužba sečil. Neželeni učinki neznane pogostnosti so: dehidracija, zobni karies, angionevrotični edem, kožna okužba in kožna razjeda, suha koža, otekanje sklepov. **Način in režim izdaje:** Rp. **Imetnik dovoljenja za promet:** Boehringer Ingelheim International GmbH, Binger Strasse 173, D-55216 Ingelheim am Rhein, Nemčija. Za **podrobnejše informacije** glejte Povzetek glavnih značilnosti zdravila, z dne 03.05.2011.

SAMO ZA STROKOVNO JAVNOST.

Spiriva 03/januar 2012

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Podružnica Ljubljana
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