

THE SURGICAL TREATMENT OF LUNG CANCER

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Lung cancer is a malignant epithelial tumor which grows slowly and deceitly, often without symptoms, fastly occupying other organs, and the results of the treatment are modest. This pessimistic definition of the lung cancer urges the doctors of different specialities every day to improve diagnostics and to advance the treatment of this evil illness.

In the last fifty years with people aged from 40-50 lung cancer has become occurring the most of all cancers. The number of people with lung cancer is fastly increasing in all economically developed countries. The incidence shows permanent, almost frightening increasment, and the absolute incidence is almost doubleing every ten years.

According to some information lung cancer makes 40% of all deatnes caused by malignes deseases in men. Some of the outside effects are blamed to be the cause for this increasing number of people with lung cancer, such as industrial gases, petrol, oil steams, dust, smoke from the factories, and the products of their burning.

Of course, in this time there is a frequent reminder of the danger from smoking cigarettes. The assumption of the ethiological bond between smoking and lung cancer has been given in 1913.

Depending on different studies the lung cancer is 4-10 times more often accuring in smokers then in non-smokers.

Beside the direct risk of the smoking, the lung cancer can be initiated by organic and non-organic substances.

Asbest, arsen, niel, chrom, berilijum, insecticides, already mentioned petrol, radiation, inhaling warm smoke and organ compounds are high risk for lung cancer. In urban and domestic areas there is over 60,000 different chemicals used, and every year there is even more sustances which can not be neglected.

Even though it has been proved that the outside factors cause 80% of malignes lung neoplasmas, other things such as genetic factors, imunological factors and other base and local factors influence the cancerogenesis.

The lung cancer is a solid epithelial tumor which can develop from tracheobronchial epithel or the alveolar epithel. In 95% of cases it develops in bronchs, and in only 3-5% cases in alveoles. According to the place in bronches where it is situated it can be divided into central, if it is up to the sixth generation of bronchal spreadation, between the sixth and twelvth generation it is called intermediar, and after the twelfth generation it is called periphery tumor. We can find centrals in 55% of the cases, intermediar in 11%, and 34% on the periphery.

The lung cancer has an infiltrative growth, it does not regard for the borders of lobus or organ, and it spreads by lympho, blood and per continuitatem.

The WHO has made a classification in 1981, and in 1999 it has made a new classification of the lung cancer according to the histological picture in to four groups, and every group has subtypes and their combinations.

The main group are:

- Carcinoma planocellulare
- Carcinoma microcellulare
- Adenocarcinoma
- Carcinoma macrocellulare

Pathohistological verification of the tumors is important for the treatment options. For the practical uses the classification of the malignes lung cancers on non-microcellulare and microcellulare is very important.

Non-microcellular cancers of bronchs are grouped because of their mutual charasteristic, that if they are restricted, they are potencionally resectabiles. Once the diagnose has been set, patiens with this cancer can be divided into three groups which show the broadening of the tumor and possible treatment.

The first group of the patients have a tumor which can be operated on (fase I and II). That is the group with the best prognosis, depending on the kind of the tumor and the host factors. Patients with the restricted desease and a containdication for the surgical treatment are exposed to radiotherapy.

The second group of the patients includes localised (T3-T4) advanced desease (N2-N3). This group os treated by radiotherapy or the combination of radiotherapy and other modalities. Some patients with T3 or N2 can be treated only surgically.

The third group of patients has methastasis(M1) at the time of seting the diagnosis. This group can only be treated with radiotherapy or chemotherapy because of the paliation of the symptoms which come from the primary tumor.

Setting the stage of the desease has a very important treatment and prosnosis implications. The stage of the desease is based on the combination of clinical (physical exam, radiological and laboratory exams) and pathological (biopsy of the lymphatic nodes, bronchoscopy, mediastinoscopy or paramedial stenotomy or other types of thoracotomies). The new international system of staging the bronch cancer has been accepted in 1997 by the American Comity for cancer and by the International union for cancer. This revision has been made in order to make better specifications for the groups od patients.

Stage I has been divided into two categories according to the size of the tumor – IA-T1N0M0 and IB-T2N0M0.

Stage II has been divided into two categories according to the size of the tumor and the state of the lymphatic nodes:

IIA – T1N1M0 and

IIB – T2N1M0. T3N0 has been moved to stage IIIA from the version of the staging from 1986, to stage IIB.

Other changes are about the classification of the multiple tumor nodes. Satelite tumor nodes in the same lobus in which is the primary lesion, and which are not lymphatic nodes can be classified as T4 lesions. Intrapulmonary ipsilateral metastasis in one lobus different from the one in which the primary tumor is, can be classified as M1 lesions (stage IV).

The stages of non-microcellular cancer of the bronchs have been shown in this table:

	N0	N1	N2	N3	M1
T1	I A	II A	III A	III B	IV
T2	I B	II B	III A	III B	IV
T3	II B	III A	III A	III B	IV
T4	III B	III B	III B	III B	IV
M1	IV	IV	IV	IV	

In the treatment of the lung cancer following methods is used:

-surgical

-chemotherapy

-radiotherapy

-the combination of the mentioned methods

-symptom based treatment.

All surgical methods in the lung cancer are known. Which operation to perform depends on more than one element which has to be respected?

In the first stage of surgical intervention the therapy for the lung cancer in pneumonectomy has been recognized as the only radical method with taking out every enlarged lymphatic gland in mediastinum.

Later through practice it has been seen that this position is not justified, because it has been shown that the borders of lobe in the most cases are the borders of cancer spreading in the stage when it can be operated on, and that the possible lobectomy is radical.

As it has been proven that the most efficient therapy is surgical, one of the most important questions is to define the stages of operability and inoperability.

Although the base principles of non-operability have been set, they can be discussed.

The existing elements which show the close or distant spreading of the primary disease lymphatically or by blood imply that these states are inoperable.

Metastasis of Para tracheal and contra lateral lymphatic nodes, supraclavicular, axillar and abdominal show that these states are too inoperable.

Spreading of the tumor to the surroundings is the state of inoperability.

Also the existing pleural drain, mostly sanguinolent in lung cancer is the sign of absolute inoperability.

The paralysis of recurrent nerve is too the sign of inoperability, but according to some reports effort should be made in further diagnostics because it is not always the case that if the tumor in spreading on recurrent nerve that is spreading on the great blood vessels.

The paralysis of nerve phrenicus, and the involvement of any main branch of pulmonary artery trunk are always the signs of inoperability.

If all we take all we have mentioned in to the TNM classification we can see that stages I and II are absolutely operable.

The progress in surgical treatment of the lung cancer is motivated by the wish to widen the radical procedures and in many cases the statistics show the justification of these goals.

In stage III some cases can be operable even with T3, if the spreading on the thoracic wall is not so great to make postresectional plastic impossible, or if the depth of the surgical treatment in other directions is not very big.

Some authors inform about successful radical surgeries in stage IIIB with T4N0M0, with partial resections and the plastics of vena cava, atria's and trachea.

Even in stage IV if the distant metastasis is solitary and if there is technical possibility of its extirpation it can be operated on.

Earlier it was thought that the patients with lung cancer over 70 years of age should not be operated upon, because of the greater operative risk.

The experience of many authors is contrary to this, and there are many results which justify surgical treatment in these patients.

The greatest risk in elderly is the state of lung function.

Spared resections in segmentectomy and cuneiform excursion have been often used in elderly patients and according to the postoperative results and watching the patients have earned the right to be called radical.

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THE ROLE OF FAMILY MEDICINE TEAM MEMBERS IN ASTHMA MANAGEMENT

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Asthma is a chronic and dynamic disease, which causes remarkable physical, emotional and social limitations in life of patients. These limitations are higher if asthma is not well controlled^{1,2,3}.

Results of studies in the United Kingdom have shown that health care outcomes in asthmatic patients are better if primary and secondary health care are integrated and if a role of nurse in counseling and control of patients is more significant⁴.

There is a need to increase a significance of family physicians and nurses in the process of diagnostic and control of asthma. This task is achievable by education family medicine team members and introducing a new diagnostic methods and management of asthma. An especial attention needs to be applied in increasing knowledge and skills in daily practice of family medicine nurses.

Patients are not well educated and informed about their disease and its control. Particularly, they have to be educated in avoiding of exacerbation of disease. More than 40% patients did not react properly in the case of asthma exacerbation⁵. Only 3% children with asthma have a written asthma action plan for the self-control of asthma. Education of patients, family physicians and nurses is a key activity in the increase of the asthma control^{1,2,3}. Complex task of family physicians and nurses in health care of asthmatic patients could be divided in two large groups. Early recognition and diagnosis of asthma, Management of asthma.

Educations of patients, family physicians and nurses have to follow curriculums based on those two groups' tasks.

A. Early Recognition and Diagnosis of Asthma

Diagnosis of asthma is clinical and it is based on physician's skills to recognize symptoms and signs connected with disease^{1,2,6}. Measurement of lungs function by spirometry significantly raises reliability of diagnosis. Patients with asthma as other patients with lungs diseases could have many symptoms and signs, but the most specific for asthma are 1) wheezing, 2) shortness of breath, 3) chest tightness, and 4) cough. These symptoms are particularly important if they are vary, periodic, seasonal or if they getting worse during the night or if they are provoked by triggers, including physical exercise.

Considering the reality that asthma in family medicine is often unrecognized or managed under diagnosis of other lungs disorders, family physicians and nurses have to search actively for the possibility of asthma in their patients. They should to ask followed questions to all patients as a screening tool for asthma⁷.

Have you had an attack or have wheezing any time in your life?

Have you had a troublesome cough at night?

Have you had shortness of breath or wheezing after physical effort?

Have you had cough, shortness of breath or wheezing after exposure to certain allergens or in seasons?

Have you had shortness of breath any time in your life?

This short screening questioner with symptoms and risk factors for asthma (family history of asthma, other atopic diseases, allergen, irritants and pollutants exposure, and smoking) highly increase suspicion for this disease. Family physician and nurse give especial attention to particularly difficult diagnostic groups: children, elderly, occupational asthma, seasonal

asthma and cough variant asthma. Asthma could be classified by etiology or severity of symptoms or pattern of airflow obstruction or by daily regime of medication use.

B. Management of Asthma

Global Initiative for Asthma (GINA) tasks for the asthma management is proven in GOAL study (Gaining Optimal Asthma Control) by the strict therapy in 41% of all patients⁸. Definition of "total control" of asthma is the complete and continuous absence of asthma symptoms with no daytime symptoms, no night-time waking, no activity limitations, no sudden worsening of the disease requiring hospitalization or emergency room visits, and no use of 'rescue' medications for a minimum assessment period of seven out of eight weeks.

Six interrelated parts of asthma management are proposed by GINA, Bosnia and Herzegovina Asthma National Program. These parts are based on understanding of asthma as chronic, progressive inflammatory disease of airways.

Educate patients to develop a partnership in asthma management,

Assess and monitor asthma severity with both symptom reports and, as much as possible, measurements of lung function,

Avoid exposure to risk factors,

Establish individual medication plans for long-term management in children and adults,

Establish individual plans for managing exacerbations,

Provide regular follow-up care.

1. Patient education

Patients and their family members have to be educated for the successful asthma control. This education is continuous activity and every visit has to be used for some education. Nurses gain a new more important role in the process of education. The topics for education of asthma patients are 1) Asthma pathophysiology (bronchoconstriction and inflammation); 2) Asthma drugs, ways of action, side effects, prejudices; 3) Use of inhalers, discs and spacers; 4) Significance, types and prevention of asthma attack triggers; 5) Symptoms and signs of asthma, especially signs of exacerbation; 6) Role and use of peak flow meter, results interpretation; 7) Adjustment of therapy, exacerbation procedure; 8) Effective use of health care system; and 9) Written Asthma Action Plan.

2. Assessment and monitoring of the asthma severity

Asthma severity is assessed by symptoms, measurement of lungs function (spirometry and peak flow meter) and needs for asthma drugs. The best ways for symptom assessment is a patient asthma diary and a flow sheet with formatted questions in medical charts. Asthma diary and flow sheets, also, assess quality of life and daily activities.

3. Avoiding exposure to risk factors

Triggers (allergens and irritants) could induce airway inflammation or to precipitate acute bronchospasm⁹. Although drugs are the main asthma treatment, trigger avoidance is very important part of the asthma control. The most important triggers are pollens, molds, mites, cockroach, animals' allergen, air pollutants, foods, physical effort and airways infections.

4. Individual medication plans

Step ways approach to pharmacological therapy is needed to achieve total control of this chronic and dynamic disease. A use of medication has to be individually tailored and based on the estimation of asthma severity. The goal is to relief symptoms and improves of lung function as fast as possible with fewer numbers of medications. This goal is achievable by the step up (progression to the next step) if it is needed or step down if it is possible. Patient compliance, a use of inhalers and trigger prevention has to be checked before every step up on the higher level of pharmacological therapy.

Considering effects of the asthma medication, they could be divided in two groups.

Basic medication (controllers) used daily on long-term basis. The most effective controllers are inhaled glucocorticosteroids. Other drugs from this group are long acting inhaled and oral beta 2-agonists, cromones, long-acting methylxanthines and leucotriene modifiers.

Reliever medications (relievers) rapidly relieve bronchoconstriction and accompanying symptoms. These drugs are rapid acting inhaled and oral beta2-agonists, systemic glucocorticosteroids, short-acting methylxanthines and anticholinergics.

Other (alternative) methods of the asthma healing (acupuncture¹⁰, homeopathy¹¹, herbal medicine, ionizes, osteopathy, chiropractic manipulation¹², Buteyko breathing technique¹³, yoga breathing techniques, hypnosis and mineral therapy) are not yet proven in the studies as successful treatment for relieves symptoms or improvement of lungs function.

Family physician and nurse should to know that a use of inhalers is followed by the patients' prejudices and misunderstandings¹⁴. Our patients believe that inhalers have "significant side effects"; these are "final (before death) option". A role of family medicine team members is to reassure and educate patients about inhalers.

5. Individual plans for managing exacerbations (asthma action plan)

A little number of primary health care physicians offers a written asthma action plan to their patients and provides education for following this plan¹⁵. Every patient should be educated about procedures in the case of acute exacerbation (asthma attack). The best way for that is introducing the written asthma action plan for every patient with clear instruction how to recognize severity of the exacerbation and what action patient have to take. Use of this approach to the exacerbation of asthma will decrease number of visits to emergency rooms and hospitalizations¹⁶.

6. Providing a regular follow-up care

After the establishing diagnosis of asthma, patients should to have regular follow-up visits every one to six months. The quality of asthma control will be increased if physician and nurse use a flow sheet for regular follow-up visits¹⁷. This flow sheet has to be part of the regular medical charts of all asthma patients in our country. The structure of control visit in the flow sheet should have next parts: 1) Symptom frequency (number and time of the exacerbations); 2) Lung function measurements results (peak flow meter); 3) Use of medication, especially relievers; 4) Triggers prevention; 5) Influence of asthma on the life quality; 6) Use of emergency rooms or hospitalization; 7) General health and co morbid diseases and 8) Discussion and asthma education.

Patients and his family members have to be treated with full respect as partners in the process of health care.

Conclusion

The fact is that asthma is often unrecognized and poorly treated in our environment. There is a need for an additional education of family medicine team members if the tasks of GINA program have to be gained in our country. A curriculum of additional asthma education have to include all six interrelated parts of the asthma management with especial attention on the asthma diagnosis skills, patient education, use of the written asthma action plan and regular follow-up care. After this education, family medicine nurse will have more significant role in health care of asthmatic patients.

Health care of asthma patients should be integrated in the functional ensemble with family medicine team members, pulmonary diseases specialists, emergency medicine specialists, patients' asthma schools, asthma patients' association and local community authorities.

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THE VALIDITY OF CYTOLOGICAL DIAGNOSTICS OF BRONCHOPULMONARY CARCINOMA

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In the Clinic for Pulmonary Diseases of the Clinical Centre in Banja Luka in the last nine years, the routine cytological analysis of different materials obtained from respiratory system by exfoliation or aspiration is being carried out¹. The simplicity of performing fiberbronchoscopy enables providing of the representative material, by which the possibilities of the cytological diagnostics are significantly widened². By introducing cytology into the routine work of pulmologists, the “quality” and speed of diagnostic procedure is substantially improved by which more rational therapy approach is enabled.

This paper presents the results of cytological analysis for the years 2003 and 2004.

After the smear preparation and painting by MGG, all the received materials were analyzed under light microscope of the producer Nikon, with standard zooms.

A number of 1632 patients were cytologically elaborated in the given period.

The overall positivity of the cytological analysis of the material was examined. The results of the cytological analysis with endoscopic findings were compared with morphological type of malignant disease, as well as the results of cytological analysis according to the received results of histological analysis of bioptic sample.

Among 1632 examined patients, there were 676 patients with the cytological confirmation of malignant disease. In relation to the overall number of examined patients in the two-year examination period, that amount makes 41.42%. The following table presents positivity of different cytological materials.

Table 1: The positivity of different cytological materials

Manner of obtaining the materials	Number of analysis	Positive cytological results	Negative cytological results	Percentage of positiveness
Aspiration catheter (CA)	362	332	30	91,72%
Bronchial aspiration tap (TBNA)	369	346	23	93,77%
Percutaneous needle tap (TTP)	75	72	3	96,00%
Pleural tap (PP)	56	55	1	98,21%
Needle tap of lymph knot (PLN)	32	29	3	90,62%
Abdominal tap	3	3	0	100%
Pericardial tap	1	1	0	100%
Wrist tap	1	1	0	100%
Pleuroscopy	2	2	0	100%

With bronchoscopy treated patients, the positiveness of cytological findings depends on endoscopic findings and there are substantial differences. The following table presents the positiveness with directly perceived malignant changes.

Table 2: Positiveness of cytological materials with directly perceived malignant changes

Directly perceived malignant changes N=333				
Manner of obtaining the materials	Number of analysis	Positive cytological results	Negative cytological results	Percentage of positiveness
Aspiration catheter (CA)	257	250	7	97,27%
Bronchial aspiration tap	199	194	5	97,48%

(TBNA)				
Percutaneous needle tap (TTP)	2	2	0	100%
Pleural tap (PP)	1	1	0	100%

In the group of patients at which the endoscopic changes are characterized as indirect signs of malignity, the materials obtained by bronchial or percutaneous needle aspiration tap show higher positiveness, which can be seen from the following table.

Table 3: Positiveness of cytological materials with indirect signs of malignity

Indirect signs of malignity N=144				
Manner of obtaining the materials	Number of analysis	Positive cytological results	Negative cytological results	Percentage of positiveness
Aspiration catheter (CA)	87	73	14	83,91%
Bronchial aspiration tap (TBNA)	120	110	10	91,67%
Percutaneous needle tap (TTP)	9	9	0	100%
Pleural tap (PP)	7	6	1	85,71%
Needle tap of lymph node (PLN)	4	4	0	100%

At patients with regular endoscopic findings, the positiveness of the material obtained by bronchial aspiration tap during the performing of the bronchoscopy led by the X-ray diascopy has significantly higher positiveness in comparison to the material obtained by catheterization. Percutaneous needle aspiration taps have high positiveness in this group as well (table 4).

Table 4: Positiveness of the cytological materials with regular endoscopic findings

Regular endoscopic findings N=82				
Manner of obtaining the materials	Number of analysis	Positive cytological results	Negative cytological results	Percentage of positiveness
Aspiration catheter (CA)	18	9	9	50,00%
Bronchial aspiration tap (TBNA)	49	42	7	85,71%
Percutaneous needle tap (TTP)	36	34	2	94,44%
Pleural tap (PP)	1	1	0	100%
Needle tap of lymph node (PLN)	5	5	0	100%

Squamous-cell carcinoma is most often cytologically proved in the material obtained by catheter aspiration directly from the tumor. With the other types of the tumors, needle aspiration taps have an advantage. At patients with microcellular carcinoma, the material obtained by bronchial needle tap is emphasized (table 5).

Table 5: Positiveness of cytological materials according to the type of tumor

Histological type	CA	TBNA	TTP	PP	PLN	Other
Squamous carcinoma N=393	240	197	43	5	14	4
Adenocarcinoma N=101	25	48	13	27	6	4
Microcellular carcinoma N=134	62	86	10	3	9	-
Macro cellular carcinoma N=7	2	3	1	-	-	-
Mesothelium N=15	-	-	-	14	-	-
Lymphoma N=8	-	2	5	-	3	-
Metastasis	-	4	1	2	-	-
Canceroid N=4	1	4	-	-	-	-
Suspicious malignant cells N=5	1	3	1	2	-	-

Histological solution was found in our institution for 324 patients. It can be supposed that the number of solved findings after the histological analysis is greater, but not all of the findings were filed in our institution since they were sent to other institutions, i.e. where the bronchoscopy was performed. With 30/324 (ca 9%) of the patients, there is a difference in morphological solution (table 6).

Table 6: Differences in morphological solution

Cytological result	Histological result	Number
Squamous carcinoma	Microcellular carcinoma	3
Microcellular carcinoma	Squamous carcinoma	4
Adenocarcinoma	Squamous carcinoma	8
Squamous carcinoma	Adenocarcinoma	9
Microcellular carcinoma	Adenocarcinoma	1
Squamous carcinoma	Malignant sarcoma	1
Squamous carcinoma	Dysplasia of Epithelium gr III 1	1
Squamous carcinoma	Granulomatose inflammation	1
Microcellular carcinoma	Interstitial inflammation	2

Based on the abovementioned results it can be concluded that high positiveness of cytological findings enables to set high percentage of definite morphological confirmation of malignant disease by cytological analysis. In this way, this very simple morphological method provides itself a place in diagnostic procedure of malignant disease of the respiratory tract⁵. The possibility of negative cytological findings is very low and mostly occurs if the catheter or the needle is placed outside of the malignant process or inside the necrotic part of the tumor. By comparison of the results of cytological and histological analysis, the discrepancy most often found is among non-micro tumors, i.e. there is a difference between squamous carcinoma and adenocarcinoma. This type of mistake can be explained by the fact that today it is known that almost 50% of malignant tumors do not have the unified cell image.

The working canal of fiber optic bronchoscope has significantly lower average positive value (graph 3).

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INTERACTION BETWEEN THE UPPER AND LOWER AIRWAYS

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After 186 years from the first description of hay fever by John Bostock, we still research the pathophysiology of this disease. However, the main question is: "Rhinitis and asthma are the same disease or asthma is a continuum of rhinitis?" From that reason, today is very actual the research of links between rhinitis and asthma. Our knowledge's about that are connected with epidemiological evidences, with problems of airway inflammation, remodeling of upper and lower airways, and clinical and therapeutic consequences.

What are the epidemiological questions?

There are many studies about prevalence of rhinitis in asthma. Usually, the index of rhinitis and asthma is 3:1, and symptoms of rhinitis are present in 28-90% of asthmatic patients. In the same time the rhinitis is present in 62.61% of atypic asthmatics and 45.4% of nonatypic asthmatics. Opposite from this, the risk of asthma among the subjects with allergic rhinitis were calculated to be up to 300 times that among the subjects without allergic rhinitis. More than 99% of subjects with allergic asthma also had allergic rhinitis.

The next epidemiological question between rhinitis and asthma is bronchial hyper reactivity. Many patients with allergic rhinitis have increased bronchial sensitivity to methacholine or histamine, but there are large differences in the magnitude of airway reactivity between asthmatics and rhinitis that are not explained by the allergen type or degree of reactivity.

Concerning the rhinitis as a risk factor for developing of asthma by the Copenhagen Allergy Study (Linneberg et al. 2001), the incidence of asthma depending from kinds of allergens. The incidence moved from 14% for pollen rhinitis, 16% for rhinitis with animal allergens at baseline to 27% for patients with mites in rhinitis at baseline.

The severe rhinitis is a much more risk factor for onset asthma then mild or moderate form of disease. Also, rhinitis is an independent risk factor for allergic and non-allergic asthma.

Inflammation on nasal and bronchial level

The next link between rhinitis and asthma would be inflammation on nasal and bronchial level. The nasal biopsies in asthmatics were showed the increased number of eosinophils and CD4 cells. The similar picture was finding in bronchial biopsies at the patients with seasonal allergic rhinitis. The research of mechanisms involved in nasal and bronchial inflammation was showed that the cystinil-leukotriens are responsible for developing of inflammation in asthma and rhinitis. Nasal inflammation in asthma is different from nasal inflammation in COPD. In asthmatic patients predominant cell infiltration in nasal and bronchial mucosa are eosinophils and CD4 cells, but in COPD patients CD8 cells and polymorphonuclear cells. Actually, evidence of increased number of cells in nasal mucosa, after allergen challenge is result delivering of chemotactic factors that mobilizing cell movement from bone marrow. In the same time we can follow the elevated level of bone marrow progenitors in blood, more in the atopics, than in the non-atopic subjects. Also, there is evidenced of allergen-specific immunoglobulines in BAL fluid 24 hours after allergen challenge.

Remodeling of upper and lower airways

Remodeling is a critical aspect of wound repair in all organs and represents a dynamic process that occurs in reaction to an inflammatory insult. Hallmarks of remodeling in asthma are: thickening of basement membrane, allergen deposition in submucosa and hypertrophy of smooth muscles. Bronchial biopsies in young children discovering the same kinds of remodeling in asthma pre-existing to inflammation. But in one moment of life, under the influence of allergens and other environmental exposure starting the cell inflammation that has addition influence on remodeling of airways. Nasal remodeling in rhinitis characterized with shedding the epithelium, pseudo-thickening and collagen deposition in basement

membrane, as well as the finding of fibroblasts in submucosa. In the same time, on bronchial level, the finding of these elements is more expressive. So, nasal remodeling does not appear to be significant in allergic rhinitis. On the other hand, the possible differences between the upper and lower airways look at two moments. One is the fact that the smooth muscle cells participate to inflammation and remodeling and the second is that there exist the embryologic differences between the nose and bronchi. Johasol et al (2001) are approved that muscle cells originate from asthmatics has a double fold of multiplication in cell culture than muscle cells originate from non-asthmatics. That is result the releasing of more quantity of CTGF (connective tissue growth factor) by airway smooth muscle cells in asthmatics (Burgess et al 2003).

Embryologic differences between the nose and bronchi

Embryologic differences between the nose and bronchi look at the way of embryologic origin these organs. After 25th day of gestation the bronchi's and esophagus developing from endoderm and mesoderm. In late 5th week start with developing of nasal pit from ectoderm. That is the beginner of nose; in 6th week start the forming of primary palate, in the 7th week the nostril, etc.

What are the clinic consequences of rhinitis and asthma?

- 1) Bronchial involvement in allergic rhinitis look at facts that 20 – 40% of patients with rhinitis present clinical asthma, many of them present increased non-specific bronchial hyper reactivity. When triggered appropriately with allergen, rhinitis patients develop bronchial symptoms.
- 2) Nasal involvement in asthma look at next facts: over 70% of asthmatics present symptoms of rhinitis, nasal (sinus) inflammation appears to be present in most (all) asthmatics.

Because all of that there are several recommendations like:

- Patients with persistent rhinitis should be evaluated for asthma,
- Patients with persistent asthma should be evaluated for rhinitis,
- A strategy should combine the treatment of upper and lower airways in terms of efficacy and safety.

From this point of view follow the consequences for treatment the continuum of disease e.g. and asthma and rhinitis.

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NEW HORIZONTS IN COPD

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Definition, diagnosis and staging of COPD

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.

Although COPD affects the lungs, it also produces significant systemic consequences.

Diagnosis of COPD should be considered in any patient who has the following:

- symptoms of cough,
- sputum production or
- dyspnoea or
- history of exposure to risk factors for the disease.

The diagnosis requires spirometry; post-bronchodilator FEV1/forced vital capacity <0.7 confirms the presence of airflow limitation that is not fully reversible.

Spirometry should be obtained in all persons with the following history: exposure to cigarettes and/or environmental or occupational pollutants, family history of chronic respiratory illness, presence of cough, sputum production or dyspnoea.

Table 1. - Spirometric general classification

Severity	Postbronchodilator FEV1/FVC	FEV1 % predicted
At risk Patients who: smoke or have exposure to pollutants have cough, sputum or dyspnoea have family history of respiratory disease	>0.7	≥80
Mild COPD	≤0.7	≥80
Moderate COPD	≤0.7	50-80
Severe COPD	≤0.7	30-50
Very severe COPD	≤0.7	<30

FEV1: forced expiratory volume in one second; FVC: forced vital capacity.

It is accepted that a single measurement of FEV1 incompletely represents the complex clinical consequences of COPD because: 1) many patients are practically asymptomatic; 2) persistent cough and sputum production often precede the development of airflow limitation [3] and, in others, the first symptom may be the development of dyspnoea with previously tolerated activities; and 3) in the clinical course of the disease, systemic consequences, such as weight loss [10, 11], and peripheral muscle wasting and dysfunction, [12, 13] may develop.

BMI is easily obtained by dividing the weight (in kg) over the height (in m²). Values <21 kg•m⁻² are associated with increased mortality.

Functional dyspnoea can be assessed by the Medical Research Council dyspnoea scale.

0: not troubled with breathlessness except with strenuous exercise.

1: troubled by shortness of breath when hurrying or walking up a slight hill.

2: walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on the level.

3: stops for breath after walking ~100 m or after a few minutes on the level.
4: too breathless to leave the house or breathless when dressing or undressing.

Neck vein distension, liver enlargement and peripheral edema could be due to pulmonary heart or due to severe hyperinflation.

Loss of muscle mass and peripheral muscle weakness are consistent with malnutrition and /or skeletal muscle dysfunction.

Cyanosis or bluish color of the mucosal membranes may indicate hypoxaemia.

Treatment of COPD

Smoking cessation: Smoking should be routinely evaluated whenever a patient presents to a healthcare facility. All smokers should be offered the best chance to treat this disorder.

Permanent remissions can be achieved in a substantial percentage of smokers with currently available treatments. Successful treatment of this disorder can have a substantial benefit in reducing many secondary complications of which chronic obstructive pulmonary disease (COPD) is one. Smoking cessation activities and support for its implementation should be integrated into the healthcare system.

Pharmacological therapy: The medications for chronic obstructive pulmonary disease (COPD) currently available can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status.

At present no treatment is shown to modify the rate of decline in lung function.

The change in lung function after brief treatment with any drug does not help in predicting other clinically related outcomes.

The inhaled route is preferred.

Changes in forced expiratory volume in one second (FEV1) following bronchodilator therapy can be small but are often accompanied by larger changes in lung volume, which contribute to a reduction in perceived breathlessness.

Combining different agents produces a greater change in spirometry and symptoms than single agents alone.

Long-term oxygen therapy: Long-term oxygen therapy (LTOT) improves survival, exercise, sleep and cognitive performance.

Reversal of hypoxaemia supersedes concerns about carbon dioxide (CO₂) retention.

Arterial blood gas (ABG) is the preferred measure and includes acid-base information; arterial oxygen saturation as measured by pulse oximetry (SpO₂) is adequate for trending. Oxygen sources include gas, liquid and concentrator. Oxygen delivery methods include nasal continuous flow, pulse demand, reservoir cannulas and transtracheal catheter.

Physiological indications for oxygen include a SpO₂ <7.3 kPa (55mmHg). The therapeutic goal is to maintain SpO₂ >90% during rest, sleep and exertion. Active patients require portable oxygen.

If oxygen was prescribed during an exacerbation, recheck arterial blood gases in 30–90 days.

Withdrawal of oxygen because of improved arterial oxygen tension (Pa, O₂) in patients with a documented need for oxygen may be detrimental. Patient education improves compliance.

Pulmonary rehabilitation: Pulmonary rehabilitation is a multidisciplinary program of care that is individually tailored and designed to optimize physical and social performance and autonomy.

This therapy results in significant and clinically meaningful improvements in multiple outcome areas, including dyspnoea, exercise ability, health status and healthcare utilization. Pulmonary rehabilitation should be considered for patients with chronic obstructive pulmonary disease (COPD) who have dyspnoea or other respiratory symptoms, reduced exercise tolerance, a restriction in activities because of their disease, or impaired health status. There are no specific pulmonary function inclusion criteria that indicate the need for

pulmonary rehabilitation, since symptoms and functional limitations direct the need for pulmonary rehabilitation.

This comprehensive intervention includes exercise training, education, psychosocial/behavioral intervention, nutritional therapy, outcome assessment and promotion of long-term adherence to the rehabilitation recommendations.

Nutrition: Weight loss as well as a depletion of fat-free mass (FFM) may be observed in stable chronic obstructive pulmonary disease (COPD) patients, irrespective of the degree of airflow limitation.

Weight loss and being underweight is associated with an increased mortality risk.

Weight loss and particularly muscle wasting contribute significantly to morbidity, disability and handicap in COPD patients. Muscle wasting may also be present in patients with a stable weight.

Weight loss and loss of fat mass are primarily the result of a negative balance between dietary intake and energy expenditure, while muscle wasting is a consequence of an impaired balance between protein synthesis and protein breakdown.

In advanced stages of COPD both energy balance and protein balance are disturbed. Therefore, nutritional therapy may only be effective if combined with exercise or other anabolic stimuli. Nutritional intervention *per se* should focus more on prevention and early treatment of weight loss to preserve energy balance.

Surgery in COPD: Patients with a diagnosis of chronic obstructive pulmonary disease (COPD) have a 2.7–4.7-fold increased risk of postoperative pulmonary complications.

COPD is not an absolute contraindication to any surgery.

The further the procedure from the diaphragm the lower the pulmonary complication rate.

Preoperative pulmonary function studies have a well-documented role in the evaluation of patients undergoing lung surgery.

Smoking cessation at least 4–8 weeks preoperatively and optimization of lung function can decrease postoperative complications.

Early mobilization, deep breathing, intermittent positive-pressure breathing, incentive spirometry and effective analgesia may decrease postoperative complications.

Surgery for COPD: Bullectomy and lung volume reduction surgery may result in improved spirometry, lung volume, exercise capacity, dyspnoea, health-related quality of life and possibly survival in highly selected patients.

Lung transplantation results in improved pulmonary function, exercise capacity, quality of life and possibly survival in highly selected patients.

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PULMONARY HYPERTENSION

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Pulmonary hypertension is a disease that leads to severe limitations of functional status and poor survival. Often affects young people, especially women. Pulmonary hypertension is defined as elevation in systolic pulmonary artery pressure over 30 mmHg, or mean pulmonary artery pressure over 25 mmHg at rest and over 30 mmHg during exertion. According to mean pulmonary artery pressure (mPAP), pulmonary hypertension is divided into three degrees: 1. mean pulmonary artery pressure from 25 to 35 mmHg; 2. mPAP from 36 to 45 mmHg; and 3. mPAP over 45 mmHg. Clinical features include progressive dyspnoea, exertion limitation, deterioration of right ventricle function and finally right ventricle failure and death. Mean survival in patients with idiopathic pulmonary hypertension is from 2 to 8 years. Survival in patients with pulmonary hypertension previously known as secondary depends on underlying disease that caused pulmonary hypertension. Knowledge about existence, importance and treatment modalities of pulmonary hypertension was poor for almost one hundred years after the first Romberg's description of pulmonary vascular sclerosis. Due to that reason, pulmonary hypertension was classified into two categories: primary and secondary. Finally, in the last decade, World Health Organization became aware of importance and consequences of pulmonary hypertension, especially on total morbidity and mortality and in 1998 recommended first clinical classification, better known as “Evian classification”, with diagnostic and therapeutic guidelines. Since then, further fundamental findings in the biochemistry, pathophysiology and genetics of pulmonary hypertension have been discovered, new diagnostic procedures were developed, and new drugs for treatment of pulmonary hypertension were introduced. Because of that, during The 2003 Third World Symposium on Pulmonary Arterial Hypertension held in Venice, Italy, second, revised clinical classification of pulmonary hypertension was proposed.

Clinical classification of pulmonary hypertension:

1. Pulmonary arterial hypertension
2. Pulmonary hypertension with left heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
5. Miscellaneous.

The main vascular changes in pulmonary arterial hypertension are vasoconstriction, smooth – muscle cell and endothelial cell proliferation, and thrombosis. These findings suggest the presence of disturbance in the normal relationships between vasodilators (prostanoids, adenosine, β_2 agonists, nitric oxide -NO, ANP - atrium natriuretic peptide, BNP – brain natriuretic peptide) and vasoconstrictors (angiotensin II, endothelin, tromboxan, epinephrine, vasopresine, leukotriens, serotonin), growth inhibitors and mitogenic factors, and disbalance between antithrombotic and prothrombotic factors. These homeostatic imbalances are probably consequences of pulmonary endothelial – cell dysfunction or injury cause by hypoxic vasoconstriction and other causes. Diagnostic procedure is consisted of basic and additional tests. Basic diagnostic procedures are medical history, physical examination, laboratory tests, ECG, chest X – ray, lung function testing and echocardiography. During echocardiography, we can determine pulmonary artery pressure, right ventricle pressure, tricuspid regurgitation. Additional tests are: gene markers, immunologic testing, HIV and hepatitis markers, liver enzymes, abdominal ultrasound, chest CT scan, positron emission

tomography - PET, magnetic resonance imaging - MRI, exertion testing, pulmonary angiography, perfusion and ventilatory lung scan.

Final diagnostic procedure is right heart catheterization in rest and exertion, during which haemodynamic testing of pulmonary hypertension reversibility and pharmacological testing are performed.

Because of importance of pulmonary vasoconstriction in pathophysiology of pulmonary hypertension main therapeutic choice were vasodilators. Over the last decades many drugs from different classes, including adrenergic agonists and antagonists, arterial vasodilators, nitrates, angiotensin – converting enzyme inhibitors and calcium channel blockers along with oxygen were given to patients with pulmonary hypertension. In the last ten years, various new prostanoids were introduced such as intravenous epoprostenol, subcutaneous trepostinil and inhaled iloprost. Significance of NO was recognized and safe application systems for its use were developed. Problems with previously mentioned drugs are high prices and complicated ways of usage, therefore further improvement in treatment of pulmonary hypertension was discovery of phosphodiesterase inhibitors (sildenafil) and endothelin receptor antagonists (bosentan) which are used orally.

Positioning of new drugs in a treatment of pulmonary hypertension is not yet well defined and confirmed in clinical trials, but based on basic and clinical findings it seems that early diagnosis and treatment of this disease is justified.

ASTHMA CONTROL IN CHILDHOOD

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Asthma is chronic inflammatory disease of lower airways (mastocytes, eosinophils, T-lymphocytes) with bronchial hyper-reactivity and consequent bronchoobstruction. Bronchoconstriction is chronic and reversible process, leading to irreversible changes: hypertrophy and hyperplastic of smooth muscles, thickening of reticular basal membrane At the border of epithelium and lamina propria.

Asthma is often compared to the iceberg, with one third of symptoms visually evident and two thirds of it with lowered values of FEV/PEF, bronchoobstruction, bronchial hyperactivity and inflammation, with result of remodeling. (1,2)

Asthma prevalence is increasing 8-15-20%.

Symptomatology:

- Recurrent episodes of coughing and wheezing,
- Night attacks,
- Seasonal symptoms,
- Symptoms due to exposure to allergens,
- Dyspnoea.

ETIOLOGY OF ASTHMA IN CHILDHOOD

1. Viral infections (Early respiratory infection with RSV is connected to asthma of older children, due to interaction of immune system of the child with genetic predisposition for asthma development)
2. Atopia present in family (both parents), and atopia of mother especially is tightly connected to asthma and rhinitis appearance
3. Allergens: Home dust, dermatophagoideus, animal hair, pollen, and fungi, nutritive allergens (egg, milk, chocolate, nuts, peanuts, peas, tomato, berry fruits and fish)
4. Tobacco smoke: Tobacco smoking, especially tobacco smoking of mother including prenatal exposure of the child, correlates with increased episodes of bronchoobstruction and increased bronchial hyper-reactivity and decreased lung function.
5. Air pollution
6. Exercise
7. Emotional stress
8. Chemical and physical irritants
9. Medicines (aspirin)

DIAGNOSIS

Identification of childhood asthma, concerning asthma phenotype, has been problem yet due to various clinical asthma syndromes.

During infancy, a number of situations have been associated to wheezing. Wheezing has been connected to neurodermitis and increased body weight of children, especially boys. Wheezing has been associated with children whose parents had episodes of wheezing during early childhood, so called happy wheezes. Prematurely, bronchopulmonal dysplasia, cystic fibrosis and exposure to tobacco smoke have been associated to wheezing too.

In older children, wheezing indicates asthma, but coughing without wheezing indicates atypical asthma.

Components of diagnosis:

- Recurrent episodes of bronchoobstruction
- Improved pulmonary function after administration of bronchodilator

- Roentgenogram of the chest
- Laboratory evaluation: ECP, IGE
- Pulmonary function testing (spirometry)
- Allergy skin testing: prick test

ASTHMA CLASSIFICATION

The classification of asthma has been based on diurnal and nocturnal symptoms for children up to the age of 5 years, since they cannot cooperate adequately for spirometry. For older children, spirometric evaluation (FEV₁ and PEF) has been essential for classification of severity of asthma. (3,4)

Using the criteria mentioned above, the severity of asthma has been graduated as follows:

- *Grade 1 or mild, intermittent asthma
- *Grade 2 or mild, persistent asthma
- *Grade 3 or moderate, persistent asthma
- *Grade 4 or severe, persistent asthma

TREATMENT

Acute treatment with symptomatic medicines –relievers:

- Short acting β_2 agonists
- Systemic corticosteroids
- Anticholinergics
- Methylxanthines

Long-term treatment with anti-inflammatory medicines-Controllers

- Inhalatory corticosteroids
- Long acting β_2 agonists
- Chromons
- LR agonists
- Methylxanthines (retard)

ASTHMA CONTROL

Asthma control definition (GOAL study-Gaining Optimal Asthma control)

- Without diurnal symptoms
- Without usage of β_2 agonist
- Morning PEF= \geq 80 % (of expected for every day)
- Without night awakening
- Without exacerbation
- Without urgent interventions
- Without changes of therapy, without increases of doses

Growing out from asthma and growing out from pediatricians:

The huge number of infants will have improvement of wheezing up to 6 years, while the others will have persistent asthma.

Symptoms of atopic asthma do not disappear around puberty, while 30-80% develop severe asthma later.

Disturbed airflow, process of remodeling and inflammation has been present even during the periods of remission without symptoms.

Growing out of asthma (evaluation of inflammation and remodeling) has been controlled through the analysis of eosinophils in sputum, NO measurement in expired air, evaluation of bronchial hyper-reactivity to adenosin-monophosphate and bronchial mucous biopsy.

The asthma control with inhalatory corticosteroids has been achieved with flutikazon propionate using Baby-haler, for the age up to 4 years and combination of medicines

(salmeterol+flutikazon propionate), using Baby –haler and volumatic, for older children. (5,6,7)

The final objective of the treatment is the improvement of quality of life for infants and their parents, but also to have the physicians who treat the asthmatic children more satisfied.

The advantage of treatment with Seretide has come out of synergistic action of salmeterol and flutikazon. The places of action are at the molecular receptor and cellular level. Steroids have increased the synthesis of β_2 receptors at the cell membrane and have inhibited their desensibilisation, while β_2 agonists act at the inactive glucocorticoid receptors and increase glucocorticoid receptor complex translocation to the nucleus.

The effects of Seretide treatments are numerous: elimination of diurnal and nocturnal deterioration, without salbutamol, improvement of morning PEF, good tolerance and low incidence of side effects.

As a conclusion, a strong recommendation for early and long-term treatment with inhalatory corticosteroids has remained. May be, we will soon have a confirmation of ICS effects on changing the course of the disease and increase of percent of children who have grown out of asthma.

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PALLIATIVE CHEMOTHERAPY IN LUNG CANCER PATIENTS

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Lung cancer continues to be the leading cause of cancer - related deaths all over the world. Yearly it causes more than 1 million deaths worldwide. Despite the well-recognized link between tobacco use and development of lung cancer, the number of new cases continues to rise, especially among women. In girls and women 15 to 64 years of age, lung cancer is now the leading cause of death from cancer, and this disease remains the most common cause of death from cancer in men (1).

During the past 20 years, numerous efforts are made to reduce the death rate among patients with lung cancer.

Approximately 75% to 80% of cases are of the non-small-cell histology, and the majority of patients present with either locally advanced disease (stage III) or metastatic disease (stage IV). The majority of these patients requiring chemotherapy or require chemotherapy at the time of relapse after surgical resection. The role of chemotherapy in this stage of lung cancer continues to be a subject of debate. Palliative chemotherapy – defined, as treatment in circumstances where the impact of intervention is insufficient to result in major survival advantage but improves tumor related symptoms – is not a new concept. In 1948 in the journal, *Cancer* a paper titled “The use of nitrogen mustard in the palliative treatment of carcinoma (with particular reference to lung carcinoma)”. This was the first reference to chemotherapy in lung cancer and the principal author was David Karnofsky (2). Choosing the optimal palliative therapy is complex. A balance must be struck between the benefits and risks of treatment. There is as great a need for objective measures in selecting patients for palliative treatment as there is in the curative management. Multivariate analyses have identified a number of independent factors that predict the outcome of treatment. Patients suitable for palliative chemotherapy are those with stage IIIB or IV disease and fair performance status (ECOG 0 – 1, and possibly 2).

The first studies, in the 1960s and 1970s, showed no benefit from chemotherapy and as a result, radiotherapy became the standard treatment for palliating NSCLC. However, these trials used drugs that are now considered inactive (3).

Support of treating patients with advanced NSCLC came from an international collaborative meta-analysis using updated data on patients from 52 randomized clinical trials testing the addition of chemotherapy to best supportive care only (4). They all came to the same conclusion: chemotherapy, mainly cisplatin – based regimens has a beneficial impact on survival, although modest. The improvement of the 1-year survival rate was around 10% and the gain on the median survival time was estimated to be 1.5 months. The trial performed by the European Organization for Research and Treatment of Cancer (EORTC) compared cisplatin and etoposide vs. carboplatin and etoposide and concluded that no significant differences in survival were apparent but that patients treated with carboplatin and etoposide had significantly less leucopenia, nausea and vomiting and diarrhea (5).

The 1990s heralded the arrival of novel agents with significant activity against NSCLC and new enthusiasm for treatment of advanced NSCLC with chemotherapy. These novel agents include the taxanes (paclitaxel and docetaxel), a new vinca alkaloid (vinorelbine), a novel deoxycytidine analog (gemcitabine), and the topoisomerase I inhibitors (irinotecan and topotecan). The numerous analyses are suggesting an improvement in survival for patients treated with a platinum-containing compound plus a newer agent, paclitaxel, gemcitabin or vinorelbine (6).

Docetaxel is demonstrating the most consistent responses in the second-line treatment. The study conducted by Frances Shepherd and randomized from 36 centers (7) has shown that patients with a good performance status who progressed after platinum-based chemotherapy received a survival benefit when were treated with docetaxel at 75mg/m².

Recent studies demonstrate that elderly patients with NSCLC treated with chemotherapy live longer with a better quality of life. They also demonstrate that careful attention should be paid to coexisting co morbidities in elderly patients. The age alone should not be an independent negative prognostic

factor. (8). Small cell lung cancer (SCLC) accounts for 20-25 percent of all new cases of lung cancer. At diagnosis, 40 percent of patients have limited disease. With chemotherapy plus radiotherapy and the selective use of prophylactic cranial irradiation, the median survival of these patients is 18 to 24 months. It is sensitive to chemotherapy and this is the treatment modality of choice both for palliative or curative therapy. Platinum - based regimen is a standard treatment for patients with ED SCLC. As these patients have a short disease free period, they should receive second line regimen with the same protocol or with a new combination of chemotherapeutics.

It was reported (9) that a new combination of irinotecan and cisplatin for the treatment of extensive small-cell lung cancer is 3 months prolonging the median survival (12.8 m vs. 9.4 m with etoposide plus cisplatin).

Many studies have suggested the idea of a “chemotherapy plateau” being reached in patients with lung cancer. A large body of work has begun to define molecular mechanisms of oncogenesis and suggest new targets for cancer therapy. A major advancement in the field of oncology has been the recognition that alternations in proteins and genes involved in cellular signaling, the cell cycle and control of programmed cell death are hallmarks of cancer.

There is a pressing need for new drugs to treat lung cancer. There are some major new agents under evaluation: pemetrexed disodium (alimta), glufosfamide, oxaliplatin, tyrosine kinase inhibitor – gefitinib and erlotinib, angiogenesis inhibitors – monoclonal antibody that targets the receptor for vascular endothelial cells was studied and Thalidomide, Cox-inhibitors and apoptosis markers (10).

While advanced lung cancer continues to be a lethal disease in front of all of us is question: Chemotherapy for advanced lung cancer: is the glass half-full or half empty? (11)

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MULTI DRUG RESISTANT TB

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Multi drug resistant TB (MDR-TB) is defined as resistance to at least INH and RMP. Other drug resistant TB is defined as resistance to one or more drugs not including both INH and RMP. Toward type resistance, MDR TB can be genetics and no genetics. Consequential is genetics, whose result is mutation on bacterium chromosome, change structure reception for drugs; isoniazid – mutation katG, inhA and ahpC gene (90%), rifampicin – mutation on 81-bp gene (rpoB) (96%), pirazinamid– mutation on pncA gene (72-97%), streptomycin – mutation rrs or rpsL gene, etambutol – mutation embA and embB gene (47-65%). Just, high grading of activities of anti-tuberculosis drugs INH and RMP (early bactericidal and sterilizing) is the most important resistance.

According to the report WHO, prevalence of MDR in countries of former Yugoslavia is very rare.

Drug resistance among new cases (formerly “primary drug resistance”) is the presence of resistant strains of *M. tuberculosis* in a newly diagnosed patient who has never received TB drugs or has received them for less than one month of treatment. Previously untreated patients are found to have drug-resistant organism, presumably because they are been infected from an outside source of resistant bacilli.

Drug resistance among previously treated cases (formerly “acquired drug resistance”) is that found in a patient who has previously received at least one month of TB therapy.

This form MDR there are long away of epidemic meaning.

Causes of anti-TB drug resistance: biological; initial bacterial population, factors inside the host, insufficient concentrations, patient’s drug inactivation status, Clinical; Treatment with single drug, insufficient duration of treatment, adding single drug to failing regimen, quack medicine, Pharmaceutical and pharmacological; Insufficient concentration, inadequate bioavailability, improper storage conditions, confusion of trade names, incorrect dispensing of drugs, Administrative; Insufficient supplies, bureaucratic influence in the ordering, substandard purchase because of cost and government regulations, administrative delays, Sociological; Noncompliance, irregularity in drug intake, premature discontinuation.

In addition, we should keep in our mind that propensity development MDR TB has patients with next: HIV infections, malignant diseases, renal failure, diabetes mellitus, malnutrition, patients after operation of upper parts of GI tract, patients on immunosuppressive therapy (15 mg Prednizolon per day at less to weeks).

Clinical symptoms, signs, and X-ray investigation are not typical to infection with MDR TB. Microbiology diagnostics has been done by usual investigations. Every bacteriological test require test on resistance.

Therapy MDR TB has treated by expensive, less effective and more toxic drugs, in special hospitals. The general recommendation is that treatment MDR TB should start with at less 5 or more AT drugs, which have proof on absence resistance. Treatment must last minimal until giving negative sputum. After that, treatment should continue with at lees 3 AT drugs during minimal 9 months. Same cases require 24 months treatment (patients with immune deficiency syndrome). Drug treatment can be combining with surgery treatment. There is not consensus: when should do surgery resection and how long treat patients by drugs after operations.

New DOTS-Plus is a case-management strategy under development designed to manage MDR-TB using 2nd line drugs within the DOTS strategy in low- and middle-income countries. Established as a technical committee to revise applications for treatment of MDR-TB (compliance with WHO guidelines for MDR-TB).

At prevention: DOTS in place, Government Commitment (funds, political support), Laboratory capacity, Surveillance or survey have done for the area, DOT for every dose Management system for anti-TB drugs (including II line) in place.

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DETERMINATION OF PARTITION COEFFICIENTS AND IN VITRO PERMEATION OF PYRAZINAMIDE THROUGH ARTIFICIAL MEMBRANE

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Background: Pyrazinamide (PZA), an analog of nicotinamide, is a drug that has to be converted to the active form pyrazinoic acid (POA) by the bacterial pyrazinamidase (PZase) in order to show bactericidal activity against *Mycobacterium tuberculosis*. Inside *M. tuberculosis*, acidic pH enhanced the intracellular accumulation of POA, the active derivative of PZA, after conversion of PZA by pyrazinamidase. In contrast, at neutral or alkaline pH, POA was mainly found outside *M. tuberculosis* cells. PZA-resistant *M. tuberculosis* complex organisms did not convert PZA into POA¹

Objectives: We aimed to investigate the influence of pH of the medium on lipophilicity of PZA expressed by, $\log P_{o/w}$ [2]. Investigation of *in vitro* permeability extent through the in-house prepared artificial membrane, and the influence of pH on it, will be performed [3].

Material and methods: Partition coefficient between water and octan-1-ol ($P_{o/w}$) was determined by shake-flask method. Shaking, during 24 hours saturated the two phases. After that, the partitioning equilibrium of solution was reached after 1 hour of intensive shaking at constant temperature. Phosphate buffers (pH 5.0 and pH 7.0) were used as the aqueous phase. After separation of the equilibrated phases the concentration of the solute was determined by UV spectrophotometer at the absorption maximum around 269 nm using calibration curves.

In vitro permeability of PZA was investigated using appropriate in-house prepared diffusion cell consisting of two compartments separated by artificial membrane. Polytetrafluoroethylene filters (pore size 0.45 μ m), were impregnated with mixture of phosphatidylcholine and cholesterol (22: 78 w/w). Chloroform/ methanol solution (70/ 30 v/v) was used as a solvent to prepare the solution for impregnation. Pyrazinamide was dissolved in phosphate buffer solutions (pH 5.0 and pH 7.0) and placed on one side of the membrane. Blank buffer was placed on the other side. After 20 hours of unstirred permeation, the acceptor compartment was sampled and the content of PZA determined. Quantification of PZA in the acceptor compartment was performed by using UV/ Vis spectrophotometer method at the absorption maximum around 269 nm using calibration curves.

The results obtained for $\log P_{o/w}$ PZA at pH 5.0 show the value of -1.05 with the relative permeation (%) of pyrazinamide 85.6 ± 12.0 ; $\log P_{o/w}$ PZA at pH 7.0 show the value of -1.10 with the relative permeation (%) of pyrazinamide 100.0 ± 12.9 .

Conclusion: The results presented show that the permeation extent is increased at pH near the physiological and support the influx PZA in *M. tuberculosis*.

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MANAGEMENT OF SEVERE, END-STAGE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. COPD has a variable natural history and not all individuals follow the same course. A simple classification of disease severity is into four stages (1).

Very severe COPD (Stage IV) is characterized by severe airflow limitation ($FEV_1 < 30\%$ predicted) or the presence of chronic respiratory failure with an arterial pressure of O_2 (PaO_2) less than 8.0 kPa (60 mmHg) with or without arterial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mmHg). Respiratory failure may also lead to effects on the heart such as pulmonary heart (right heart failure). Several features of COPD make end-of life issues particular poignant. Comorbidities such as cardiovascular diseases and malignancies may accelerate the demise of many patients with COPD. Thus, dyspnoea, air hunger, functional decline and ever-present possibility of mechanical (invasive and noninvasive) ventilation amplify end-of-life issues.

The treatment of patients with COPD should follow the Global initiative for chronic obstructive lung disease (GOLD). The treatment differs in stable disease and exacerbation (1). Exacerbations in very severe COPD are associated with acute respiratory failure, representing a significant burden on the health care system. The most common causes of an exacerbation are infections of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified (2).

Assessment of the severity of exacerbation is based on medical history, symptoms, and physical examination, pulmonary function tests, arterial blood gases, other laboratory tests, chest radiography and ECG.

PHARMACOLOGICAL TREATMENT

Bronchodilators are the mainstay of current drug therapy for COPD. Bronchodilators cause only a small (< 10 percent) increase in FEV_1 in patients with COPD, but these drugs may improve symptoms by reducing hyperinflation and thus dyspnoea, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. At present, no treatment has modified the rate of decline in lung function. The inhaled route is preferred.

Three types of bronchodilators are in common clinical use: beta-agonists, anticholinergic drugs and methylxanthines. They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on regular basis to prevent or reduce symptoms. In patients with severe and very severe stage of COPD whose symptoms are not adequately controlled with short-acting bronchodilators, adding regular treatment with a long-acting inhaled bronchodilator is recommended.

Corticosteroids: Systemic corticosteroids accelerate improvement in airflow, gas exchange, and symptoms and reduce the rate of treatment failure. The optimal duration of corticosteroid therapy for an acute exacerbation of COPD remains uncertain, but 30 to 40 mg of oral prednisolone daily for 10 to 14 days is a reasonable compromise between efficacy and safety. In severe and very severe COPD patients regular treatment with inhaled corticosteroids reduce frequency of exacerbations, improves health status, and should be added to regular bronchodilator treatment (3).

Antibiotics

Acute exacerbations of COPD are commonly assumed to be due to bacterial infection, since they may be associated with increased volume and purulence of the sputum. However, it is increasingly recognized that exacerbations may be due to viral infections of the upper respiratory tract or may be non-infective, so that antibiotic treatment is not always a guaranty. The bacteria that have been isolated during exacerbations are generally sensitive to most broad-spectrum antibiotics.

NONPHARMACOLOGIC TREATMENTS

Pulmonary rehabilitation improves patients' exercise capacity, reduces dyspnoea, improves the quality of life, and reduces the number and duration of hospitalization related to respiratory disease. It is appropriate for patients with clinically significant exertion symptoms and is most effective when delivered as a multifaceted program incorporating individually tailored aerobic physical training, comprehensive education about the disease, psychosocial counseling, and nutritional support (4).

Nutritional screening is recommended in the assessment of COPD and it can be based on measurement of body mass index and weight change. Weight loss and particularly muscle wasting contribute significantly to morbidity, disability and handicap in COPD patients. Therefore, nutritional therapy may be effective if combined with exercise or other anabolic stimuli.

Oxygen therapy is the cornerstone mode of treatment in COPD. It is one of the principal non-pharmacological treatments for patients with very severe COPD. COPD constitute the large and most homogeneous group of patients with hypoxemia. Two modes of oxygen therapy are applied in COPD, one during an acute exacerbation of the disease and the other, the long-term oxygen therapy (LTOT) in chronic, stable hypoxemic COPD patients. LTOT is indicated if hypoxemia, pulmonary hypertension and or respiratory failure are present.

Administration of O₂ in COPD patients is not without risks. Thus, O₂ delivery needs proper management. The goal of oxygen therapy is to increase PaO₂ above 7.98 kPa or to produce an arterial oxygen saturation (SaO₂) >90%. It should be mentioned that due to inhomogeneity it could take 20-30 min to achieve a steady state after a change in the fractional concentration of O₂. Hence, measurement of arterial blood gas at shorter intervals may be misleading. The major risk of O₂ therapy during acute exacerbation of COPD is CO₂ retention.

Specific criteria for the selection of patients with very severe COPD who need LTOT are:

PaO₂ at or below 7,3 kPa (55 mmHg) or SaO₂ at or below 88% with or without hypercapnia; or PaO₂ between 7,3 kPa (55mmHg) and 8,0 kPa (60 mmHg) or SaO₂ of 89% if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).

Different types of systems deliver LTOT but oxygen concentrators are reliable, and widely available.

The long-term administration of oxygen (>15 hours per day at low flow of 1.5 – 2.5 L/min by nasal cannule) to patients with chronic respiratory failure has been shown to increase survival. The precise mechanism by which continuous LTOT improves survival is not well understood. However, the benefit of LTOT on several haemodynamic variables could explain the prolonged survival. Early home oxygen administration in COPD reverses polycythaemia, improves pulmonary hypertension, right and left ventricular function and exercise tolerance. Chronic hypoxaemic patients with COPD are at risk of developing severe desaturation episodes, especially during sleep, which are associated with life-threatening arrhythmias leading to sudden death. Oxygen toxicity, CO₂ retention and the possibility of accidents during the storage and handling of oxygen are the main hazards of home oxygen therapy.

Pulmonary hypertension with pulmonary heart is an important complication of COPD especially in severe cases with marked hypoxia. Chronic hypoxia is believed to cause structural changes in the pulmonary vascular bed, which could account for the increased role in the development of pulmonary hypertension in COPD, the logical treatment of hypoxic pulmonary hypertension is the prolonged administration of oxygen. Pulmonary hypertension worsens prognosis and should therefore be treated. At present long-term oxygen therapy is both the most logical and the best treatment of pulmonary hypertension in COPD.

Ventilatory support Patients with COPD may need mechanical ventilatory support at some point in the evaluation of the disease. It can be applied in acute respiratory failure due to acute exacerbation of the disease, as well as in stable patients with COPD.

Although both noninvasive ventilation (using either negative or positive pressure devices) and invasive (conventional) mechanical ventilation are essentially designed to manage and treat acute episodes of COPD, for years noninvasive ventilation has been applied in patients with very severe COPD and chronic respiratory failure.

The main goals of mechanical ventilation in patients with acute exacerbation of COPD are: 1) to improve pulmonary gas exchange; 2) to support alveolar ventilation; and 3) to unload respiratory muscles.

Noninvasive positive-pressure ventilation should be considered when there is a need for ventilatory assistance, as indicated by such symptoms as worsened dyspnoea, acute respiratory acidosis, and worsened oxygenation (5).

Possible surgical interventions should be considered for patients with end-stage emphysema, which has become refractory to medical therapy and is progressing inexorably. All patients have dyspnoea as their cardinal symptom and as a result will have a poor quality of life. Surgical therapy of emphysema has typically been considered in three clinical situations: 1) localized bullous disease with relatively normal lung parenchyma; 2) bullous disease associated with background of generalized emphysema and 3) generalized emphysema without bullous disease.

Bullectomy is an older surgical procedure for bullous emphysema. By removing a large bulla that does not contribute to gas exchange, the adjacent lung parenchyma is decompressed.

Lung volume reduction surgery (LVRS) is a surgical procedure in which parts of the lung are resected to reduce hyperinflation, making respiratory muscles more effective pressure generators by improving their mechanical efficiency. LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates.

Lung transplantation remains an appropriate consideration for individuals who have end-stage emphysema and who show a progressive deterioration in quality of life and exercise tolerance. Both single and bilateral lung transplantations can be considered as suitable treatment options for individual patients.

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LUNG CANCER TODAY

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Lung cancer (LC) becomes health problem all over the world. Some epidemiological data from the world and Bosnia and Herzegovina (B&H) are summarized in the next table:

SITE	Incidence			Mortality			Prevalence		ICD-10
	Cases	Crude Rate	ASR (W)	Deaths	Crude Rate	ASR (W)	1-year	5-year	
World LC-M	965241	30.9	35.5	848132	27.1	31.2	380807	938759	C33-C34
World LC-F	386891	12.6	12.1	330786	10.7	10.3	162377	423467	C33-C34
B&H LC-M	1529	76.2	63.0	1268	63.2	52.3	713	1752	C33-C34
B&H LC-F	384	18.7	13.2	312	15.2	10.5	185	474	C33-C34

Source: WHO report 2000, Crude and Age - Standardized (World) rates, per 100,000 GLOBOCAN 2002, IARC, M-male, F-female

LC in the world is the first by incidence and mortality in male. The same is in B&H. In female in the world LC incidence

LC, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), two types behave differently and are, therefore, evaluated and treated differently. SCLC is a more aggressive disease and is often more advanced at the time of diagnosis. Treatment usually involves chemotherapy and radiation therapy. NSCLC includes adenocarcinoma, squamous cell, and large cell cancer. Surgery is the primary treatment for early stage non-small cell lung cancer.

Ninety percent of lung cancers are related to smoking. The risk of lung cancer is 30 times greater in smokers than in non-smokers and correlates with the total exposure to cigarettes, referred to as pack-years.

Exposure to air pollution, radiation and industrial chemicals, such as arsenic, nickel, chromium and asbestos also increase the risk of lung cancer. Asbestos alone increases by four times the risk of getting lung cancer. The combination of asbestos and smoking increase the risk 90 times. Asbestos exposure is also associated with mesothelioma.

Lung cancer may be found as a mass or tumor on the chest X-ray of a patient with no symptoms, but most patients have symptoms when diagnosed. Symptoms may include a new cough, a change in an existing cough, a bloody cough, pneumonia, rib or shoulder pain, hoarseness, loss of appetite, weight loss, facial swelling, headaches or bone pain.

A chest X-ray is the first step in evaluating lung cancer. CT scan is usually done to show the lung mass, lymph nodes and the rest of the chest cavity in much detail. A diagnosis of lung cancer, however, requires a biopsy.

An MRI (magnetic resonance imaging) may be part of the evaluation for a lung mass. It is especially useful in evaluating the brain and bones, but it does not visualize the lung well.

A PET scan is a relatively new nuclear medicine technique that may be very helpful in evaluating and identifying the stage of a lung mass. If a lung mass "lights up" on the PET scan, it is a lung cancer most of the time. If the mass does not light up on the PET scan, it is not likely to be a cancer. The test also evaluates the entire body to see search for any evidence that the tumor has spread to lymph nodes or other areas of the body.

Although the tests mentioned before may suggest the presence of cancer, a biopsy is needed to make the diagnosis.

A patient can cough up a sputum sample to look for cancer cells. Sputum cytology will diagnose 75% of tumors located in the bronchi, but only 25% of tumors located toward the edge of the lung.

A needle biopsy is a technique in which surgeon inserts a needle through the chest into a lung mass. This is usually done at the radiology department with a use of CT scan to accurately guide the needle. This will diagnose 60 to 90% of lung cancers, depending on the size and location of the cancer. Even under the best circumstances, however, a needle biopsy sometimes fails to diagnose some lung cancers.

Another method to obtain tissue is flexible bronchoscopy, under light sedation or a general anesthetic. If a tumor is seen in the windpipe, a tissue sample can be obtained. Most lung cancers are not visualized with the bronchoscope because they are located toward the edge of the lung, rather than in a major bronchus.

Cervical mediastinoscopy is a surgical procedure that is done under general anesthesia in the operating room. Through a one-inch incision in the neck, the surgeon follows the windpipe into the chest to remove lymph nodes. This procedure can be done on an outpatient basis. It is an important test because it not only can diagnose a lung cancer, but it also indicates the extent of the tumor so it helps determine the proper treatment.

A surgical biopsy may be necessary to determine whether or not a lung mass is a cancer. Often, the biopsy can be obtained by thoracoscopy or video-assisted thoracic surgery (VATS). A camera is placed through one of the incisions, while the pathologist places surgical instruments through the other incisions to remove the lung mass for examination. If cancer is found, then a complete cancer operation is performed while the patient is still asleep.

Small cell cancer accounts for about 25% of all lung cancer. It is staged as either limited disease (confined to the chest) or extensive disease (spread outside the chest). Small cell cancer is usually treated with chemotherapy and radiation therapy. It is rarely treated with surgery because by the time it is diagnosed it has usually spread to other parts of the body, even if the tests do not prove it.

There are four stages of non-small cell lung cancer. This staging system is important for determining the prognosis and treatment for lung cancer. Stage I is a cancer confined to the lung. Stage II is a cancer that has spread to lymph nodes near the tumor and within the lung. Stage III cancer is confined to the chest, but it has spread more widely through the tissues in the chest. Stage IV cancer has spread to other parts of the body, such as the brain, liver or bones.

The staging (evaluation) of a lung cancer involves a history and physical examination, as well as several other tests. Pulmonary function tests are done to see if the patient has enough lung function so that an operation can be performed safely. Other tests, such as a bone scan or a brain scan, may be done to see if the tumor has metastasized to other parts of the body.

Multimodality therapy is often required, and the surgeons, pulmonary specialists-oncologists and radiation therapy specialist work together to formulate the best treatment plan for each patient.

As with all cancers, lung cancer may be treated with surgery, chemotherapy, radiation therapy or a combination thereof. The treatment depends on the type and the extent of the cancer. Surgery offers the best chance of a cure for lung cancer and is the treatment of choice for early stage non-small cell lung cancer, but it is not very effective for more advanced stage cancers. It is performed when the tumor appears to be confined to the lung and when the procedure can be performed safely. The operation involves removing the cancer and lymph nodes from the chest. Chemotherapy and radiation are rarely curative, and they are usually given to slow down advanced tumors that cannot be resected.

The most common lung cancer operation is a lobectomy, which have a higher cure, rate than a wedge resection or segmentectomy for a Stage I lung cancer. The cure rate for lung cancer surgery varies from 20 to 80%, depending on the stage of the tumor.

Chemotherapy prior to a resection, to prevent recurrence of cancer after an operation or for patients who have extensive cancer that cannot be resected. There are many different chemotherapy drugs, and the side effects vary with the different medicines. Chemotherapy alone does not cure non-small cell lung cancer, but it is the primary treatment for small cell lung cancer.

Radiation therapy is an X-ray treatment that usually takes a short time and is given every day for several weeks. Like chemotherapy, it may be given prior to surgery, after surgery or instead of surgery. The side effects are usually minimal and may include tiredness; skin burns similar to sunburn, esophagitis and nausea. Although radiation may cure lung cancer, only 5 to 10% of patients who receive this therapy are considered cured.

Conclusion: LC is in the first place by incidence and mortality in male in the world and B&H, too. In female LC becomes very often disease by incidence and mortality rate in the world and B&H. Some standard diagnostic tools and treatment options were given. It is necessary work in prevention of disease - smoking session and early diagnostic.

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