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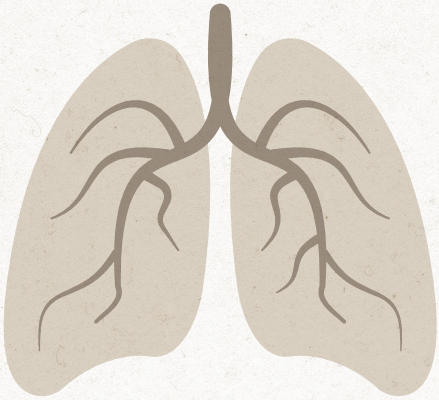

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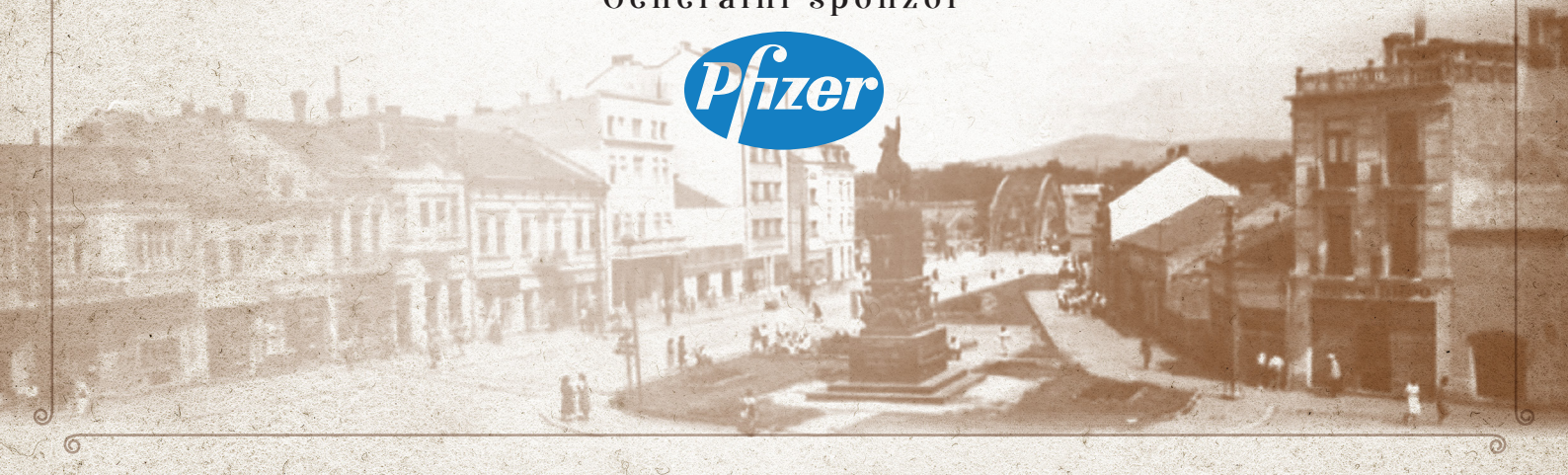

CONTENTS/SADRŽAJ

Snežana Kutlešic Stević

LUNG DISEASES AFFECTING ONLY WOMEN - CHALLENGES OF UNDERSTANDING, POSSIBILITIES OF SOLVING

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Basic differences in anatomy and physiology between men and women influence without doubt both the course of a respiratory disease and its response to treatment. Some pulmonary diseases occur disproportionately or almost exclusively in women. Respiratory conditions that occur only in women include (1), thoracic endometriosis syndrome (2), pregnancy-associated pulmonary embolization (3), Lady Windermere syndrome (4), tumors of the female reproductive tract. These diseases may be underdiagnosed by clinicians, either due to their relative rarity or to clinical manifestations that mimic those seen with other respiratory diseases.

(1) Thoracic endometriosis syndrome

Endometriosis is characterized by the presence of endometrial-like glands and stroma outside the uterine cavity and is believed to affect 6%–10% of reproductive-age women. Endometriosis within the lung parenchyma or on the diaphragm and pleural surfaces produces a range of clinical and radiological manifestations. This includes catamenial pneumothorax, hemothorax, hemoptysis, and pulmonary nodules, resulting in an entity known as thoracic endometriosis syndrome.

(2) *Pregnancy-associated pulmonary embolization*

Trophoblastic pulmonary embolism usually occurs after evacuation of a molar pregnancy when the uterus is larger than dates and the level of human chorionic gonadotropin is > 100,000 mIU/mL. It has a dramatic onset, with dyspnea, tachypnea, bilateral pulmonary infiltrates and low PO2 levels. Unlike other kinds of embolus, the presence of trophoblastic tissue in the maternal circulation is not considered abnormal. Between 30% and 80 % of obstetric patients have trophoblastic cells in their peripheral circulation. However, the quantity of trophoblastic tissue found in pulmonary vessels may indicate that trophoblastic pulmonary embolism led to maternal death. The diagnosis of trophoblastic PE is based on both clinical information and pathological outcomes. There are two histopathological patterns of trophoblastic pulmonary embolism: one composed of intact trophoblastic cells similar to those seen in chorionic villi and identified easily by H&E staining; the other consists of amorphous and fragmented trophoblastic cells that are more difficult to identify by routine staining.

Amniotic fluid pulmonary embolism , also known as anaphylactoid syndrome of pregnancy, is one of the catastrophic complications of pregnancy in which amniotic fluid, fetal cells, hair, or other debris enters into the maternal pulmonary circulation, causing cardiovascular collapse.

(3), *Lady Windermere syndrome*

Reich and Johnson first used the term “Lady Windermere syndrome” in 1992. They described 6 elderly women who were immunocompetent, had no significant smoking history or underlying pulmonary disease, and developed Mycobacterium avium complex (MAC) pulmonary infection

limited to the right middle lobe or lingula. They hypothesized that these women could have had the habit of voluntary suppression of cough, responsible for the inability to clear the secretions from the right middle lobe and lingula. This habit resulted in a focus of inflammation in these areas, which in turn predisposed to a MAC infection. They named this condition Lady Windermere syndrome after Oscar Wilde's Victorian-era play Lady Windermere's Fan to suggest the fastidious behavior.

(4) *Tumors of the female reproductive tract*

The diagnosis of Meigs's syndrome or Demons–Meigs syndrome, must meet the following criteria: a) presence of a benign tumor of the ovary – fibroma, thecoma, granulosa cell tumor or Brenner tumor, b) ascites, c) pleural effusion, and d) a resolution of ascites and pleural effusion after removal of the tumor.

The lung is a distant metastatic site of gynecologic cancers. These metastases can be solitary, multiple, or may manifest by pleural effusion. The diagnosis and management of lung metastasis is challenging because each type of gynecological cancer has different clinical characteristics, and differentiation from primary lung tumors is often very difficult.

***Key words*:** *Pulmonary diseases, Women, Thoracic endometriosis syndrome, Pregnancy-associated pulmonary embolization, Lady Windermere syndrome, Tumors of the female reproductive tract.*

PLUĆNE BOLESTI SAMO KOD ŽENA – IZAZOVI RAZUMEVANJA, MOGUĆNOSTI REŠAVANJA

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Osnovne razlike u anatomiji i fiziologiji između muškaraca i žena bez sumnje utiču na tok respiratorne bolesti i na odgovor na lečenje. Neke plućne bolesti javljaju se nesrazmerno ili skoro isključivo kod žena. Respiratorna stanja koja pogađaju isključivo žene uključuju: (1) sindrom torakalne endometrioze, (2) plućnu emboliju povezanu sa trudnoćom, (3) sindrom gospođe Vindermir, (4) tumore ženskog genitalnog trakta. Kliničari teško mogu dijagnostikovati ove bolesti, bilo zbog njihove relativne retkosti, bilo zbog kliničkih manifestacija koje oponašaju one koje se vide kod drugih respiratornih bolesti.

(1) Sindrom torakalne endometrioze

Endometriozu karakteriše prisustvo žlezda i strome nalik na endometrijum izvan uterusne šupljine i veruje se da pogađa 6 – 10% žena u reproduktivnom dobu. Endometrioza unutar plućnog parenhima ili na površini dijafragme i pleure prouzrokuje niz kliničkih i radioloških manifestacija. Ovo uključuje katamenialni pneumotoraks, hemotoraks, hemoptizije i plućne čvorove, što rezultira entitetom poznatim kao sindrom torakalne endometrioze.

(2) Plućna embolija povezana sa trudnoćom

Trofoblastna plućna embolija obično se javlja nakon tretmana molarne trudnoće kada je datumski materica veća od očekivane, a nivo humanog horionskog gonadotropina je > 100.000 mIU/ml. Ima dramatičan početak, sa dispnejom, tahipnejom, bilateralnim plućnim infiltratima i niskim nivoom PO2. Za razliku od drugih vrsta embolusa, prisustvo trofoblastnog tkiva u cirkulaciji majke ne smatra se abnormalnim. Između 30 i 80% akušerskih pacijentkinja ima trofoblastne ćelije u perifernoj cirkulaciji. Međutim, količina trofoblastnog tkiva pronađena u plućnim sudovima pokazuje da li je trofoblastična plućna embolija dovela do smrti trudnice. Dijagnoza trofoblastne plućne embolije zasniva se i na kliničkim informacijama i na patološkim autopsijskim nalazima. Postoje dva histopatološka obrasca trofoblastne plućne embolije: jedan se sastoji od intaktnih trofoblastnih ćelija sličnih onima koje se vide u horionskim resicama i koje se lako identifikuju rutinskim H&E bojenjem; drugi se sastoji od amorfnih i fragmentovanih trofoblastnih ćelija koje je teže identifikovati rutinskim bojenjem.

Plućna embolija amnionskom tečnošću, takođe poznata kao anafilaktoidni sindrom trudnoće, jedna je od katastrofalnih komplikacija trudnoće kod koje amnionska tečnost, fetalne ćelije, lanugo dlake ili mekonijum ulaze u plućnu cirkulaciju majke, izazivajući kardiovaskularni kolaps.

(3) Sindrom gospođe Vindermir

Rajh i Džonson su prvi put upotrebili termin „sindrom gospođe Vindermir" 1992. godine. Opisali su šest starijih žena koje su bile imunokompetentne, nisu imale značajnu istoriju pušenja ili plućne bolesti, a razvile su plućnu infekciju Micobacterium avium kompleksa (MAC), ograničenu na desni srednji režanj ili lingulu. Pretpostavili su da su ove žene mogle imati naviku

dobrovoljnog suzbijanja kašlja, odgovornu za nemogućnost čišćenja sekreta iz desnog srednjeg režnja i lingule. Ova navika dovodi do žarišta upale u ovim oblastima, što zauzvrat predisponira MAC infekciju. Ovo stanje su nazvali sindromom gospođe Vindermir po drami Oskara Vajlda iz viktorijanske ere ”*Lady Windermere's Fan*”, da bi sugerisali suzdržano, fino ponašanje.

(4) Tumori ženskog genitalnog trakta

Majgsov sindrom ili Demons–Majgsov sindrom dijagnostikuje se na osnovu sledećih kriterijuma: a) prisustvo benignog tumora jajnika – fibroma, tekoma, tumora granuloza ćelija ili Brenerovog tumora b) ascitesa c) pleuralnog izliva i d) rezolucije ascitesa i pleuralnog izliva nakon uklanjanja tumora.

Plućne metastaze sa pleuralnim izlivom ili bez njega vrlo su česte kod bolesnica sa malignim tumorima ženskog genitalnog sistema. Dijagnostikovanje i tretman metastaza u plućima je izazovno, jer svaka vrsta ginekološkog tumora ima različite kliničke karakteristike, a razlikovanje od primarniih tumora pluća često je vrlo teško.

Ključne reči: *plućne bolesti, žene, sindrom torakalne endometrioze, plućna embolija povezana sa trudnoćom, sindrom gospođe Vindermir, tumori ženskog genitalnog trakta.*

SLEEP, BREATHE, BE HELTHY

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The man of the 21st century is greatly endangered by his life-style and working pace, and his quality of life and health are seriously impaired by poor sleep quality and breathing difficulties. The obesity pandemic significantly contributes to this and affects 20% of men and 9% of middle-aged women in the world who have obstructive sleep apnea OSA with significant implications on the development and worsening of hypertension, coronary disease, atherosclerosis and cerebrovascular insults, as well as on increased mortality in traffic accidents caused by sleepiness due to OSA. It is estimated that about 5-15% of the adult world population have chronic obstructive pulmonary disease (COPD), with 3.2 million deaths annually, and about 262 million people worldwide have bronchial asthma. Their life is marked by dramatic breathing disorders, both when awake and possibly during sleep. During sleep, even in cases of healthy people, during the so-called REM phase of sleep, which is characterized by dreaming and rapid eye movements, the breathing capacity decreases up to 40% compared to capacity in the awake state. This is caused by altered breathing mechanics, reduced muscle contractility and altered control of breathing by brain, leading to hypoventilation and ventilation/perfusion mismatch, and can lead to decreased blood oxygen saturation. Compared to the healthy people who have physiological variations in breathing during sleep, with OSA patients there is a significant narrowing of the upper airways at the level of the palatopharyngeal region that leads to snoring and pauses in breathing during sleep, resulting in significant desaturations, and finally resulting in short-term arousals. Disturbed architecture of sleep thus leads to the development of daytime sleepiness, depression, decline in cognitive abilities and numerous mechanisms of oxidative stress, pro-inflammatory processes with impaired endothelial function and multiple implications for the cardiovascular, endocrinological system and metabolic status are also triggered. In the pathophysiological sense, intermittent hypoxemia that develops in patients with OSA has more severe systemic consequences than chronic progressive hypoxemia that exists in patients with COPD. Patients with breathing problems during wakefulness must be recognized early enough and be examined with respiratory polygraphy or polysomnography during sleep, and this also applies to patients who are obese, with pronounced daytime sleepiness, refractory hypertension, diabetes mellitus, hypothyroidism, and if adequate therapy is applied, complications can be delayed and their survival prolonged.

***Key words*:** *obstructive sleep apnea, chronic obstructive pulmonary diseases, hypoxemia, quality of life*

SPAVAJ, DIŠI, BUDI ZDRAV

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Čovek XXI veka je veoma ugrožen načinom života i rada, a osnovne životne i radne aktivnosti, kvalitet života i zdravlje ozbiljno su narušeni lošim kvalitetom sna i teškoćama u disanju. Pandemija gojaznosti tome značajno doprinosi i utiče na to da između 20% muškaraca i 9% žena srednjih godina u svetu ima opstruktivnu sleep apneu (OSA) sa mnogobrojnim implikacijama za nastanak i pogoršanje hipertenzije, koronarnih bolesti, ateroskleroze i cerebrovaskularnih inzulta, kao i povećanu smrtnost u saobraćajnim udesima uzrokovanih pospanošću. Smatra se da oko 5 – 15% odrasle populacije ima hroničnu opstruktivnu bolest pluća (HOBP), od čega 3,2 miliona godišnje umire, dok bronhijalnu astmu ima oko 262 miliona ljudi u svetu. Njihov život je obeležen dramatičnim poremećajima disanja, kako u budnom stanju tako i tokom sna. Tokom sna se i kod zdravih ljudi, u tzv. REM fazi sna koju karakterišu sanjanje i brzi pokreti očnih jabučica, disajni kapacitet smanjuje i do 40% u odnosu na stanje budnosti. To je uzrokovano izmenjenom mehanikom disanja, smanjenom muskularnom kontraktilnošću i izmenjenom kontrolom disanja od strane mozga, koja dovodi do hipoventilacije i ventilaciono-perfuzionog disbalansa, te može dovesti do smanjenja saturacije krvi kiseonikom. Kod osoba sa OSA, osim ovih fizioloških varijacija disanja tokom sna uobičajenih za zdrave ljude, postoji značajno suženje gornjih disajnih puteva na nivou palatofaringealne regije koja dovodi do hrkanja, kao i pauza u disanju tokom sna, čiji su rezultat značajne desaturacije, koje pak dovode do kratkotrajnih buđenja.

Tako narušena arhitektonika sna dovodi do razvoja dnevne pospanosti, depresije, pada kognitivnih sposobnosti, a pokreću se i brojni mehanizmi oksidativnog stresa, proinflamatornih procesa sa oštećenjem endotelne funkcije i mnogostrukih implikacija na kardiovaskularni, endokrinološki sistem i metabolički status. U patofiziološkom smislu intermitentna hipoksemija koja se razvija kod pacijenata sa OSA ima teže sistemske posledice od hronične progresivne hipoksemije koja postoji kod pacijenata sa HOBP-om. Bolesnike kojima se na vreme prepoznaju smetnje sa disanjem tokom budnog stanja treba sagledati i respiratornom poligrafijom ili polisomnografijom tokom sna. To važi i za one koji su gojazni, sa izraženom dnevnom pospanošću, refraktarnom hipetenzijom, dijabetesom, hipotireoidizmom. Ako se na vreme primeni adekvatna terapija, mogu se odložiti komplikacije i može se produžiti preživljavanje.

Ključne reči: *opstruktivna sleep apnea, hronična opstruktivna bolest pluća, hipoksemija, kvalitet života*

HOW TO ASSESS THE CLINICAL SIGNIFICANCE OF OBSTRUCTIVE SLEEP APNEA?

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New findings on the pathophysiology, epidemiology, and outcome of obstructive sleep apnea (OSA) have called into question the relevance of the apnea-hypopnea index (AHI) in the classification of OSA severity. Therefore, a multicomponent assessment system that integrates symptomatology and comorbidity in patients with OSA is proposed. According to the so-called Baveno classification, the patients with AHI ≥ 15 are divided into 4 groups: Group A (less pronounced symptoms, without significant cardiovascular and metabolic comorbidities); group B (pronounced symptoms, without significant comorbidities); group C (less severe symptoms, significant comorbidities) and group D (severe symptoms and significant comorbidities).
The effect of positive airway pressure therapy (CPAP) after 2-3 years of therapy was shown only in groups B-D, while in group A no effect of treatment on the outcome was shown. The current understanding is that AHI is a necessary prerequisite for the diagnosis of OSA, but due to a poor correlation with subjective and objective indicators of daytime sleepiness, quality of life and the effect of CPAP therapy on the prognosis of cardiovascular disease, a better stratification of patients with OSA is needed. Therefore, the Baveno classification of patients with OSA may provide better guidance for therapeutic decisions in OSA.

***Key words*:** *OSA, AHI, Baveno classification*

KAKO PROCENITI KLINIČKI ZNAČAJ OPSTRUKTIVNE SLEEP APNEE?

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Nova otkrića o patofiziologiji, epidemiologiji i ishodu opstruktivne sleep apnee (OSA) doveli su u pitanje relevantnost indeksa apnee-hipopnee (AHI) u klasifikaciji težine OSA. Zbog toga je predložen višekomponentni sistem procene koji integriše simptomatologiju i komorbiditete kod bolesnika sa OSA. Takozvanom Baveno klasifikicijom bolesnici sa AHI ≥ 15 podeljeni su u četiri grupe: grupa A (manje izraženi simptomi, bez značajnih kardiovaskularnih i metaboličkih komorbiditeta); grupa B (izraženi simptomi, bez značajnih komorbiditeta); grupa C (manje izraženi simptomi, značajni komorbiditeti) i grupa D (izraženi simptomi i značajni komorbiditeti).
Pokazano je da efekat terapije pozitivnim pritiskom u disajnim putevima (CPAP) nakon 2 − 3 godine terapije postoji samo u grupama B−D, dok u grupi A nije pokazan bilo kakav efekat lečenja na ishod. Savremeno shvatanje je da je AHI neophodan preduslov za dijagnozu OSA, ali da zbog loše korelacije sa subjektivnim i objektivnim pokazateljima dnevne pospanosti, kvalitetom života i efektom terapije CPAP na prognozu kardiovaskularnih bolesti, potrebna bolja stratifikacija bolesnika sa OSA. Zbog toga Baveno klasifikacija bolesnika sa OSA može pružiti bolje smernice za terapijske odluke u OSA.

Ključne reči: *OSA, AHI, Baveno klasifikacija*

SURGEON IN THE SERVICE OF EFFICIENT BREATHING DURING SLEEP

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In most adults, first-line therapy forobstructive sleep apnea(OSA) consists of behavioral modification, including weight loss if appropriate, and positive airway pressure (PAP) therapy. For patients who fail or do not tolerate PAP therapy, treatment options include oral appliances and surgical therapy. The choice among various second-line options depends on the severity of the OSA and the patient's anatomy, risk factors, and preferences.

The knowledge of the concept of obstruction/collapse of upper airways can help us in elucidating the usually present confusion and facilitate decision-making about the treatment plan. *Obstruction* reflects the anatomical deformities that can be shown in routine physical examination and awake fiberoptic nasopharyngoscopy, such as septal deviation, tonsillar hypertrophy, long uvula, long epiglottis, etc. By contrast, *collapse* always implies neurological deficiency without a clear lesion demarcation and becomes a narrowing only in sleep. OSA patients may have both obstruction and collapse with different proportion in individual patients such as tongue collapse with lingual tonsil hypertrophy, and soft palate collapse with palatal tonsillar hypertrophy.

Surgical treatment of OSA includes a wide spectrum of procedures and approaches that enlarge and/or stabilize the upper airway. These procedures can be categorized as nasal, upper pharyngeal, lower pharyngeal, and global upper airway procedures. Careful patient and procedure selection, especially related to the anatomy, physiology, and function of the upper aerodigestive tract, and perioperative risk management are important considerations in the surgical evaluation of patients with OSA.

***Key words*:** *OSA; sleep surgery*

KIRURG U SLUŽBI EFIKASNOG DISANJA TOKOM SPAVANJA

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Kod većine odraslih bolesnika sa opstruktivnim poremećajem disanja tokom spavanja (OSA) prva linija liječenja obuhvaća promjenu ponašanja, uključujući gubitak tjelesne mase i primjenu uređaja za disanje s povišenim tlakom (PAP). Metoda izbora liječenja kod bolesnika kod kojih je PAP terapija neuspješna ili je ne toleriraju je primjena oralnih udlaga ili kirurško liječenje. Izbor druge linije liječenja ovisi o težini OSA, anatomiji bolesnika, faktorima rizika i preferencijama kirurga.

Poznavanje koncepta opstrukcija/kolapsa gornjih dišnih puteva može nam pomoći u razjašnjenju često prisutne konfuzije i olakšati plan liječenja. *Opstrukcija je* uvijek rezultat anatomskih deformacija koje se vide na rutinskom kliničkom pregledu i feberendoskopiji nazofarinksa u budnom stanju, kao što je devijacija septuma, hipertrofija tonzila, duga uvula, dugi epiglotis itd. Nasuprot, *kolaps* dišnog puta uvijek je posljedica neurološkog deficita bez jasne granice i prisutan je samo u spavanju. Bolesnici sa OSA mogu imati oboje, opstrukciju i kolaps, individualno u različitim omjerima, kao što je kolaps jezika s hipertrofijom lingvalne tonzile i kolaps mekog nepca s hipertrofijom palatinalnih tonzila.

Kirurško liječenje OSA uključuje niz procedura i postupaka proširenja i/ili stabiliziranja gornjih dišnih puteva. Procedure se mogu podijeliti na nazalne gornje i donje faringealne i globalne procedure gornjih dišnih puteva.

Kod bolesnika sa OSA vrlo je važna pažljiva selekcija bolesnika i procedura, ovisno o anatomiji, fiziologiji i funkciji gornjih aerodigestivnih puteva i mogućim preoperativnim rizikom.

Ključne reči: *OSA; kirurško liječenje*

UNRECOGNIZED SLEEP APNEA IN SURGICAL PATIENTS −AN UNACCEPTABLE RISK

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Introduction: Patients with obstructive sleep apnea (OSA) who undergo anesthesia are more likely to develop perioperative complications such as difficult intubation, hypoxemia, pneumonia, myocardial infarction, pulmonary embolism, atelectasis, cardiac arrhythmia, cerebrovascular insult, myocardial infarction, stroke, cardiac death, and unplanned admission to intensive care units. OSA affects 22% - 82% of all individuals in the preoperative cohort, with 82% - 93% remaining without the diagnosis and treatment. The aim of this paper is to highlight the characteristics of the perioperative approach to patients at risk of OSA.
Patient report: A patient with a permanent catheter in preoperative preparation for urological surgery complained of afternoon sleepiness, occasional forgetfulness, loud snoring, evidenced pauses in breathing during sleep, obesity. Moderate OSA was verified by respiratory polygraphy. After the examination, the planned operation was performed without complications with increased supervision of the anesthesiologist.
Conclusion: The patients with high-risk or verified OSA require specific plans for perioperative care in order to lower the risk of complications during surgery.

***Key words*:** *obstructive sleep apnea, anesthesia, perioperative risk*

NEPREPOZNATA SLEEP APNEA HIRURŠKIH BOLESNIKA − NEDOPUSTIV RIZIK

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Oboleli od opstruktivnog poremećaja disanja tokom spavanja, sleep apnee, podvrgnuti procedurama pod anestezijom, imaju povećan rizik za razvoj perioperativnih komplikacija: otežane intubacije, razvoja hipoksemije, pneumonije, infarkta miokarda, plućne embolije, atelektaze, srčane aritmije, cerebrovaskularnog inzulta, infarkta miokarda, moždanog udara, srčane smrti, neočekivanog prijema u jedinicu intenzivne nege. U preoperativnoj kohorti 22 − 82% od ukupnog broja svih bolesnika ima opstruktivni poremećaj disanja tokom spavanja, od toga 82 – 93% nije dijagnostifikovano preoperativno i ne leči se. Cilj rada bio je ukazati na specifičnosti perioperativnog pristupa bolesnicima sa rizikom od opstruktivnog poremećaja disanja tokom spavanja.

Rad opisuje bolesnika sa permanentnim kateterom u preoperativoj pripremi za urološku operaciju sa tegobama: popodnevna pospanost, povremena zaboravnost, glasno hrkanje, posvedočene pauze pri disanju u snu, gojaznost. Respiratornom poligrafijom verifikovan je opstruktivni poremećaj disanja tokom spavanja srednje teškog stepena. Nakon sprovedenog ispitivanja, načinjena je planirana operacija uz pojačan nadzor anesteziologa bez komplikacija.

Bolesnici sa visokim rizikom ili verifikovanim opstruktivnim poremećajem disanja tokom spavanja moraju imati posebne planove za perioperativno zbrinjavanje u cilju smanjenja perioperativnog rizika razvoja komplikacija.

Ključne reči: *opstruktivna sleep apnea, anestezija, perioperativni rizik*

DIAGNOSTICS OF AIRWAY OBSTRUCTION – WHAT IS NEW, WHAT WE NEED

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Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic non-communicable diseases of the respiratory system and represent a significant health problem. In the diagnosis and assessment of the degree of respiratory function disorder in patients with suspected obstructive ventilation disorder, spirometry and, to a lesser extent, body plethysmography are most often used. Impulse oscillometry (IOS) is a relatively new method in diagnostics and has been so far the least used one. The procedure is simple to perform and it depends minimally on the cooperation of the patient. For IOS and body plethysmography, a measurement maneuver is used during quiet breathing. Spirometric testing is based on performing a forced breathing maneuver, which requires a high degree of cooperation from the examinee, so the acceptability of the results is sometimes problematic. In one research at our institution as part of a doctoral dissertation, in patients with asthma, no difference was registered between the three methods in the detection of obstructive ventilation disorder in patients with symptoms of the disease, while the sensitivity increased with the use of all three methods. All three methods were weakly correlated with the degree of dyspnoic complaints in patients with asthma. All COPD patients had spirometrically registered airway obstruction. The sensitivity of impulse oscillometry increased with the degree of airway obstruction. By combining all three methods, optimal results useful for clinical practice could be obtained.

***Key words*:** *spirometry, body plethysmography, impulse oscillometry (IOS)*

DIJAGNOSTIKA OPSTRUKCIJE DISAJNIH PUTEVA – ŠTA JE NOVO, ŠTA NAM TREBA

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Astma i hronična opstruktivna bolest pluća (HOBP) su najčešće hronične nezarazne bolesti respiratornog sistema i predstavljaju značajan zdravstveni problem. U dijagnostici i proceni stepena poremećaja disajne funkcije kod bolesnika sa sumnjom na opstruktivni poremećaj ventilacije najčešće se koriste spirometrija i, manjim delom, telesna pletizmografija. Impulsna oscilometrija (IOS) predstavlja relativno novu metodu u dijagnostici i najmanje je do sada korišćena. Procedura je jednostavna za izvođenje i minimalno zavisi od saradnje pacijenta. Za IOS i telesnu pletifmografiju koristi se manevar merenja pri mirnom disanju. Spirometrijsko testiranje bazira se na izvođenju forsiranog disajnog manevra, što zahteva visok stepen saradnje ispitanika, pa je prihvatljivost rezultata nekad problematična. U jednom istraživanju u našoj ustanovi, u okviru doktorske disertacije, kod pacijenata sa astmom nije registrovana razlika između tri metode u detekciji opstruktivnog poremećaja ventilacije kod pacijenata sa simptomima bolesti, dok se upotrebom sve tri metode povećala senzitivnost. Sve tri metode bile su u slaboj korelaciji sa stepenom dispnoičnih tegoba kod pacijenta sa astmom. Svi bolesnici sa HOBP-om imali su spirometrijski registrovanu opstrukciju disajnih puteva. Senzitivnost impulsne oscilometrije raste sa stepenom opstrukcije disajnih puteva. Kombinacijom sve tri metode dobijaju se optimalni rezultati korisni za kliničku praksu.

***Ključne reči*:** *spirometrija, telesna pletizmografija, impulsna oscilometrija (IOS)*

”REAL LIFE” CHALLENGES IN MODERN TREATMENT OF BRONCHIAL ASTHMA

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Asthma is a common, potentially life-threatening chronic inflammatory disease of the airways, with various phenotypes, characterized by variable broncho-obstruction with unpredictable recurrent episodes of worsening symptoms. Exacerbations are more frequent and severe when there is poorly controlled and severe asthma, but they also occur in patients with mild asthma, which is the most common disease form. An uncontrolled disease leads to decreased quality of life and affects various aspects of life (mobility, sleep, daily activities, mental functions, depression, vitality, sexual activity).

Despite the recommendations, advances in knowledge, education, new and effective drugs and inhalers, a large number of patients (about 50%) does not have an optimal asthma control.

The recommendations are based on a "graded" pharmacotherapeutic approach and the use of inhaled corticosteroids (ICS) is mandatory, along with other preventive drugs (long-acting bronchodilators, antileukotrienes, oral corticosteroids, biological therapy), according to the severity and degree of control of asthma.

The obstacles, responsible for the failure of therapeutic interventions, originate on the part of the patient, the doctor and the health system. The most important are excessive use of SABA, poor adherence to ICS and other drugs, improper use of inhalers, neglect of symptoms, lack of acceptance of the disease and considering it "light" and not serious, lack of adherence to doctor's treatment and lifestyle advices, behavioral diseases and anxiety, smoking, obesity, poor doctor-patient relationship, inadequate or poor education about the disease, personal beliefs, "self-management" interventions, social support, non-pharmacotherapeutic measures, availability of health care and professional factors.

***Key words*:** *asthma, adherence, asthma control*

REAL LIFE IZAZOVI U SAVREMENOM TRETMANU BRONHIJALNE ASTME

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Astma je česta, potencijalno životnougrožavajuća hronična inflamacijska bolest disajnih puteva, sa različitim fenotipovima, koju karakteriše varijabilna bronhoopstrukcija sa nepredvidljivim rekurentnim epizodama pogoršanja simptoma. Egzacerbacije su češće i teže kada postoji loše kontrolisana i teška astma, ali se javljaju i kod obolelih sa lakom astmom, koja je najčešća. Nekontrolisana bolest dovodi do smanjenja kvaliteta života i utiče na razne aspekte života (mobilnost, san, svakodnevne aktivnosti, mentalne funkcije, depresija, vitalnost, seksualna aktivnost).

Pored preporuka, napretka u saznanjima, edukacije, novih i efikasnih lekova i inhalera, veliki broj obolelih (oko 50%) nema optimalnu kontrolisanu astmu.

Preporuke su zasnovane na „stepenastom" farmakoterapijskom pristupu, primena inhalacijskih kortikosteroida (ICS) je obavezna, uz ostale preventivne lekove (dugodelujući bronhodilatatori, antileukotrijeni, oralni kortikosteroidi, biološka terapija), u odnosu na težinu i kontrolu astme.

Barijere, odgovorne za neuspeh terapijskih intervencija, potiču od pacijenata, doktora i zdravstvenog sistema. Najvažnije su preterana primena SABA, loša adherenca ICS i ostalih lekova, nepravilna primena inhalera, zanemarivanje simptoma, neprihvatanje bolesti i smatranje da je „laka" i da nije ozbiljna, neprihvatanje saveta lekara za lečenje i način života, bolesti ponašanja i anksioznost, pušenje, gojaznost, odnos između obolelog i doktora, edukacija o bolesti, ubeđenja, *self-management* intervencije, socijalna podrška, nefamakoterapijske mere, dostupnost zdravstvene nege i profesionalni faktori.

Ključne reči: *astma, adherenca, kontrola astme*

MANAGEMENT OF A SEVERE SUFFOCATION ATTACK IN THE RESPIRATORY INTENSIVE CARE UNIT - A MESSAGE FROM AN EXPERIENCED PHYSICIAN

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Suffocation is one of the clinical symptoms common to many diseases, but it most often occurs as a result of diseases of the respiratory or cardiovascular system and can be considered as the sixth vital parameter. Suffocation should be distinguished from the subjective feeling of lack of air (dyspnea), although in everyday clinical practice, they are synonymous. In an intensive care unit (ICU) dyspnea is a very common symptom that, on the one hand, is not given sufficient attention, and on the other hand, it is very often impossible to detect it, because most critically ill patients have an altered mental status or are unresponsive. Dyspnea can be acute if it occurs within a few hours or days, and chronic, when it occurs for more than 4 weeks, or it can be an acute exacerbation of chronic dyspnea.

Treatment of severe acute dyspnea in an ICU does not only involve the application of basic therapeutic procedures to ensure good oxygenation (oxygen therapy, non-invasive and invasive mechanical ventilation, administration of opioids, bronchodilators), but also a good assessment of the presence of clinical symptoms and signs that would indicate possible further deterioration of the patient. The patient's mental state is evaluated, as well as the presence of bradypnea or tachypnea, cyanosis, use of auxiliary respiratory muscles, fatigue when speaking, assuming a forced sitting position, marbled skin, etc. The degree of dyspnea, together with respiratory frequency and hypoxemia, have a prognostic significance regarding the identification of patients who are candidates for endotracheal intubation.

***Key words*:** *dyspnea, intensive care unit, respiratory failure*

ZBRINJAVANJE TEŠKOG NAPADA GUŠENJA U JEDINICI INTENZIVNE RESPIRATORNE NEGE – PORUKA ISKUSNOG LEKARA

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Gušenje je jedan od kliničkih simptoma koji je zajednički za mnoge bolesti, ali se najčešće javlja kao posledica oboljenja disajnih organa ili kardiovaskularnog sistema i može se smatrati čestim vitalnim parametrom. Gušenje treba razlikovati od subjektivnog osećaja nedostatka vazduha (*dyspnea*), mada su u svakodnevnoj kliničkoj praksi to sinonimi. U jedinici intenzivnog lečenja (JIL) dispnea je veoma čest simptom kojem se, sa jedne strane, ne pridaje dovoljna pažnja, a s druge strane, često ju je nemoguće detektovati, s obzirom na to da je većina životno ugroženih bolesnika izmenjenog mentalnog statusa ili nekontaktibilna. Dispnea može biti akutna, ukoliko se javi u toku nekoliko sati ili dana i hronična, kada se javlja duže od četiri nedelje, ili može biti akutizacija hronične dispnee. Stepen dispnee kod životno ugroženih bolesnika određuje kliničar, uvidom u osnovne vitalne parametre koji odražavaju kardiorespiratornu funkciju.
Zbrinjavanje akutne dispnee teškog stepena u JIL ne podrazumeva samo primenu osnovnih terapijskih procedura za obezbeđivanje dobre oksigenacije (oksigenoterapija, neinvazivna i invazivna mehanička ventilacija, primena opioida, bronhodilatatora) već i dobru procenu prisutnosti kliničkih simptoma i znakova koji ukazuju na moguću dalju deterioraciju bolesnika. Procenjuje se mentalno stanje bolesnika, prisustvo bradipneje ili tahipneje, cijanoza, upotreba pomoćne disajne muskulature, zamaranje prilikom govora, zauzimanje prinudnog sedećeg položaja, marmorizovana koža itd. Stepen dispnee, zajedno sa respiratornom frekvencijom i hipoksemijom, ima i prognostički značaj u odnosu na identifikaciju bolesnika koji su kandidati za endotrahealnu intubaciju.

Ključne reči: *gušenje, jedinica intenzivnog lečenja, respiratorna insuficijencija*

"REAL LIFE" CHALLENGES IN CURRENT DIAGNOSIS AND ASSESSMENT OF SEVERITY OF COPD

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With a global prevalence of 4 - 10%, chronic obstructive pulmonary disease (COPD) is, next to asthma, the most common chronic non-communicable respiratory disease. Despite its global health and socioeconomic importance, COPD is still unrecognized and inadequately treated in a large number of patients. Quality spirometry is a prerequisite for the diagnosis and treatment of these patients. A ratio of forced expiratory volume in the first second to forced vital capacity (FEV1/FVC) of less than 70% is currently used as the gold standard for the diagnosis of COPD. However, this parameter is imprecise, which is why the latest 2022 guidelines from the American Thoracic Association and the European Respiratory Society (ATS/ERS) suggest using the lower limit of normal and the z-score in the diagnosis and classification of COPD severity. Further, the FEV1/FVC ratio < 70% detects the patients with existing lung function impairment and does not allow detection of early COPD. A combination of clinical features, other functional tests and imaging methods can help in the detection of early COPD, before manifest loss of lung function. A special problem are the patients with preserved FEV1/FVC but with another pulmonary function impairment (Preserved ratio impaired spirometry (PRISm)), constituting a distinct subpopulation of patients whose prognosis is similar to COPD patients, but who are, as a rule, excluded from clinical studies and therapeutic protocols.

***Key words*:** *COPD, diagnosis, spirometry*

REAL LIFE IZAZOVI U SAVREMENOJ DIJAGNOSTICI I PROCENI STEPENA TEŽINE HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA

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Sa globalnom prevalencom 4 − 10% hronična opstruktivna bolest pluća (HOBP) je, pored astme, najčešća hronična nezarazna respiratorna bolest. I pored globalnog zdravstvenog i socio-ekonomskog značaja, HOBP je i dalje neprepoznata i neadekvatno lečena kod velikog broja bolesnika. Kvalitetna spirometrija je preduslov za dijagnostiku i tretman ovih bolesnika. Odnos forsiranog ekspiratornog volumena u prvoj sekundi i forsiranog vitalnog kapaciteta (FEV1/FVC) manji od 70% danas se koristi kao zlatni standard za postavljanje dijagnoze HOBP-a. Međutim, ovaj parametar je neprecizan, zbog čega najnoviji vodič Američkog torakalnog udruženja i Evropskog respiratornog udruženja (ATS/ERS) iz 2022. godine predlaže upotrebu donje granice normalnosti i z-skora u dijagnostici i klasifikaciji stepena težine HOBP-a. Takođe, odnos FEV1/FVC < 70% detektuje bolesnike sa već postojećim oštećenjem plućne funkcije i ne omogućava ranu detekciju HOBP-a. Kombinacija kliničke slike, drugih funkcionalnih ispitivanja i imidžing metoda može pomoći u detekciji ranog HOBP-a, pre manifestnog gubitka plućne funkcije. Poseban problem predstavljaju bolesnici sa očuvanim FEV1/FVC, ali sa drugim oštećenjem plućne funkcije (*Preserved ratio impaired spirometry* (PRISm), koji su posebna subpopulacija bolesnika, čija je prognoza slična pacijentima sa HOBP-om, a po pravilu su isključeni iz kliničkih studija i terapijskih protokola.

Ključne reči: *HOBP, dijagnostika, spirometrija*

"REAL LIFE" CHALLENGES IN THE CURRENT TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disability and death in adults. Despite its importance, COPD remains among the most neglected diseases worldwide, with studies showing that 75% of COPD patients are underdiagnosed or undertreated. Smoking is still considered the most important risk factor, but other risk factors, primarily early ones, are rarely considered. In recent years, the importance of early recognition of COPD and timely interventions to prevent the deterioration of lung function, which is most pronounced in the early development of COPD, has been increasingly emphasized. Although current guidelines recommend using inhaled corticosteroids (ICS) only after multiple exacerbations, recent studies indicate that optimizing therapy before these adverse events could reduce the risk of irreversible loss of lung function and worsening of symptoms. Well-known strategies such as smoking cessation, regular physical activity, proper nutrition, regular vaccination, and good adherence still represent significant challenges in daily practice that, in the future, can be overcome by applying digital technologies. Therefore, healthcare professionals must find a way to adopt a more comprehensive approach to all patients with COPD and support them in making decisions that will ensure a quality life with COPD.

***Key words*:** *COPD, early COPD, diagnostics, therapy*

REAL LIFE IZAZOVI U SAVREMENOM TRETMANU HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA

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Hronična opstruktivna bolest pluća (HOBP) jedan je od vodećih uzroka invaliditeta i smrti odraslih. Uprkos svom značaju, HOBP ostaje među najzanemarenijim bolestima širom sveta, a studije pokazuju da je 75% bolesnika sa HOBP-om nedovoljno dijagnostikovano ili lečeno. Pušenje se i dalje smatra najvažnijim faktorom rizika, ali se o drugim faktorima rizika, prvenstveno ranim, retko razmišlja. Poslednjih godina sve se više naglašava važnost ranog prepoznavanja HOBP-a i blagovremenih intervencija u cilju sprečavanja propadanja plućne funkcije, koje je najizraženije u ranom razvoju bolesti. Premda savremene smernice preporučuju primenu inhalacijskih kortikosteroida (ICS), tek nakon višestrukih egzacerbacija, novije studije ukazuju na to da bi optimizacija terapije pre ovih neželjenih događaja mogla smanjiti rizik od nepovratnog gubitka plućne funkcije i pogoršanja simptoma. Dobro poznate strategije, kao što su prestanak pušenja, redovna fizička aktivnost, odgovarajuća ishrana, redovna vakcinacija i dobra adherenca, još uvek predstavljaju značajne izazove u svakodnevnoj praksi, koji u budućnosti mogu biti prevaziđeni primenom digitalnih tehnologija. Zdravstveni radnici moraju pronaći način za sveobuhvatniji pristup svim bolesnicima sa HOBP-om i podržati ih u donošenju odluka koje će im obezbediti kvalitetan život.

Ključne reči: *HOBP, rani HOBP, dijagnostika, terapija*

PNEUMONIA IN POSTCOVID PERIOD OF TIME - experiences and challenges for adequate care

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Pneumonia is the most common disease in the lower respiratory tract infection and occurs more often in people over 65 years old. It is believed that about 1% of the population gets pneumonia every year. For the last three years in the era of the global pandemic of SARS CoV2 infection, we have been focused on the treatment, care and prevention of the development of this infection. The ACE2 receptor on various organs mediates the entry of SARS-CoV-2 virus into host cells, and its expression pattern and level are closely related to the susceptibility and symptoms of COVID-19. Respiratory transmission is the main mode of spread of SARS-CoV-2 infection. (Wu I. et al., 2020; Zeng L et al., 2020; Zhang Ks. et al., 2020).

A severe and severe clinical picture of infection caused by SARS CoV2 requires hospital treatment and occurs in about 20% of patients. The prognosis is often uncertain in patients with associated diseases (diabetes, obesity, kidney and heart failure, hypothyroidism...), but also in middle-aged patients. Most people who develop COVID-19 make a full recovery. Evidence suggests that around 10% - 20% of patients experience post-acute and long-term effects of covid after recovering from the initial illness. These sub-acute (lasting longer than 3 weeks) and long-term effects (lasting longer than 12 weeks) are collectively known as the post/post COVID-19 condition or "long-term COVID". Further research on this topic is being conducted to better understand the causes, symptoms and consequences. Patients most often complain of increased fatigue, shortness of breath and cognitive dysfunction (confusion, forgetfulness or lack of mental focus and clarity). Symptoms may persist from the onset of the disease or develop after recovery. Discomfort can affect a person's ability to carry out daily activities such as work or household chores. There does not appear to be a relationship between the initial severity of the COVID-19 infection and the likelihood of developing the condition after COVID-19 (WHO, 2022).

Another problem of the post-covid period would be related to the problems of bacterial resistance to many antibiotics. We are faced with the uncontrolled administration of antibiotics to patients in the initial stages of various viral infections, especially in the context of SARS CoV2 infection. Clear recommendations for the administration of antibiotics in covid 19 are for probable or proven bacterial infection, within the covid hospital and/or the need for increased surveillance. Antibiotics are then recommended as for community-acquired pneumonia.

One of the studies showed that antibiotics were prescribed in about 74% of patients with SARS CoV2 infection even though bacterial infection was proven in only 8.6% of patients. Antibiotic prescribing was higher with increasing patient age and patients requiring mechanical ventilation. The study concluded that unnecessary antibiotic use had a high rate in patients with COVID-19 (B J. Langford, ClinMicrobiol Infect 2021;27:520).

***Key words*:** *covid infection, pnenumonia, antibiotics, resistence*

PNEUMONIJE U POSTOKOVID ERI − iskustva i izazovi za adekvatno zbrinjavanje

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Pneumonije su najčešća bolest u okviru infekcije donjih disajnih puteva i češće se javljaju kad starijih od šezdeset pet godina. Smatra se da oko 1% populacije godišnje oboli od pneumonije. Poslednje tri godine u eri svetske pandemije SARS-CoV-2 infekcije bili smo usmereni na lečenje, zbrinjavanje i preveciju razvoja ove infekcije. Receptor ACE2 na različitim organima posreduje ulasku virusa SARS-CoV-2 u ćelije domaćina, a njegov obrazac i nivo ekspresije usko su povezani sa osetljivošću i simptomima COVID-19. Respiratorni prenos je glavni način širenja SARS-CoV-2 infekcije- (Vu I. i sar., 2020; Zeng L i sar., 2020; Zhang Ks. i sar., 2020).
Teža i teška klinička slika infekcije izazvane SARS-CoV-2 zahtevaju bolničko lečenje i javljaju se kod oko 20% obolelih. Prognoza je često neizvesna kod pacijenata sa pridruženim bolestima (dijabetes, gojaznost, bubrežna i srčana slabost, hipotireoza…), ali i kod pacijenata srednjeg životnog doba. Većina ljudi koja razvije COVID-19 potpuno se oporavi. Dokazi sugerišu da oko 10 − 20% pacijenata doživljava postakutne i dugotrajne efekate kovida nakon što se oporavi od početne bolesti. Ovi subakutni (traju duže od tri nedelje) i dugoročni efekti (traju duže od dvanaest nedelja) zajednički su poznati kao stanje posle/post COVID-19 ili „dugotrajni COVID“. Dalja istraživanja na ovu temu sprovode se kako bi se bolje razumeli uzroci, simptomi i posledice. Pacijenti se najčešće žale na pojačan umor, nedostatak daha i kognitivnu disfunkciju (zbunjenost, zaboravnost ili nedostatak mentalnog fokusa i jasnoće). Simptomi mogu potrajati od početka bolesti ili se razviti nakon oporavka. Tegobe mogu uticati na sposobnost osobe da obavlja svakodnevne aktivnosti, kao što su posao ili kućni poslovi. Čini se da ne postoji veza između početne težine infekcije COVID-19 i verovatnoće razvoja stanja nakon COVID-19. (SZO, 2022.)
Drugi problem postkovid perioda odnosio bi se na probleme rezistencije bakterija na mnoge antibiotike. Suočeni smo sa nekontrolisanim davanjem antibiotika pacijentima u početnim fazama različitih virusnih infekcija, posebno u okviru SARS-CoV-2 infekcije. Jasne preporuke za davanje antibiotika u COVID-19 jesu za verovatnu ili dokazanu bakterijsku infekciju, u okviru kovid bolinice i/ili potrebe za pojačanim nadzorom. Preporuka propisivanja antibiotika je tada kao za vanbolničke pneumonije.
Jedna od studija je pokazala da su se antibiotici propisivali kod oko 74% pacijenata sa SARS-CoV-2 infekcijom iako je bakterijska infekcija dokazana samo kod 8,6% pacijenata. Propisivanje antibiotika bilo je veće sa povećanjem starosti pacijenata i pacijentima kojima je bila potrebna mehanička ventilacija. U studiji se ukazuje na visok procenat nepotrebne upotrebe antibiotika kod pacijenata sa COVID-19 (B J. Langford, ClinMicrobiol Infect 2021;27:520).

Ključne reči: *kovid infekcija, pneumonija, antibiotici, rezistencija*

CYSTIC FIBROSIS OF THE LUNGS – NEW ASPECTS AND CHALLENGES OF THE TRANSITION FROM A PEDIATRICIAN TO A DOCTOR FOR ADULTS

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Today, more and more people with cystic fibrosis are over 18 years old. With growing up, transitioning from childhood to adulthood, new manifestations and complications of the underlying disease appear. A process of transition is necessary, that is, the transition from a pediatric to an adult institution, where the care of a patient with cystic fibrosis is taken over by a doctor for adults. A longer life span brings new problems and complications, which already exist but also the new ones that exist in adulthood, which are rarely seen in pediatric age. Adults with cystic fibrosis have more severe lung disease, more exacerbations and hospitalizations, more chronic infections with Pseudomonas aeruginosa, and more antibiotic-resistant bacteria. Transition is a process in which an adolescent or young adult, with a chronic disease, cystic fibrosis, gradually moves from a pediatric to an adult institution.The transition has three parts: the period before the patient's transfer to an adult institution, transfer to an adult institution itself, and period after the transfer. A prerequisite for a successful transition is honest, positive and open communication and cooperation between the patient, family, pediatrician and adult pulmonologist. For a successful treatment of adult patients with cystic fibrosis it is necessary to have a center for cystic fibrosis, a patient registry, a multidisciplinary team, a specialized institution with medical services, while adhering to the standards and principles of treatment of these patients.

Key words: *cystic fibrosis, CFTR, adults, transition*

CISTIČNA FIBROZA PLUĆA – NOVINE I IZAZOVI KAD LEKAR ZA ODRASLE PREUZIMA BREME PEDIJATRA

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Danas je sve više osoba sa cističnom fibrozom starijih od 18 godina. Odrastanjem, prelaskom iz dečijeg u odraslo doba, javljaju se nove manifestacije i komplikacije osnovne bolesti. Neophodan je proces tranzicije, odnosno prelazak iz pedijatrijske u ustanovu za odrasle, gde brigu o bolesniku sa cističnom fibrozom preuzima lekar za odrasle.
Duži životni vek nosi nove probleme i komplikacije, postojećih bolesti, koje se retko viđaju u pedijatrijskom dobu. Odrasli sa cističnom fibrozom imaju težu plućnu bolest, više egzacerbacija i hospitalizacija, više hroničnih infekcija sa Pseudomonas aeruginosa i više bakterija rezistentih na antibiotike.
Tranzicija je proces u kojem adolescent ili mlađa odrasla osoba, s hroničnom bolešću, cističnom fibrozom, postepeno prelazi iz pedijatrijske u ustanovu za odrasle. Tranzicija ima tri dela: period pre samog prelaska pacijenata u ustanovu za odrasle, sam prelazak u ustanovu za odrasle i period nakon prelaska. Uslov uspešne tranzicije je iskrena, pozitivna i otvorena komunikacija i saradanja pacijenta, porodice, pedijatra i pulmologa za odrasle. Za uspešno lečenje odraslih pacijenata sa cističnom fibrozom neophodno je postojanje centra za cističnu fibrozu, registra pacijenata, multidiciplinarnog tima, specijalizovane ustanove sa medicinskim službama, uz pridržavanje standarda i principa lečenja ovih pacijena.

Ključne reči: *cistična fibroza, CFTR, odraslo doba, tranzicija*

"REAL LIFE" CHALLENGES IN THE CONTEMPORARY PERCEPTION OF PULMONARY FIBROSIS IN THE POST-COVID PERIOD

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Interstitial lung diseases (ILD) are a group of about 200 entities characterized by heterogeneity in the extent of inflammation and/or fibrosis. Idiopathic pulmonary fibrosis (IPF) is the prototype of a progressive fibrosing lung disease associated with significant mortality. A part of ILD, non-IPF patients may have a progressive clinical course similar to IPF, despite the use of conventional therapies. Although it was previously identified as progressive fibrosing ILD (PF-ILD), it is now defined as progressive pulmonary fibrosis (PPF), according to the recently published ATS/ERS/JRS/ALAT clinical practice guidelines.

PPF is characterized by at least two of the three criteria: worsening of respiratory symptoms, physiological (absolute decline in FVC ≥ 5% and/or DLCO ≥ 10% predicted within the past year of follow-up) and/or radiological (HRCT) evidence of disease progression, with no alternative explanation. Risk factors associated with PPF are male gender, more advanced age, lower initial FVC and DLCO, and radiological and/or histological features of usual interstitial pneumonia (UIP).

PPF patients are often treated with immunosuppressants depending on the underlying IBP subtype. It remains to be determined how effective immunosuppression is in patients when a progressive non-IPF fibrotic phenotype becomes apparent. Based on current treatment guidelines, initiation of antifibrotic therapy is recommended when the conventional treatment for PPF has not contributed to the desired effect. In addition to medication, non-pharmacological treatment methods (application of oxygen therapy, pulmonary rehabilitation and lung transplantation) and treatment of comorbidities are also important.

***Key words*:** *pulmonary fibrosis, progression, diagnosis, treatment*

REAL LIFE IZAZOVI U SAVREMENOM SAGLEDAVANJU PLUĆNIH FIBROZA U POSTKOVID ERI

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Intersticijumske bolesti pluća (IBP) čine grupu oko 200 entiteta koje karakteriše heterogenost u obimu zapaljenja i/ili fibroze. Idiopatska plućna fibroza (IPF) je prototip fibrozirajuće bolesti pluća, progresivna je i povezana sa značajnom smrtnošću. Deo bolesnika sa IBP-om, koji nije IPF, može imati progresivan klinički tok sličan IPF-u i pored primene konvencionalnih terapija. Iako je ranije identifikovana kao progresivna fibrozirajuća IBP (PF-IBP), prema ATS/ERS/JRS/ALAT smernicama kliničke prakse iz 2022. godine definisana je kao progresivna plućna fibroza (PPF).

Napredovanje plućne fibroze karakterišu najmanje dva od tri kriterijuma: pogoršanje respiratornih simptoma, fiziološki (pad apsolutnih vrednosti FVC ≥ 5% i/ili DLCO ≥ 10% za poslednju godinu dana praćenja) i/ili radiološki (HRCT) dokazi progresije bolesti, bez drugog objašnjenja. Faktori rizika koji su u vezi sa PPF-om su: muški pol, starije životno doba, niži FVC i DLCO na početku i radiološke i/ili histološke karakteristike uobičajene intersticijumske pneumonije (UIP).

Bolesnici sa PPF-om često se leče imunosupresivima u zavisnosti od osnovnog podtipa IBP-a. Ostaje da se utvrdi koliko je imunosupresija efikasna kod bolesnika kada progresivni ne-IPF fibrozni fenotip postane očigledan. Na osnovu aktuelnih smernica, uvođenje antifibrotske terapije preporučuje se kada konvencionalni tretman za PPF nije doprineo željenom efektu. Pored medikamentoznog, važne su i nefarmakološke metode lečenja (primena oksigenoterapije, plućna rehabilitacija, transplantacija pluća) i lečenje komorbiditeta.

Ključne reči: *plućna fibroza, progresija, dijagnostika, lečenje*

"REAL LIFE" CHALLENGES IN THE CONTEMPORARY PERCEPTION OF TUBERCULOSIS IN THE POST-COVID ERA

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Throughout history, pandemics of viral infections such as HIV, Ebola, and Influenza have disrupted healthcare systems, including the control of endemic diseases. Those processes resulted in an increased burden of endemic diseases in post-pandemic periods.
The current coronavirus disease 2019 (COVID-19) pandemic could cause severe dysfunction in tuberculosis (TB) prevention and control, which is still the leading infectious disease by morbidity and mortality, particularly in low- and middle-income countries, where the burden of TB is still substantial.
The health and economic crisis created by the current COVID-19 pandemic and the public health measures taken to stop the spread of the virus could potentially impact TB prevention and control in many different ways. The proportion of the cumulative disease burden associated with the COVID-19 pandemic, due to failures in endemic disease management, might end up being more significant than that directly caused by COVID-19 itself.
Health systems must attempt to maintain routine services for endemic infectious diseases at the highest level possible, recognizing that it may, out of necessity, be lower than pre-pandemic levels. It is also essential that health systems have a sustainable plan for returning to the full-service levels as soon as possible, in order to control better major endemic diseases such as TB. Economic analyses of the impact of the pandemic should include the indirect effects, such as disruption of routine services and subsequent burden of TB and other endemic infectious diseases.
Public health vigilance is necessary to mitigate the impact of COVID-19 on TB prevention and control, with plans in place to manage any increases in TB burden in future years.

***Key words*:** *COVID-19, pandemic, endemic, tuberculosis, impact, control*

REAL LIFE IZAZOVI U SAVREMENOM SAGLEDAVANJU TUBERKULOZE U POSTKOVID ERI

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Tokom istorije, pandemije virusnih infekcija kao što su HIV, ebola i influenca poremetile su sisteme zdravstvene zaštite, uključujući prevenciju i kontrolu endemskih bolesti. Takav poremećaj produkovao je veće opterećenje endemskim bolestima u postpandemijskim periodima. Trenutna pandemija bolesti korona virusa 2019 (COVID-19) mogla bi da izazove ozbiljnu disfunkciju u prevenciji i kontroli tuberkuloze (TB), zarazne bolesti koja uzrokuje više smrtnih slučajeva od bilo koje druge, posebno u zemljama sa niskim i srednjim prihodima, gde je opterećenje vrlo visoko.

Zdravstvena i ekonomska kriza izazvana aktuelnom pandemijom COVID-19, kao i javnozdravstvene mere preduzete da bi se zaustavilo širenje virusa, mogle bi da imaju potencijalni uticaj na prevenciju i kontrolu TB na više načina, s dodatnim stvaranjem tzv. *real life* izazova u postkovid eri. Udeo kumulativnog opterećenja svih masovnih zaraznih bolesti povezanog sa pandemijom COVID-19, zbog neuspeha u upravljanju endemskim zaraznim bolestima, mogao bi da bude veći od onog koji je direktno izazvan samim COVID-19.

Od suštinskog je značaja da zdravstveni sistemi pokušaju da održe rutinske usluge za endemske zarazne bolesti na najvišem mogućem nivou, shvatajući da se to nekad ne može kvalitativno i kvantitativno ostvariti na nivou pre pandemije. Takođe je od suštinskog značaja da zdravstveni sistemi imaju plan za povratak na pun nivo usluga što je pre moguće, posebno za kontrolu velikih endemskih zaraznih bolesti kao što je tuberkuloza. Ekonomske analize uticaja pandemije treba da obuhvate indirektne efekte, kao što su poremećaj rutinskih usluga i naknadno opterećenje zdravstvenih sistema i sistema socijalnih usluga tuberkulozom i drugim endemskim zaraznim bolestima.

S tim u vezi, neophodna je budnost javnog zdravlja, kako bi se ublažio uticaj pandemije COVID-19 na prevenciju i kontrolu TB, sa postavljenim održivim planovima za upravljanjem bilo kojim povećanjem opterećenja tuberkulozom u narednim godinama.

Ključne reči: *COVID-19, pandemija, tuberkuloza, uticaj, kontrola*

"REAL LIFE" CHALLENGES IN THE CONTEMPORARY PERCEPTION OF GRANULOMATOSIS IN THE POST-COVID PERIOD

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Sarcoidosis (the most common granulomatosis) is a diagnostic challenge given the overlapping clinical-radiological features with lymphoma, tuberculosis, certain autoimmune diseases and nowadays, its possible development after COVID-19.
The first case report of COVID-19-induced pulmonary sarcoidosis (*Capaccione*) has been reported in a patient with previous SARS-CoV-2 infection (occurring one year after COVID-19). In further cases (*Behbahani, Polat Ekinci*), a "sarcoid-like reaction" (erythema nodosum, skin biopsy) was reported, with no radiological evidence of pulmonary sarcoid, occurring several weeks after COVID-19. The mechanism by which COVID-19 could potentially trigger sarcoidosis, an inflammatory condition characterised by increased inflammatory cytokine release, was postulated by *Capaccione*. It was also supported by a meta-analysis (2016) which suggested possible triggering of sarcoidosis by infections (Mycobacterium tuberculosis, Propionibacterium acnes) that stimulated the development of granulomas with corresponding increases in the concentrations of inflammatory cytokines produced by immune cells in the affected tissues/organs. Given that sarcoidosis is frequently asymptomatic and in view of the fact that most individuals with SARS-CoV-2 infection during this ongoing pandemic do not undergo post-infection imaging (given that only a minority are admitted to hospitals or do not undergo X-ray as outpatients), there may be additional cases of COVID-19 associated sarcoidosis that remain undiagnosed or that are yet to develop.
These cases will help raising the awareness of COVID-19 associated sarcoid disease, enhancing the clinical and radiological vigilance and drawing greater attention of physicians and radiologists to this potential association. It may also give the impetus to further scientific and clinical studies of this largely unrecognised potential complication of COVID-19.

***Key words*:** *sarcoidosis, COVID-19, postpandemia*

REAL LIFE IZAZOVI U SAVREMENOM SAGLEDAVANJU GRANULOMATOZA U POSTKOVID ERI

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Sarkoidoza (najčešća granulomatoza) je dijagnostički izazov s obzirom na preklapanje kliničko-radioloških karakteristika sa limfomom, tuberkulozom, određenim autoimunim bolestima i mogućim razvojem nakon COVID-19 u današnje vreme.
Prvi slučaj (*Capaccione*) plućne sarkoidoze izazvane COVID-19 zabeležen je kod bolesnika sa prethodnom infekcijom SARS-CoV-2 (koja se javila godinu dana nakon COVID-19). Naredni slučajevi (*Behbahani, Polat Ekinci*) prijavili su *sarcoid-like reaction* (eritema nodosum, biopsija kože) bez radioloških nalaza plućne sarkoidoze, par nedelja nakon COVID-19. *Capaccione* je pretpostavio da je COVID-19 potencijalno mogao da izazove sarkoidozu – stanje usled povećanog oslobađanja inflamatornih citokina. U prilog tome govori i studija (2016), metaanaliza, koja podržava razvoj sarkoidoze indukovane infekcijama (Mycobacterium tuberculosis, Propionibacterium acnes); stimuliše razvoj granuloma sa odgovarajućim povećanjem koncentracije inflamatornih citokina koji proizvode imune ćelije u zahvaćenim tkivima/organima. S obzirom na to da je sarkoidoza često asimptomatska i da većina osoba sa SARS-CoV-2 infekcijom tokom ove pandemije i ne uradi radiogram grudnog koša (svega mali procenat bude primljen u bolnicu ili uradi radiogram ambulantno), može se razmatrati da će biti slučajeva COVID-19 udruženih sa sarkoidozom koja ostaje nedijagnostikovana ili koja tek treba da se razvije.
Svi ovi i budući slučajevi proširiće svest o sarkoidozi i mogućoj povezanosti sa COVID-19, čime će intenzivirati kliničku i radiološku budnost, te dovesti do veće pažnje među lekarima i radiolozima. To daje podsticaj daljim naučnim i kliničkim studijama ove uglavnom neprepoznate potencijalne komplikacije COVID-19 u postpandemijskoj eri.

Ključne reči: *sarkoidoza, Covid-19, postpandemija*

BRONCHIECTASIS - A CHALLENGE IN DIAGNOSIS AND CARE FROM THE PULMONOLOGY WARD TO THE INTENSIVE CARE UNIT

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Bronchiectasis presents a clinical syndrome characterized by cough, expectoration and the presence of abnormal thickening and dilatation of the bronchial wall, which can be visualized by imaging methods. Bronchiectasis is diagnosed from very young to elderly patients, with varying incidence worldwide. Henkle et al showed in 2018 that the prevalence of bronchiectasis in the United States was 701 cases per 100,000 inhabitants, was higher among women and increased with age. In China, it is estimated that 1.5% of women and 1.1% of men in the general population have bronchiectasis. The increase in the diagnosis of bronchiectasis may be due to improved recognition of the disease, but it may also be related to an increase in the underlying causes of the disease. Bronchiectasis sometimes complicates asthma and chronic obstructive pulmonary disease, and also coexists with numerous congenital and hereditary diseases, such as cystic fibrosis, primary ciliary dyskinesia, etc. They can also occur in patients with autoimmune diseases and various immunodeficiencies. In addition to cough and expectoration, the clinical presentation may include occasional hemoptysis or systemic symptoms. Special characteristics of bronchiectasis are the tendency to exacerbations and chronic infections. Patients with the phenotype of frequent exacerbations have a higher five-year mortality rate. Given the heterogeneity of the syndrome, the treatment is holistic and personalized, includes non-pharmacological and pharmacological measures aimed at improving mucociliary clearance, fighting infection, and in selected cases surgical treatment can be applied.

Key words: *bronchiectasis*

BRONHIEKTAZIJE – IZAZOV U DIJAGNOSTICI I ZBRINJAVANJU OD PULMOLOŠKE AMBULANTE DO ODELJENJA INTENZIVNE NEGE

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Bronhiektazije predstavljaju klinički sindrom koji karakteriše kašalj, iskašljavanje i prisustvo abnormalnog zadebljanja i proširenja zida bronhija, koje se može vizualizovati radiografskim metodama. Bronhiektazije se dijagnostikuju kod veoma mladih i kod starijih pacijenata, sa variranjem incidence širom sveta. Henkle i saradnici su prikazali u 2018. godini da je prevalencija bronhiektazija u Sjedinjenim Američkim Državama bila 701 slučaj na 100.000 stanovnika; bila je veća među ženama i povećavala se sa godinama. U Kini se procenjuje da 1,5% žena i 1,1% muškaraca u opštoj populaciji ima bronhiektazije. Porast u dijagnostikovanju bronhiektazija može biti posledica poboljšanog prepoznavanja bolesti, ali može biti povezano i sa povećanjem osnovnih uzroka oboljenja. Bronhiektazije ponekad komplikuju astmu i hroničnu opstruktivnu bolest pluća, a takođe koegzistiraju sa brojnim kongenitalnim i hereditarnim oboljenjima, kao što su cistična fibroza, primarna cilijarna diskinezija itd. Mogu nastati i kod pacijenata sa autoimunim oboljenjima i različitim imunodeficijencijama. Klinička prezentacija, sem kašlja i iskašljavanja, može podrazumevati povremene hemoptizije ili sistemske simptome. Posebne odlike bronhiektazija su sklonost ka egzacerbacijama i hroničnim infekcijama. Pacijenti sa fenotipom čestih egzacerbacija imaju veću stopu petogodišnjeg mortaliteta. S obzirom na heterogenost sindroma, tretman je holistički i personalizovan, uključuje nefaramkološke i farmakološke mere, usmerene na poboljšanje mukocilijarnog klirensa, suzbijanje infekcije, a u selektovanim slučajevima može se primeniti i hirurško lečenje.

***Ključne reči*:** *bronhiektazije*

COMMUNICATION – A FUNDAMENTAL SKILL IN CARING FOR THE PATIENTS WITH TERMINAL ILLNESSES

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Communication is a fundamental skill in health care. In palliative care it is not limited only to communication with the patient, but also includes communication with members of his family/ caregivers. Communication in health should be open, allowing an exchange of information and impressions, no matter how difficult and „shocking“ the information are. Healthcare professionals should encourage communication, so that the patient and his family can freely ask questions regarding the disease, treatment and prognosis.
Good communication should help the patient in choosing the most optimal type of treatment at the time. The basic goals in communication with the patient with a terminal illness and his family/caregivers members are adequate and understandable delivery of bad news, disease prognosis, treatment goals and selection of therapeutic procedure. A proper approach and adequate infromation through clear and unambiguous communication of the disease trajectory and prognosis can have a decisive influence on patients current and future behavior, and potentially on the therapeutic choice and treatment outcome.
Communication with the patient in the terminal phase of the disease is of great importance. It depends on the personal preference of the health care professionals and how much empathy will be brought into the relationship with the patient and his family. Poor communication can worsen the existing mental state of the patient and his family. Empathy should be one of the hallmarks of good communication in health.
The communication skills can be improved through various programs: educational workshops, communication skills courses, information on specialized websites - "online" education, etc.

Key words*: *Health Communication, Palliative care, Lung diseases

KOMUNIKACIJA NAŠA NASUŠNA KOJOM POČINJE I ZAVRŠAVA SVE U ZBRINJAVANJU PACIJENATA U TERMINALNOM STADIJUMU BOLESTI

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Komunikacija je fundamentalna komponenta u palijativnom zbrinjavanju. Ona nije i ne ograničava se samo na komunikaciju sa bolesnikom, nego podrazumeva i komunikaciju sa članovima njegove porodice. Komunikacija između bolesnika i članova njegove porodice i zdravstvenih radnika treba da bude otvorena, da omogući slobodnu razmenu informacija i utisaka, bez obzira koliko oni bili teški i potresni. Od strane zdravstvenh radnika, posebno lekara i medicinskih sestara, komunikacija bi trebalo da bude podstaknuta i ohrabrena tako da pacijent i njegova porodica slobodno postavljaju pitanja u vezi sa bolešću, lečenjem i prognozom.
Dobra komunikacija trebalo bi da pomogne bolesniku u odabiru najoptimalnijeg vida lečenja u momentu odlučivanja. Osnovni ciljevi u komunikaciji sa bolesnikom i članovima njegove porodice su adekvatno i razumljivo saopštavanje loših vesti, prognoze bolesti, ciljeva lečenja i odabira terapijskog postupka. Pravilan pristup u prenošenju informacija, jasno i nedvosmisleno saopštavanje toka i prognoze bolesti za bolesnika i članove njegove porodice imaće presudan uticaj na njihovo trenutno i buduće ponašanje, a potencijalno i na izbor terapijskog postupka i ishoda lečenja.
Komunikacija sa bolesnikom u terminalnoj fazi bolesti od velikog je značaja. Od lične sklonosti lekara i medicinskih sestara zavisi koliko će uneti topline u odnos sa bolesnikom. Loša komunikacija može da pogorša postojeće psihičko stanje bolesnika i njegove porodice. Empatija treba da bude jedno od obeležja dobre komunikacije.
Komunikacione veštine zdravstvenih radnika mogu se unaprediti kroz razne programe: edukativne radionice, kurseve komunikacionih veština, informacijama na specijalizovanim veb sajtovima onlajn edukacije i sl.

Ključne reči: *komunikacija u zdravstvu, palijativno zbrinjavanje, plućne bolesti*

BRONCHOSCOPY 'OUR DAILY BREAD', WITH WHICH THE TREATMENT OF PATIENTS WITH LUNG CANCER BEGINS

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Bronchoscopy is necessary and in clinical practice very often the only method in the diagnosis of lung cancer. The diagnostic contribution of bronchoscopy differs depending on the location of the lesion (central or peripheral). Regarding central lesions, the sensitivity of biopsy of a visible endobronchial lesion is 74%. At least three to five biopsy specimens are recommended to increase the diagnostic rate in endobronchial biopsy. The sensitivity of fiberoptic bronchoscopy (FB) in the diagnosis of a central tumor increases to 88% with the addition of bronchoalveolar lavage, brushing and endobronchial needle aspiration (TBNA). In the American College of Chest Physicians guidelines for the diagnosis of lung cancer, the sensitivity of FB procedures in the diagnosis of peripheral tumors (78%) was lower than that for central tumors (88%). A minimum of six biopsy specimens is recommended to increase the diagnostic rate of transbronchial biopsies.

Since the flexible bronchoscope was developed in 1966, there has been no greater technological advance in diagnostic bronchoscopy than the introduction of curvilinear and radial endobronchial ultrasound (EBUS). More than a decade of clinical trials have shown that EBUS staging of lymph node involvement is not only effective and safe, but can replace mediastinoscopy for nodal staging when performed correctly and thoroughly.

However, with the expanding portfolio of targeted and immunotherapeutic agents available for patients with unresectable malignancy, diagnostic and staging information from EBUS alone is no longer sufficient, and additional material must be obtained to perform molecular and immune profiling of tumors. The combined use of navigation platforms (EMN-electromagnetic navigation and vortex bronchoscopy) and radial EBUS seems to be the most effective for biopsy of peripheral lesions. On the other hand, one should consider whether CT-guided needle aspiration or direct surgical resection would be a more cautious approach than using the latest bronchoscopic technology. The methodology of using ultrathin bronchoscopes (UTB), electromagnetic navigation bronchoscopy (ENB) and cryobiopsy should contribute to the rapid and accurate diagnosis of lung cancers in the early stages. The development of bronchoscopic techniques for ablation with the achieved standards of stereotactic radiation should improve the therapeutic efficiency in both early and advanced stages of lung cancer.

The new bronchoscopic methodology should help in decision-making about indications and in evaluation of the application of new therapeutic modalities.

Key words: *lung cancer, bronchoscopy, endobronchial ultrasound*

BRONHOSKOPIJA NAŠA NASUŠNA KOJOM POČINJE SVE U ZBRINJAVANJU PACIJENATA SA MALIGNOMIMA PLUĆA

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Bronhoskopija je neophodna i, vrlo često u kliničkoj praksi, jedina metoda u dijagnostici raka pluća. Dijagnostički doprinos bronhoskopije razlikuje se u zavisnosti od lokacije lezije (centralna ili periferna). Što se tiče centralnih lezija, osetljivost biopsije vidljive endobronhijalne lezije je 74%. Preporučuje se najmanje tri do pet biopsijskih uzoraka da bi se povećala stopa dijagnoze u endobronhijalnoj biopsiji. Osetljivost fiberoptičke bronhoskopije (FB) u dijagnostici centralnog tumora povećava se na 88% uz dodatak ispiranja bronha, četkanja i aspiracije endobronhijalnom iglom (TBNA). U smernicama *American College of Chest Phisicians* za postavljanje dijagnoze karcinoma pluća, osetljivost FB procedura u dijagnostici perifernih tumora (78%) bila je niža nego kod centralnih tumora (88%). Preporučuje se najmanje šest uzoraka biopsije da bi se povećala stopa dijagnoze kod transbronhijalnih biopsija.
Otkad je razvijen fleksibilni bronhoskop 1966. godine, nije bilo većeg tehnološkog napretka u dijagnostičkoj bronhoskopiji od uvođenja krivolinijskog i radijalnog endobronhijalnog ultrazvuka (EBUS). Na osnovu više od decenije kliničkih ispitivanja pokazalo se da određivanje stadijuma zahvaćenosti limfnih čvorova pomoću EBUS-a nije samo efikasano i sigurano, već može da zameni medijastinoskopiju za nodalni stejdžing kada se izvodi pravilno i temeljno.
Međutim, sa širenjem portfolija ciljanih i imunoterapeutskih agenasa dostupnih za pacijente sa neresektabilnim malignitetom, samo dijagnostičke i informacije o stadijumu iz EBUS-a više nisu dovoljne, već se mora nabaviti dodatni materijal da bi se izvršila molekularna i imunoprofilacija tumora. Kombinovana upotreba navigacionih platformi (EMN – elektromagnetna navigacija i virtuelna bronhoskopija) i radijalnog EBUS-a izgleda da je najefikasnija za biopsiju perifernih lezija. Sa druge strane, treba razmotriti da li bi aspiracija iglom vođena CT-om ili direktna hirurška resekcija bili oprezniji pristup od upotrebe najnovije bronhoskopske tehnologije. Metodologija primene ultratankih bronhoskopa (UTB), elektromagnetna navigaciona bronhoskopija (ENB) i kriobiopsija treba da doprinesu brzoj i preciznoj dijagnostici plućnih karcinoma u ranom stadijumu. Razvoj bronhoskopskih tehnika za ablaciju, uz dostignute standarde stereotaktičkog zračenja, trebalo bi da unapredi terapijsku efikasnost kako ranih tako i odmalklih stadijuma karcinoma pluća.
Nova bronhoskopska metodologija treba da pomogne u odlukama o indikacijama i evaluaciji primene novih terapijskih modaliteta.

***Ključne reči*:** *plućni karcinom, bronhoskopija, endobronhijalni ultrazvuk*

"REAL LIFE" CHALLENGES IN THE BRONCHOLOGIST - PATHOLOGIST - ONCOLOGIST RELATIONSHIP: EXPERIENCES AND RECOMMENDATIONS

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New scientific knowledge has opened a whole new era in the treatment of non-small cell lung cancer, now with more success and with reduced mortality. Pulmonary oncology has changed dramatically, it is completely profiled, and therefore depends on diagnostic methods. Treating a patient according to his tumor profile, through precise and personalized therapy, is not a novelty, but an absolute necessity. It is necessary to point out that in almost 50% of patients with lung cancer it is possible to detect recognizable genetic features, and with the development of multiple targeted therapies, the way of treating advanced NSCLC has been revolutionized. There is no pulmonary oncology without adequate tissue sampling, available clinical pathology, comprehensive genetic testing, or a multidisciplinary approach. Understanding and availability of diagnostic and therapeutic procedures requires a unity among pulmonologists/bronchologists, radiologists, pathologists, molecular biologists, geneticists, clinical pharmacologists, and oncologists. In our conditions, this process does not flow at a sufficient speed, but it is undeniably progressing.

***Key words*:** *pulmonary oncology, multidisciplinary approach*

REAL LIFE IZAZOVI NA RELACIJI BRONHOLOG – PATOLOG – ONKOLOG: ISKUSTVA I PREPORUKE

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Nova naučna saznanja otvorila su potpuno novu eru u liječenju nemikrocelularnog raka pluća, sada sa više uspjeha i uz smanjenu smrtnost. Plućna onkologija se dramatično promjenila, profilisana je u potpunosti, te zbog toga zavisi od dijagnostičkih metoda. Liječenje bolesnika prema njegovom profilu tumora, kroz preciznu i personalizovanu terapiju nije novost, nego apsolutna potreba. Potrebno je istaći da je kod gotovo 50% bolesnika sa karcinomom pluća moguće detektovati prepoznatljiva genska obilježja, a uz razvoj višestrukih ciljanih terapija revolucionarno se mijenja način liječenja uznapredovalog NSCLC-a. Nema plućne onkologije bez adekvatnog uzorkovanja tkiva, dostupne kliničke patologije, sveobuhvatnog genskog testiranja, odnosno multidisciplinarnog pristupa. Razumjevanje i dostupnost dijagnostičkih i terapijskih postupaka zahtjeva jedinstvo između pulmologa/bronhologa, radiologa, patologa, molekularnog biologa, genetičara, kliničkog farmakologa i onkologa. U našim uslovima ovaj proces ne teče dovoljnom brzinom, ali nesporno napreduje.

Ključne reči: *plućna onkologija, multidisciplinarni pristup*

"REAL LIFE" CHALLENGES IN THE RELATIONSHIP BETWEEN A BRONCHOLOGIST AND A THORACIC SURGEON, MODERN ATTITUDES IN THE PREOPERATIVE PREPARATION OF PATIENTS WITH BRONCHIAL CANCER

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Bronchial carcinoma is still the leading cause of mortality from malignant diseases in both sexes in Serbia and in the world. A large number of different diagnostic procedures are used in order to diagnose and determine the stage of the disease. Bronchoscopy is a basic invasive procedure, both in order to establish a pathohistological diagnosis of the disease, and in order to determine the stage of the disease. The role of the bronchologist in the preoperative preparation and evaluation of the patient consists in the complete exploration of the tracheo-bronchial tree and the correct interpretation of the endoscopic findings, as well as in providing adequate samples, cytopathological and pathohistological, qualitatively and quantitatively. In patients with a tumor in the large airways, bronchoscopy is absolutely necessary preoperatively, i.e. if anatomical resection is required (lobectomy, bilobectomy and/or pneumonectomy) with taking biopsies from the carina and samples with endoscopically visible direct and indirect signs of the tumor process. In patients with enlarged lymph nodes of the mediastinum, and a negative result of transbronchial needle puncture and a positive result of PET-CT, it is necessary to perform a mediastinoscopy, as a diagnostic surgical procedure, before surgical resection. Bronchoscopy has its important place even after completion of treatment with induction therapy, chemo- and/or radiotherapy, in order to determine the retreatment TNM stage and decide on further operative treatment, especially in the case of initially positive endoscopic findings as well as positive N2 lymph glands in the mediastinum.
Different bronchoscopic techniques have their important place in an adequate preoperative assessment and form an integral part of the diagnostic algorithm in the complete preparation and assessment of patients with bronchial cancer for operative treatment.

***Key words*:** *bronchial carcinoma, bronchoscopy, thoracic surgery*

REAL LIFE IZAZOVI NA RELACIJI BRONHOLOG–GRUDNI HIRURG, SAVREMENI STAVOVI U PREOPERATIVNOJ PRIPREMI BOLESNIKA SA KARCINOMOM BRONHA

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Karcinom bronha je i dalje vodeći uzrok mortaliteta od malignih bolesti kod oba pola u Srbiji i u svetu. Veliki broj različitih dijagnostičkih procedura koristi se u cilju postavljanja dijagnoze i određivanja stadijuma bolesti. Bronhoskopija je osnovna invazivna procedura, kako u cilju postavljanja patohistološke dijagnoze oboljenja tako i u cilju određivanja stadijuma bolesti. Uloga bronhologa u preoperativnoj pripremi i proceni bolesnika sastoji se u kompletnoj eksploraciji traheo-bronhijalnog stabla i pravilnoj interpretaciji endoskopskog nalaza, kao i u obezbeđivanju adekvatnih uzoraka, citopatoloških i patohistoloških, kvalitiativno i kvantitativno. Kod bolesnika sa tumorom u velikim disajnim putevima bronhoskopija je apsolutno neophodna preoperativno, tj. ukoliko je potrebna anatomska resekcija (lobektomija, bilobektomija i/ili pneumonektomija), sa uzimanjem biopsija sa karina i uzoraka sa endoskopski vidljivih direktnih i indirektnih znakova tumorskog procesa. Kod bolesnika sa uvećanim limfnim čvorovima medijastinuma, a negativnim nalazom transbronhijalne iglene punkcije i pozitivnim nalazom PET/CT-a, potrebno je uraditi medijastinoskopiju, kao dijagnostičku hiruršku proceduru, pre hirurške resekcije. Bronhoskopija ima svoje značajno mesto i nakon završenog lečenja indukcionom terapijom, hemioterapijom i/ili radioterapijom, u cilju određivanja retretmanskog TNM stadijuma i odluke o daljem operativnom lečenju, pogotovu u slučaju incijalno pozitivnog endoskopskog nalaza, kao i pozitivnih N2 limfnih žlezda u medijastinumu.
Različite bronhoskopske tehnike imaju svoje značajno mesto u adekvatnoj preoperativnoj proceni i čine sastavni deo dijagnostičkog algortima u kompletnoj pripremi i proceni bolesnika sa karcinomom bronha za operativno lečenje.

Ključne reči: *karcinom bronha, bronhoskopija, grudna hirurgija*

EMERGENCY BRONCHOSCOPY IN PULMONOLOGY – OUR EXPERIENCES AND RECOMMENDATIONS

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We consider emergency bronchoscopy to be the evacuation of secretion, removal of foreign objects from the airways, management of acute bleeding, tracheal stenosis, occlusion tumors and rare cases of nectrotizing tracheobronchitis.
The goal of the paper is to present our own experience and results in the management of emergencies in bronchology.
We have used the material from our clinic from the last five years. We reviewed the medical records of all patients treated with emergency bronchoscopy in the period from 2018-2023. The standard method of targeted sampling were used.
From 2018-2023, around 5000 broncoscopies were performed, out of which 230 were emergency interventions. Of these, there were 125 hemoptyses, 40 foreign body extractions, 20 tracheal stenoses, 45 occlusions of the tracheobronchial tree with tumor masses, and one necrotizing tracheobronchitis.
Emergency bronchoscopy has been performed in our clinic for several decades. In recent years, the number of interventions has increased significantly due to the treatment of bronchial tumors and tracheal stenoses. Emergency bronchoscopy is often the only method of treatment for patients with advanced bronchial cancer and tracheal stenosis of malignant or any other origin. If we exclude the cases where patients with hemoptysis died, all other performed interventions were successful.

***Key words*:** *bronchoscopy, hemoptysis, foreing body, tumors, tracheal stenosis*

URGENTNA BRONHOSKOPIJA U PULMOLOGIJI – NAŠA ISKUSTVA I PREPORUKE

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Pod urgentnom bronhoskopijom kod nas podrazumjevamo: evakuaciju sekreta, uklanjanje stranih tijela iz disajnih puteva, zbrinjavanje akutnih krvarenja, stenoze traheje, tumore sa okluzijama i rijetke slučajeve nekrotizirajućeg traheobronhitisa.
Cilj rada bio je da pokaže naše iskustvo i rezultate zbrinjavanja urgentnih stanja u bronhologiji.
Koristili smo materijale iz naše klinike, u periodu od prethodnih pet godina. Pregledali smo sve istorije bolesti bolesnika koje smo tretirali kao urgentnu bronhoskopiju, u periodu od 2018. do 2023. godine. Korišćene su standardne metode ciljano uzetih uzoraka.
U periodu od 2018. do 2023. godine urađeno je oko 5000 bronhoskopija, od kojih je 230 urgentnih; od toga, hemoptizije kod 125 bolesnika, ekstrakcije stranih tijela kod 40, stenoze traheje kod 20, okluzije traheobronhalnog stabla tumorskom masom kod 45 bolesnika, te jedan slučaj nekrotizirajućeg traheobronhitisa.
U našoj Klinici urgentna bronhoskopija radi se unazad nekoliko decenija. Poslednjih godina broj intervencija je značajno povećan zbog tretiranja tumora bronha i stenoza traheje. Često je urgentna bronhoskopija jedini metod zbrinjavanja bolesnika sa uznapredovalim karcinomom bronha i stenoza traheje malignog i drugog porijekla. Ako izuzmemo pojedinačne slučajeve bolesnika sa hemoptizijama koji su završili letalno, sve ostale intervencije bile su uspješne.

Ključne reči: *bronhoskopija, hemoptizije, strana tijela, tumori, stenoza traheje*

CURRENT APPROACHES IN IMMUNOTHERAPY FOR SMALL CELL LUNG CANCER

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Small cell lung cancer (SCLC) accounts for about 13-15% of all new lung cancers diagnosis. It has a particulary unfavorable prognosis and in about 70% of cases occurs in the advanced stage (extended disease). Platinum-based chemotherapy is the standard of care for both limited disease (LD) and extensive disease (ED). Although this treatment favors survival and disease control, most patients relapse, and overall survival (OS) reaches a maximum of 2 years in 21% and 7% of LD and ED, respectively. However, the advent of ICIs (immune checkpoint inhibitors), including PD-1 (inhibitors of programmed cell death protein 1) and PD-L1 (programmed death–ligand 1) in the therapeutic landscape started to change the outcome of patients with ED-SCLC. Recently published four phase III studies (IMpower 133, Caspian, Keynote-604, Reaction) tested the combination of immunotherapy (atezolizumab, durvalumab with or without tremelimubab, and pembrolizumab) in SCLC-ED patients. The IMpower 133 trial evaluated the efficacy of adding the PD-L1 inhibitor atezolizumab to standard carboplatin-etoposide showed significantly prolonged survival for patients with ED-SCLC. The Caspian trail tested the efficacy of the PD-L1 inhibitor durvalumab +/- CTL-4 inhibitor tremelimubab in combination with standard platinum based chemotherapy, and demonstrated an OS improvement compared with chemotherapy alone. The Keynote-604 trial investigated the efficacy of the PD-1 inhibitor pembrolizumab plus platinum-etoposide versus chemotherapy alone, and showed a prolonged progression free survival (PFS) in patients with added pembrolizumab. The Reaction trial randomized patients with a response after two cycles of chemotherapy to be treated with pembrolizumab in combination with chemotherapy or chemotherapy alone, with a significant OS improvement with added pembrolizumab. Despite the benefit from the combination of ICIs and chemotherapy, a significant percentage of patients shows disease progression within 2 years. Further studies, with a better undestanding of SCLC biology, would be needed for new therapeutic options to be devised for SCLC.

***Key words*:** *small cell lung cancer (SCLC), immune checkpoint inhibitors, immunotherapy, predictive factor*

SAVREMENI STAVOVI U PRIMENI IMUNOTERAPIJE KOD SITNOĆELIJSKOG KARCINOMA BRONHA

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Sitnoćelijski karcinom pluća (SCLC) obuhvata 13 − 15% svih novodijagnostikovanih karcinoma pluća. SCLC predstavlja bolest loše prognoze, odnosno, kod 70% slučajeva dijagnostikuje se u odmaklom stadijumu bolesti. Hemoterapija bazirana na platini predstavlja standard u lečenju SCLC-a, kako kod ograničene (LD), tako i kod proširene forme bolesti (ED). Premda hemoterapija poboljšava preživljavanje i kontrolu bolesti, ukupno preživljavanje u SCLC-u iznosi najviše dve godine, kod 21% bolesnika sa LD i 7% bolesnika sa ED. Napredak u lečenju ED SCLC-a postignut je primenom imunoterapije (*immune checkpoint inhibitors*), uključujući PD-1 (inhibitore programirane ćelijske smrti proteina 1) i PD-L1 (programirane smrti-liganda 1). Nedavno su objavljeni rezultati četiri studije treće faze (*IMpower 133, Caspian, Keynote-604, Reaction*) koje su ispitivale kombinacije imunoterapije (atezolizumab, durvalumab sa tremelimubabom ili bez njega, i pembrolizumab) u lečenju ED-SCLC-a. *IMpower studija* ispitivala je efikasnost PD-L1 inhibitora atezolizumaba koji je dodat hemoterapiji platina-etopozid i pokazano je značajno bolje preživljavanje u ED SCLC-u. *Caspian* studija ispitivala je aktivnost PD-L1 inhibitora durvalumaba +/- CTL4 inhibitor trevalimubab u kombinaciji sa hemoterapijom baziranom na platini i pokazala je bolje ukupno preživljavanje u odnosu na hemoterapiju. *Keynote-604* studija ispitivala je efikasnost PD-1 inhibitora pembrolizumaba dodatog platina-etopozid hemoterapiji u odnosu na hemoterapiju, pokazavši značajno duže vreme do progresije bolesti u grupi sa pembrolizumabom. U studiji *Reaction*, u kojoj su bolesnici randomizovani nakon dva ciklusa hemoterapije, dodavanjem pembrolizumaba, pokazano je takođe značajno bolje preživljavanje. Uprkos kombinaciji imunoterapije sa hemoterapijom, značajan procenat bolesnika ima relaps bolesti unutar dve godine. Buduće studije treba da se zasnivaju na boljem sagledavanju biologije tumora sa ciljem predloga novih terapijskih opcija u lečenju SCLC-a.

Ključne reči: *sitnoćelijski karcinom pluća (SCLC), immune checkpoint inhibitors, imunoterapija, prediktivni faktori*

CONTEMPORARY RECOMMENDATIONS ON IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Bronchial cancer remains to be one of the "biggest cancer killers in Europe", accounting for 20.4% of all cancer-associated deaths. Nevertheless, contemporary medicine witnesses an improvement of the global 5-year survival rate of lung cancer (30% in Japan and 24% in Israel), which is mainly due to the introduction of modern immune and targeted therapy for non-small cell lung cancer (NSCLC), as well as the improvement of supportive, palliative and end-of-life care of lung cancer patients.

Immune therapy (immune check-point inhibitors–ICIs), as part of the systemic anti-cancer treatment (SACT) is ussualy an option for stage II or III NSCLC patients, who are not candidates for curative treatment (surgery or targeted radiotherapy). It is administered either as neo-adjuvant or adjuvant therapy, or in patients with disease progression after the initial curative or classical chemotherapy. A prior assessment is necessary and encompasses death risk estimation with the assignment of specific scores („Thoracoscore"), detailed measurement of lung function (spirometry, body-pletismography, DLCO,"shuttle walk test"), mediastinalstaging, and Oncology Board assessment. Immunotherapy is indicated in squamous and non-squamous types of NSCLC, depending on the expression of PDL-1 and positivity of targetable mutations (EGFR, ALK, etc.), in combination or after platinum doublet therapy. Targeting PD-1 (pembrolizumab, nivolumab, cemiplimab) and/or PDL-1 (atezolizumab, durvalumab) blocks check point proteins, enhancing the anti-cancer immune response of the organism. Immunetherapy reduces tumor size and growth, leading to disease-free intervalprolongation, improvement of the quality of life of the patient, and increases the overall survival for up to 48 months. PD-1 and PDL-1 inhibitors can be combined with CTLA-4 inhibitors (ipilumab, tremelimumab), which additionally boost the cellular immunological response.

Controversies remain regarding the use of ICIs in targetable oncogene-addicted subpopulations. There are continuous efforts to find predictive biomarkers to identify those who would respond better to ICIs. It is important to improve patient selection and to establish the most effective concurrent or sequential combination therapies for different NSCLC clinical settings.

Key words**:** *immunotherapy, bronchial cancer, prognosis*

SAVREMENI STAVOVI U PRIMENI IMUNOTERAPIJE KOD NESITNOĆELIJSKOG KARCINOMA BRONHA

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Karcinom bronha je još uvek jedan od „najvećih ubica u Evropi"! Na plućni karcinom otpada 20,4% svih smrtnih slučajeva asociranih sa karcinomom. Ipak, savremena medicina beleži pomak u globalnom petogodišnjem preživljavanju (do 30% u Japanu i 24% u Izraelu), koji se, uglavnom, pripisuje uvođenju savremene imunološke, odnosno targetirane terapije za nesitnoćelijski karcinom bronha (NSCLC), kao i unapređenju suportivne, palijativne i terminalne nege bolesnika.

Imunoterapija (immune check-point inhibitors–ICIs), kao deo sistemske antikancer terapije (SACT), najčešće je opcija kod bolesnika sa NSCLC-om stadijuma II ili III, koji nisu kandidati za kurativnu terapiju (hirurgija ili kurativna radioterapija), kao neoadjuvantna ili adjuvantna terapija, ili kod bolesnika sa progresijom bolesti nakon kurativne ili klasične hemioterapije. Podrazumeva se prethodna procena rizika od smrti, skorovima kao što je na primer *Thoracoscore*, detaljna procena plućne funkcije (spirometrija, bodipletizmografija, DLCO, *shuttle walk test*), stejdžing medijastinuma i mišljenje onkološkog konzilijuma. Imunoterapija je indikovana kod skvamoznog i neskvamoznog tipa NSCLC-a, ovisno od ekspresije PDL-1 i prisustva targetibilnih mutacija (EGFR, ALK i sl.), u kombinaciji ili nakon platinum dublet terapije. Targetiranje PD-1 (pembrolizumab, nivolumab, cemiplimab) i/ili PDL-1 (atezolizumab, durvalumab) blokira proteine kontrolnih mesta (check-point proteins), pojačavajući antikancerski imunološki odgovor organizma. Imunoterapija uzrokuje smanjenje tumora ili usporavanje rasta, što vodi do produžavanja vremena do prve progresije bolesti, poboljšanja kvaliteta života bolesnika i uvećanja ukupnog vremena preživljavanja i do 48 meseci. PD-1 i PDL-1 inhibitori mogu se kombinovati i inhibitorima CTLA-4 (ipilumab, tremelimumab), koji mogu dodatno povećati imunološki odgovor ćelije.

Još uvek postoje kontroverzije oko upotrebe ICIs-a kod subpopulacije sa targetibilnim onkogenima. Aktuelna je potraga za biomarkerima koji bi predvideli profil bolesnika sa potencijalno najboljim odgovorom na ICIs. Neophodno je usavršavanje selekcije pacijenata i definicanje najefikasnije konkurentne ili sekvencijske terapijske kombinacije kod različitih oblika nesitnoćeliskog karcinoma bronha.

Ključne reči: *imunoterapija, karcinombronha, prognoza*

CURRENT KNOWLEDGE ABOUT THE INDICATIONS FOR CHEMOTHERAPY AND IMMUNOTHERAPY FOR NSCLC

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For a long time, chemotherapy based on platinum doublets has been the main treatment option for patients with advanced and metastatic non-small cell lung cancer (NSCLC). In recent years, the treatment of NSCLC has evolved due to targeted and immunological agents. Although the development of chemotherapy has not been as dramatic compared to the development of molecular targeted therapy and immunotherapy, evidence shows that chemotherapy is still an essential part of the treatment of NSCLC, regardless of stage, histology, driver mutations and immune status. Newer drug delivery systems such as albumin-bound paclitaxel have also shown clinical benefit in terms of efficacy and tolerability. In the era of precise or personalized medicine, the occurrence and development of immunotherapy has led to a dramatic change in the treatment and prognosis of NSCLC. Today, immunotherapeutic agents such as PD-(L)-1 inhibitors are the first-line therapy, alone or in combination with platinum-based chemotherapy. They show an advantage in overall survival in the first-line treatment. This combination has become the standard of care for patients with advanced NSCLC. Lately, new immunotherapeutic agents such as CTLA-4 inhibitors, vaccines based on dendritic cells, Car-T cell therapy, adoptive transfer of T cells, bispecific antibodies, etc. have been rapidly developed and researched. Immunotherapy shows a favorable safety profile but also new adverse effects that are usually mild and reversible.

***Key words*:** *NSCLC, chemotherapy, immunotherapy, survival*

SAVREMENA SAZNANJA O INDIKACIJAMA ZA PRIMENU HEMIOTERAPIJE I IMUNOTERAPIJE KOD NSCLC-a

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Hemioterapija na bazi platinskih dubleta bila je dugo glavna opcija za lečenje bolesnika sa uznapredovalim i metastatskim nesitnoćelijskim karcinomom pluća (NSCLC). Poslednjih godina, lečenje NSCLC-a evoluira zbog pojave ciljanih i imunoloških agenasa. Iako razvoj hemoterapije nije tako dramatičan u poređenju sa razvojem molekularne ciljane terapije i imunoterapije, dokazi pokazuju da je hemioterapija i dalje suštinski deo lečenja NSCLC-a, bez obzira na stadijum, histologiju, drajver mutacije i imunološki status. Noviji sistemi za isporuku lekova kao što je paklitaksel vezan za albumin takođe su pokazali kliničku korist u smislu efikasnosti i podnošljivosti. U eri precizne/personalizovane medicine pojava i razvoj imunoterapije doveli su do ogromne promene u lečenju i prognozi NSCLC-a. Imunoterapijski agensi iz grupe PD-(L)-1 inhibitora danas su terapija prve linije, i samostalno ili u kombinaciji sa hemioterapijom na bazi platine, pokazuju prednost u ukupnom preživljavanju u prvoj liniji lečenja. Ova kombinacija postala je standard terapije kod bolesnika sa uznapredovalim NSCLC-om. Poslednjih godina ubrzano se razvijaju i istražuju novi imunoterapijski agensi kao što su: CTLA-4 inhibitori, vakcine zasnovane na dendritskim ćelijama, Car T-ćelijska terapija, adoptivni transfer T-ćelija, bispecifična antitela i dr. Imunoterapija pokazuje povoljan bezbednosni profil, ali i nove neželjene efekte koji su najčešće blagi i reverzibilni.

Ključne reči: *NSCLC, hemioterapija, imunoterapija, preživljavanje*

PHARMACOTHERAPEUTIC CHALLENGES IN THE TREATMENT OF CHRONIC MIXED MALIGNANT PAIN

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The present day pharmacotherapeutic challenges in the treatment of the most common accompanying symptom of oncological disease – pain – include the treatment of both the nociceptive and neuropathic components of pain within the so-called mixed malignant pain syndrome. The specificity of pharmacotherapy for mixed pain is that, in addition to classic opioid analgesics, it is necessary to prescribe coanalgesics that suppress the neuropathic component of pain. The approach to each patient should be individualized and the dose of co-analgesics should be carefully titrated due to possible interactions with basal analgesia. Therefore, the correct intake of all prescribed drugs in an adequate dosage regimen and time intervals should be explained to each individual patient, in order to obtain adequate patient adherence and the desired pharmacotherapeutic response. A diagnostic tool helpful in determining the neuropathic component of pain in mixed pain is the DN4 questionnaire, which has been validated and translated into Serbian. From among coanalgesics, you should not be reluctant to prescribe antiepileptics from the gabapentinod group; selective inhibitors of serotonin and noradrenaline uptake; long-acting corticosteroids; and bisphosphonates. The dosage regimen and time of taking coanalgesics should be adjusted in relation to the time of taking basal opioid analgesia, and in accordance with the division of opioids by interaction potential and groups of coanalgesics depending on the possibility of creating interactions with analgesics. For this painful syndrome, it is necessary to prescribe adequate supplementation such as B group vitamins, vitamin E, zinc, magnesium, palmitoylethanolamide, alpha-lipoic acid, superoxide dismutase and others.

***Key words**: pharmacotherapy, chronic mixed malignant pain, opioid analgesics, coanalgesics, interactions, supplementation*

FARMAKOTERAPIJSKI IZAZOVI U LEČENJU HRONIČNOG MEŠOVITOG MALIGNOG BOLA

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Farmakoterapijski izazovi današnjice u lečenju najčešćeg pratećeg simptoma onkološke bolesti – bola obuhvataju kupiranje i nociceptivne i neuropatske komponente bola u okviru takozvanog mešovitog malignog bolnog sindroma. Specifičnost farmakoterapije mešovitog bola je, pored klasičnih opioidnih analgetika, neophodno propisivanje i koanalgetika koji kupiraju neuropatsku komponentu bola. Treba individualizovati pristup svakom bolesniku i pažljivo titrirati dozu koanalgetika zbog mogućih interakcija sa bazalnom analgezijom. Stoga, svakom bolesniku treba objasniti pravilno uzimanje svih propisanih lekova u adekvatnom režimu doziranja i vremenskim intervalima, kako bismo imali adekvatnu adherencu pacijenata i željeni farmakoterapijski odgovor. Dijagnostičko sredstvo koje nam je od pomoći za utvrđivanje neuropatske komponente bola u okviru mešovitog bola je DN4 upitnik koji je validizovan i preveden na srpski jezik. Od koanalgetika ne treba se pribojavati propisivanja antiepileptika iz grupe gabapentinodia, selektivnih inhibitora preuzimanja serotonina i noradrenalina, dugodelujućih kortikosteroida i bisfosfonata. Treba prilagoditi režim doziranja i vremensko uzimanje koanalgetika u odnosu na vremena uzimanja bazalne opioidne analgezije, a u skladu sa podelom opioida po interakcionom potencijalu i grupama koanalgetika u zavisnosti od mogućnosti stvaranja interakcija sa analgeticima. Za ovaj bolni sindrom neophodno je i propisivanje adekvatne suplemenatacije kao što su vitamini B grupe, vitamin E, cink, magnezijum, palmitoiletanolamid, alfa-lipoinska kiselina, superoksid dismutaza i drugi.

***Ključne reči*:** *farmakoterapija, hronični mešoviti maligni bol, opioidni analgetici, koanalgetici, interakcije, suplementacija*

CONTEMPORARY VIEWS ON THE IMPORTANCE OF T AND N DIAGNOSTICS IN THE TMN CLASSIFICATION OF LUNG CARCER - WHAT IS CRUCIAL IN MAKING A THERAPEUTIC DECISION

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A multimodal approach has become especially important for the treatment of locally advanced stage II-III NSCLC. Surgery plus adjuvant radiotherapy is considered as an important treatment for locally advanced lung cancer.
Precise definitions of T and N status are closely related to prognosis and treatment. However, complexity arises because there is no unity on the definition for individual T and N descriptors. The International Association for the Study of Lung Cancer (IASLC) proposed a significant change in the T descriptor in the 8th edition of the TNM classification for lung cancer in 2015, in which tumors > 5 cm to less than or equal to 7 cm are reclassified in T3, and those greater than 7 cm in T4. Moreover, stage IIB includes T3 tumors > 5 cm without lymph node involvement (T3N0), while stage IIIA includes T4 tumors > 7 cm without lymph node involvement (T4N0). However, no specific study has yet been conducted to focus on the optimal treatment modality for patients with NSCLCs measuring > 5 to 7 cm and > 7 cm based on the latest TNM disease classification.
Further, increasing attention is being paid to the role of nodal status and other high-risk factors, including vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement, and incomplete lymph node sampling in individualized clinical management.
Lymph node involvement is closely related to NSCLC treatment strategies and still belongs to the domain of an appropriate individual treatment approach in NSCLC.

***Key words*:** *non-small cell lung cancer, T status, N status, lymph node, prognosis*

SAVREMENI STAVOVI O ZNAČAJU T I N DIJAGNOSTIKE U TMN KLASIFIKACIJI KARCINOMA BRONHA – ŠTA JE KLJUČNO ZA DONOŠENJE ODLUKE O TERAPIJI

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Multimodalni pristup je postao posebno važan za lečenje lokalno uznapredovalog nemikrocelularnog karcinoma pluća (NSCLC), stadijuma II−III. Hirurgija sa adjuvantnom radioterapijom smatra se važnim tretmanom za lokalno uznapredovali karcinom pluća.
Precizne definicije T i N statusa usko su povezane sa prognozom i lečenjem. Međutim, složenost nastaje zato što ne postoji definicija jedinstva za pojedinačne T i N deskriptore. Međunarodna asocijacija za proučavanje raka pluća (IASLC) predložila je značajnu promenu u T deskriptoru u osmom izdanju TNM klasifikacije za karcinom pluća 2015. godine, u kojoj su tumori manji ili veći od 5 cm ili veličine od 7 cm reklasifikovani u T3, a oni veći od 7 cm u T4. Takođe, stadijum IIB uključuje tumore T3 > 5 cm bez proširenja limfnih čvorova (T3N0), dok stadijum IIIA uključuje T4 tumore > 7 cm bez zahvatanja limfnih čvorova (T4N0). Međutim, još uvek nije sprovedena posebna studija koja bi se fokusirala na optimalni modalitet lečenja za bolesnike sa NSCLC > 5 − 7 cm i NSCLC-om > 7 cm na osnovu najnovije TNM klasifikacije bolesti.
Takođe, sve veća pažnja poklanja se ulozi nodalnog statusa i drugim faktorima visokog rizika, uključujući vaskularnu invaziju, klinastu resekciju, tumore > 4 cm, zahvaćenost visceralne pleure i nepotpuno uzimanje uzoraka limfnih čvorova u individualnom kliničkom tretmanu.
Zahvaćenost limfnih nodusa je usko povezana sa strategijama lečenja NSCLC-a i još uvek spada u domen odgovarajućeg individualnog pristupa lečenja u NSCLC-u.

Ključne reči: *nemikrocelularni karcinom pluća, T status, N status, limfni čvor, prognoza*

CURRENT KNOWLEDGE ABOUT THE ROLE OF THE THORACIC SURGEON IN RESPIRATORY ONCOLOGY

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A dynamic development of thoracic surgery is enhanced by the constant introduction of new diagnostic and therapeutic techniques and procedures, especially in the field of respiratory oncology.

Lung cancer is an insidious disease that is most often detected at an advanced stage when surgical treatment is not possible. If lung cancer is detected at an early stage, the probability of remission and five-year survival after surgical and oncological treatment is high and amounts to 81 - 92%.

Standard operations for the treatment of lung cancer are lobectomy or pulmectomy with lymph node dissection. In cases of early lung cancer, sublobar lung resections are also performed. It is also claimed that a non-anatomic lung resection with a "clean resection margin" is sufficient in the treatment of lung cancer.

Minimally invasive video-assisted thoracic surgery (VATS) is being increasingly refined and practiced. VATS ensures less operative trauma and faster recovery of patients with adequate oncological radicality. The most common VATS techniques are uniportal, biportal, triportal, subxiphoid and robotic surgery.

A growing number of trained thoracic surgeons, introduction of VATS procedures, development of thoracic anesthesia, and improved and accelerated postoperative recovery have all significantly increased the number of operable lung cancer patients.

***Key words*:** *lung cancer, VATS, lobectomy, pneumonectomy*

SAVREMENA SAZNANJA O ULOZI TORAKALNOG HIRURGA U RESPIRATORNOJ ONKOLOGIJI

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Grudna hirurgija je hirurška grana koja je proizašla iz opšte hirurgije. Razvoj grudne hirurgije je veoma dinamičan, sa konstantnim uvođenjem novih dijagnostičko-terapijskih tehnika i procedura, naročito u oblasti respiratorne onkologije.

Karcinom pluća je podmukla bolest koja se najčešće otkriva u odmaklom stadijumu, kada hirurško lečenje nije moguće. Ukoliko se karcinom pluća otkrije u ranom stadijumu (T1a-c N0), verovatnoća remisije i petogodišnjeg preživljavanja nakon hirurškog i onkološkog lečenja je visoka i iznosi 81 − 92%.

Standardne operacije za lečenje karcinoma pluća su lobektomija ili pulmektomija uz disekciju limfnih čvorova. Kod ranih karcinoma pluća izvode se i sublobarne resekcije pluća, pri čemu nema razlike u ukupnom preživljavanju bolesnika u odnosu na standarne resekcije, s tim da je stepen recidiva veći. Postoje mišljenja da je neanatomska resekcija pluća uz „čistu marginu resekcije" dovoljna u lečenju karcinoma pluća.

Minimalno invazivna video-asistirana grudna hirurgija (VATS) se sve više usavršava i praktikuje. VATS obezbeđuje manju operativnu traumu i brži oporavak bolesnika, uz adekvatnu onkološku radikalnost. Najzastupljenije VATS tehnike su uniportni, biportni, triportni, subksifoidna i robotička hirurgija.

Sve veći broj obučenih grudnih hirurga, uvođenje VATS procedura, razvoj torakalne anestezije i poboljšan i ubrzan postoperativni oporavak značajno su povećali broj bolesnika sa karcinomom pluća koji se može operisati.

Ključne reči: *karcinom pluća, VATS, lobektomija, pulmektomija*

CURRENT KNOWLEDGE AND CHALLENGES OF THORACIC SURGERY IN THE TREATMENT OF MALIGNANT PLEURAL EFFUSIONS

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Malignant pleural effusion (MPE) refers to the presence of neoplastic cells in the pleural fluid. MPE is associated with significant morbidity and a poor prognosis overall. The management should be prompt and care plans should be individualized and formulated to involve a multidisciplinary team of healthcare professionals.

Cytological smears, cell blocks, and pleural biopsy are commonly used to diagnose pleural fluid effusions. Cell blocks are more useful in the diagnosis of malignancy because of better preserved architectural patterns, such as those seen in corresponding histopathology sections. Novel diagnostic markers are HK2-seq, Single-cell sequencing, MUC1, EpCAM, IL-6, survivin mRNA etc.

Surgical management of the condition involves thoracocentesis, chemical pleurodesis, talc poudrage, slurry pleurodesis, thoracoscopic procedures, indwelling pleural catheters, implantable pleural ports, and pleuroperitoneal shunting.

Some new questions and therapeutical strategies arise on the horizont. Will resection ever be justified In lung cancer patients in whom a MPE is found at operation? Is uniportal technique better then two port thoracoscopic techinique for the diagnosis and treatment of MPE? VATS talc insufflation may be associated with fewer recurrences of effusions compared with bedside talc slurry, so should awake-VATS be a new solution? Can pleural cell-free DNA be used to assess targetable mutations in lung adenocarcinoma patients with MPE?

Intrapleural administration of chemotherapeutic agents combined with new endogenous angiogenesis inhibitors with implicated anti-tumor activity has shown promising results in controlling MPE and improving the quality of life of the patients.

***Key words*:** *malignant pleural effusion (MPE), diagnosis, treatment, surgical strategies*

SAVREMENA SAZNANJA I IZAZOVI GRUDNE HIRURGIJE U REŠAVANJU MALIGNIH PLEURALNIH IZLIVA

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Maligni pleuralni izlivi (MPI) predstavljaju prisustvo neoplastičnih ćelija u pleuralnoj tečnosti. MPI su povezani sa značajnijim morbiditetom i lošijom sveukupnom prognozom. Tretman mora biti brz, a planiranje lečenja individualizovano od strane multidisciplinarnog tima zdravstvenih radnika.

Ćelijski razmazi, citoblok i biopsija pleure najčešće se koriste u dijagnozi pleuralnih izliva. Citoblok je korisniji u dijagnozi maligniteta zbog bolje očuvane arhitektonske građe nalik na korespondirajuće HP preseke. Novi dijagnostički markeri su HK2-seq, Single-cell seq, MUC1, EpCAM, IL-6, survivin mRNA i drugi.

Hirurški tretman podrazumeva torakocentezu, hemijsku pleurodezu, talk pudražu, rastvor talka, torakoskopske procedure, trajne pleuralne katetere, ugradne pleuralne portove i pleuroperitonealne šantove.

Neka nova pitanja i terapijske strategije pojavljuju se na horizontu. Da li će kod bolesnika sa plućnim karcinomom i MPI nađenim intraoperativno resekcija ikad biti opravdana? Da li je uniportalni pristup bolji od pristupa sa dva porta u dijagnozi MPI? VATS talk insuflacija pokazuje manje recidiva izliva u poređenju sa rastvorom talka, stoga, može li *awake*-VATS biti novo rešenje? Može li se pleuralna *cell-free* DNK koristiti za procenu target mutacija kod bolesnika sa adenokarcinom pluća i MPI?

Intrapleuralna aplikacija hemioterapeutika kombinovanih sa novim endogenim inhibitorima angiogeneze sa dokazanom antitumorskom aktivnošću pokazuje obećavajuće rezultate u kontroli MPI i unapređenju kvaliteta života pacijenata.

Ključne reči: *maligni pleuralni izlivi (MPI), dijagnoza, tretman, hirurške strategije*

ATELECTASIS – DO WE ALWAYS FIND AN UNDERLYING CAUSE?

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Atelectasis is a clinical and radiological diagnosis that requires an appropriate diagnostic and therapeutic approach. Tracheal injuries during intubation are rare, but their complications could be fatal. This case report aims to point out that tracheal injuries could be the underlying cause of atelectasis.

A 37-year-old female patient has been hospitalized at Institute for pulmonary diseases of Vojvodina in Sremska Kamenica after being treated in the regional hospital, for hypercapnic respiratory failure. The patient has suffered from chronic obstructive pulmonary disease and obesity hypoventilation syndrome. Upon admission, the patient was intubated and mechanically ventilated. Chest x-ray (CXR) demonstrated a consolidation of the lower left lobe, and therefore therapy for community-acquired pneumonia was started. Laboratory findings showed elevated inflammatory markers, hepatic enzymes, renal parameters, hyperglycemia, and an electrolyte imbalance. The patient was extubated on the third hospital day. Repeated arterial blood gas analyses showed compensated hypercapnic respiratory failure. Microbiological testing did not detect the cause of pneumonia. By the fifth hospital day, a complete collapse of the left lung was seen on CXR. Pleural ultrasound showed no signs of pleural effusion. CT lung scans showed an atelectatic left lung, without delineation of tissue changes. Flexible fiberoptic bronchoscopy revealed circular simplex stenosis of the trachea with the involvement of a 5 - 10 mm long segment, and below the stenosis, a flat floating fragment of several cm was seen. The fragment coloring was the tracheal mucosa color, and it was mobile during coughing and respirations. In further course, atelectasis of the left lung was monitored radiologically, so bronchoscopy was performed as needed. Repeated lung CT indicated a slight improvement in terms of partial aeration of the lung parenchyma in the projection to the upper left lobe. Bronchoscopy just before discharge showed that the obstructing moving fragment of the tracheal mucosa shrunk. After the partial radiological and clinical improvement, the patient was transferred to a regional hospital on the 25th hospital day with the recommendation for control by a competent pulmonologist with new chest CT findings.

The etiology of the floating fragment of the mucous tracheal membrane was understood as a lesion of the trachea during intubation, and since the microbiological substrate was not isolated, opportunistic infections were excluded as potential causes. Rehabilitation measures for assisted expectoration significantly contributed to the improvement of radiological findings.

***Key words*:** *atelectasis, tracheal injury, respiratory failure*

ATELEKTAZA – DA LI UVEK OTKRIJEMO UZROK?

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Atelektaza je klinička i radiološka dijagnoza koja zahteva odgovarajući dijagnostički i terapijski pristup. Povrede traheje tokom intubacije su retke, ali komplikacije mogu biti fatalne. Cilj ovog prikaza je da ukažemo da atelektaza može biti uzrokovana, između ostalog, i povredom zida traheje.

Bolesnica stara 37 godina hospitalizovana je u Institutu za plućne bolesti Vojvodine (IPBV) u Sremskoj Kamenici, kao premeštaj iz regionalne bolnice, zbog dekompenzovane respiratorne insuficijencije (RI) tip 2. Od komorbiditeta navode se gojaznost, hipoventilacioni sindrom i hronična opstruktivna bolest pluća (HOBP). Po prijemu u IPBV bolesnica je bila intubirana i mehanički ventilirana. Na radiogramu grudnog koša pri prijemu registrovana je levostrana pneumonija, te je primenjena dvojna antibiotska terapija za vanbolničku pneumoniju. Laboratorijski nalazi pri prijemu ukazivali su na povišene markere inflamacije, azotne materije, patološki hepatogram, hiperglikemiju, elektrolitni disbalans. Trećeg hospitalnog dana bolesnica je ekstubirana. U gasnim analizama održavala se kompenzovana tip 2 RI. Analizom uzoraka za mikrobiološki pregled nije utvrđen uzročnik pneumonije. Petog hospitalnog dana registruje se kompletna atelektaza levog hemitoraksa. Ultrazvučnim pregledom levog pleuralnog prostora nije registrovano signifikantno razdvajanje pleuralnih listova. Na CT pregledu grudnog koša opisana je atelektaza levo, bez delineacije podležuće mekotkivne promene. Bronhološkom obradom opisana je cirkularna simplex stenoza traheje sa zahvatanjem segmenta dužine 5−10 mm, a ispod stenoze viđen je pljosnat flotirajući fragment od nekoliko cm, boje sluznice traheje, pokretan pri kašlju i respiracijama. U daljem toku, radiološki se i dalje prati atelektaza levo, te su urađene eksploracije traheobronhijalnog stabla u više navrata. Kontrolni CT grudnog koša je ukazao na diskretno poboljšan nalaz u smislu delimične aeracije plućnog parenhima u projekciji na gornji levi lobus. Bronhoskopija pred otpust je pokazala da se pokretni fragment sluznice traheje, koji je opturisao istu, smanjio. Bolesnica je nakon delimičnog radiološkog i kliničkog poboljšanja 25. bolničkog dana premeštena u regionalnu ustanovu sa predlogom za kontrolu kod nadležnog pulmologa sa novim nalazom CT-a grudnog koša.

Etiologija flotirajućeg fragmenta sluznice je shvaćena kao lezija traheje prilikom intubacije, a s obzirom na to da mikrobiološki supstrat nije izolovan, isključene su oportunističke infekcije kao potencijalni uzrok. Rehabilitacione mere za potpomognutu ekspektoraciju značajno su doprinele poboljšanju radiološkog nalaza.

Ključne reči: *atelektaza, povreda traheje, respiratorna insuficijencija*

NECESSITY OF USING SCORES TO ASSESS HYPOXIA IN PATIENTS ON OXYGEN SUPPORT

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During the COVID pandemic, in addition to the significant therapeutic effect of oxygen therapy, the side effects of its excessive or prolonged use were confirmed. The uncontrolled oxygen application through a mask with flow over 15 l/min, High-Flow Oxygen Therapy (HFOT) of over 30 l/min and FiO2 of over 50%, as well as inadequate use of non-invasive ventilation resulted in more frequent occurrence of pneumothorax and pneumomediastinum, fibrous changes in the lung parenchyma and deteriorated lung function. Arterial blood gas analyses are not always interpreted correctly. In order to correctly assess the need for oxygen support, non-invasive ventilation or timely intubation, it is necessary to use the Modified Oxygenation Index (MOI) or the Oxygenation Index (OI). OI represents the ratio of the partial pressure of oxygen (PO2/mmHG) and the Fraction of Inhaled Oxygen (FiO2). MOI represents the ratio of saturation (SpO2) and FiO2 (SpO2/FiO2). FiO2 can be estimated by a special correlation with oxygen flow. MOI below 315 and OI below 300 suggest acute respiratory distress syndrome (ARDS). Prolonged administration of high doses of oxygen or HFOT is allowed only if there are rapid and evident improvements and should be followed by an early reduction of FiO2.

***Key words*:** *FiO2, Oxygenation Index (OI), High-Flow Oxygen Therapy (HFOT), side effects*

NEOPHODNOST KORIŠĆENJA SKOROVA ZA PROCENU HIPOKSIJE KOD BOLESNIKA NA KISEONIČNOJ POTPORI

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Tokom pandemije kovida, osim značajnog povoljnog učinka oksigenoterapije, osvetljena su i neka neželjena dejstva njene prekomerne ili prolongirane upotrebe. Nekontrolisana mogućnost primene kiseonika putem maske sa protokom preko 15l/min, *High Flow* ventilatora sa protokom preko 30l/min i FiO2 preko 50%, kao i neadekvanta upotreba neinvazivne ventilacije, rezulturali su češćom pojavom pneumotoraksa i pneumomedijastinuma, razvojem fibroznih promena u plućnom parenhimu i lošijim rezultatima plućne funkcije u toku oporavka. Gasne analize bolesnika nisu uvek tumačene ispravno u odnosu na primenjeni protok ili koncentraciju kiseonika. Radi pravilne procene potrebe za kiseoničnom potporom, neinvazivnom ventilacijom ili pravovremenom intubacijom, potrebno je koristiti određene skorove: modifikovani indeks oksigenacije (MIO) ili indeks oksigenacije (IO). MIO je skor koji predstavlja odnos saturacije i frakcije udahnutog kiseonika (SpO2/FiO2), dok je IO precizniji parametar i predstavlja odnos parcijalnog pritiska kiseonika (PO2/mmHG/) i frakcije udahnutg kiseonika (FiO2). FiO2 se može proceniti posebnom korelacijom sa protokom kiseonika, u zavisnosti od načina njegove isporuke. Na primer, maska sa rezervoarom protoka 15l/min ostvaruje FiO2 80−100%. Vrednost MIO < 315, tj. IO < 300 sugerišu akutni respiratorni distres sindrom. Prolongirana primena visokih doza kiseonika ili HF oksigenoterapije dozvoljena je samo ako ima brzih i evidentnih poboljšanja, uz što ranije smanjenje FiO2.

Ključne reči: *FiO2, indeks oksigenacije, high flow oksigenacija, neželjena dejstva*

THE INFLUENCE OF THE COVID-19 PANDEMIC ON MODERATE AND SEVERE ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (AECOPD)

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During the first few months of the COVID-19 pandemic, some studies found a decline in the incidence of moderate and severe AECOPD. This study's objective was to determine whether such an effect existed in patients treated at the Institute for Pulmonary Diseases of Vojvodina (IPDV).
In this cross-sectional observational study, using the Kruskal-Wallis test, AECOPD data of the patients treated as inpatients or outpatients at the IPDV in the period 2017 - 2022 were analyzed. Depending on the year of the research, the analysis revealed a statistically significant differences in the number of moderate and severe AECOPD ($H_{(4)} = 45.83$, $p = 0.000$), with a lower average number of daily cases after the first confirmed case of COVID-19 infection in Serbia on March 6, 2020. There were statistically significant differences in the number of AECOPD from March to June depending on the year ($H_{(5)} = 14.45$, $p = 0.013$). By matched-pair analysis, it was determined that in the period March – June 2020, at the time of the so-called "lockdown", there were statistically significantly fewer cases of AECOPD compared to 2019 ($p = 0.041$), similar to the same period in 2022 compared to 2019 and 2021 ($p = 0.041$ and $p = 0.048$, respectively).
Fewer hospitalizations due to moderate and severfe AECOPD were recorded during the COVID-19 pandemic, indicating that respiratory infection prevention measures implemented during the COVID-19 pandemic could also be useful in reducing the incidence of AECOPD.

***Key words*:** *acute exacerbations of chronic obstructive pulmonary disease, hospitalization, COVID-19.*

UTICAJ PANDEMIJE COVID-19 NA UMERENE I TEŠKE AKUTNE EGZACERBACIJE HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA (AEHOBP)

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U pojedinim studijama uočen je pad incidencije umerenih i teških akutnih egzacerbacija hronične opstruktivne bolesti pluća (AEHOBP) tokom COVID-19 pandemije. Cilj ovog rada bio je da se ispita da li je takav efekat postojao kod bolesnika koji su lečeni u Institutu za plućne bolesti Vojvodine (IPBV).

U ovoj opservacionoj studiji preseka, upotrebom Kruskal−Wallis testa, analizirani su podaci o AEHOBP-u bolesnika koji su ambulantno ili bolnički lečeni u IPBV u periodu 2017–2022. godine.

U zavisnosti od godine istraživanja, testiranjem su utvrđene statistički značajne razlike u broju umerenih i teških AEHOBP-a ($H_{(4)}$ = 45,83, p = 0,000), sa nižim prosečnim brojem dnevnih slučajeva nakon prvog potvrđenog slučaja COVID-19 infekcije u Srbiji, 6. 3. 2020. godine. Utvrđene su statistički značajne razlike u broju AEHOBP-a za period mart–jun u zavisnosti od godine ($H_{(5)}$ = 14,45, p = 0,013). Poređenjem po parovima, u periodu mart–jun 2020, u vreme tzv. lokdauna, bilo je statistički značajno manje slučajeva umerenih i teških AEHOBP-a u odnosu na 2019. godinu (p = 0,041), slično kao i u istom periodu 2022, u poređenju sa 2019. i 2021. godinom (p = 0,041, odnosno p = 0,048).

Tokom COVID-19 pandemije zabeležen je manji broj umerenih i teških AEHOBP-a, što ukazuje na to da bi mere sprečavanja respiratorne infekcije koje su primenjene tokom COVID-19 pandemije mogle biti korisne i u smanjenju incidencije AEHOBP-a.

Ključne reči: *akutne egzacerbacije hronične opstruktivne bolesti pluća, hospitalizacija, COVID-19.*

EVALUATION OF THE CHRONIC OBSTRUCTIVE PULMONARY DISEASE SEVERITY IN RELATION TO THE PRESENCE OF NASAL OBSTRUCTION

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The concept of united airway diseases was recognized decades ago in asthma patients. Recent studies have indicated the presence of nasal obstruction in patients with chronic obstructive pulmonary disease (COPD).
The aim of the study was to examine the impact of the upper airway symptoms on the severity of COPD.
This prospective study included 49 patients, 24 (48.98%) female and 25 (51.02%) male, aged 66.49 years, treated at the Institute for Pulmonary Diseases of Vojvodina. The severity of COPD was determined by the spirometric parameter (FEV1), and symptoms were assessed by the CAT (*COPD Assessment Test*) questionnaire, along with blood eosinophilia. The SNOT-22 questionnaire (*Sino-nasal Outcome Test*) verified the presence of the upper airway symptoms.
The nasal obstruction symptoms were found in 75.51% (37) of patients, more often in females. The correlation analysis confirmed a statistically significant association between CAT and SNOT-22 questionnaires ($r = 0.45$; $p < 0.05$), blood eosinophilia and SNOT-22 score ($r = 0.362$; $p < 0.05$). The correlation between FEV1, CAT and SNOT-22 questionnaires was not proven ($r = 0.166$; $r = 0.049$; $p > 0.05$), nor between the CAT score and blood eosinophilia ($r = 0.218$, $p > 0.05$).
The presence of nasal obstruction symptoms significantly affects the expression of COPD symptoms.

***Key words*:** *Nasal Obstruction, Eosinophilia, Pulmonary Disease Chronic Obstructive, Surveys and Questionnaires, Sino-Nasal Outcome Test*

PROCENA TEŽINE HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA U ODNOSU NA PRISUTNOST NOSNE OPSTRUKCIJE

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Koncept ujedinjene bolesti disajnih puteva prepoznat je pre više decenija kod bolesnika sa astmom. Nedavna istraživanja ukazala su na prisustvo nosne opstrukcije kod obolelih sa hroničnom opstruktivnom bolešću pluća (HOBP).
Cilj istraživanja bio je da se ispita uticaj prisutnih simptoma gornjih disajnih puteva na težinu HOBP-a.
U prospektivnu studiju uključeno je 49 bolesnika: 24 (48,98%) osobe ženskog i 25 (51,02%) osoba muškog pola, prosečne starosti 66,49 godina, lečenih u Institutu za plućne bolesti Vojvodine. Težina HOBP-a određena je spirometrijskim parametrom (FEV1%), procena simptoma upitnikom CAT (*COPD Assessment Test*), uz krvnu eozinofiliju. Upitnikom SNOT-22 (*Sino-nasal Outcome Test*) verifikovano je prisustvo simptoma gornjih disajnih puteva.
Simptomi nosne opstrukcije utvrđeni su kod 75,51% (37) pacijenata, češće ženskog pola. Korelacionom analizom potvrđena je statistički značajna povezanost CAT i SNOT-22 upitnika ($r = 0,45$; $p < 0,05$), krvne eozinofilije i SNOT-22 skora ($r = 0,362$; $p < 0,05$). Povezanost FEV1 i CAT i SNOT-22 upitnika nije dokazana ($r = 0,166$; $r = 0,049$; $p > 0,05$), kao ni CAT skora i krvne eozinofilije ($r = 0,218$, $p > 0,05$).
Prisustvo simptoma nosne opstrukcije značajno utiče na izraženost simptoma hronične opstruktivne bolesti pluća.

Ključne reči: *nosna opstrukcija, eozinofilija, HOBP, CAT, SNOT*

EFFECT OF PEMBROLIZUMAB TREATMENT IN PATIENTS WITH NON-SMALL CELL LUNG CARCINOMA

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Introduction: Pembrolizumab is a highly selective anti - programmed death ligand 1 (PD-1) monoclonal antibody, which inhibits the activity of the PD-1 receptor on activated T lymphocytes. Our aim is to demonstrate the effectiveness of Pembrolizumab in patients with PD-L1 expression greater than 50% in a case from our clinical practice.
Case report: A 56-year-old patient was examined because of a cough with expectoration of whitish sputum and fever. The initial MSCT of the chest and upper abdomen in July 2018 described in DB10 an excavated tumor lesion and a 33 x 31 mm conglomerate of lymph glands in the right hilus. Bronchological examination and pathohistological typing of the biopsies revealed the diagnosis of *Carcinoma bronchogenes squamocellulare non keratodes*. The testing was done, where PD-L1 was > 50%, and ECOG PS was 0. We decided to start the treatment with immunotherapy, with amp. Pembrolizumab a 200 mg for 3 weeks. The patient received 1L C1 in July, 2018. After 1L C4, a partial response is registered. MSCT described a tumoral change with central cavitation in DB10 27 x 22 mm, and mediastinal lymph nodes measuring up to 10 mm, and the treatment was continued with Pembrolizumab. After 1L C20, a complete response was noted, and MSCT described a right parahilar tumoral change with infiltration of the visceral pleura with the widest diameter of 10 mm and bilateral tracheobronchial lymph nodes measuring up to 10 mm. The patient received a total of 63 cycles. The signs of complete response were seen on MSCT in December, 2022. The patient was clinically stable all the time, maintained ECOG PS 0, and did not experience any toxic effects.
Conclusion: The presented case indicates a new chapter in the treatment of patients with non-small cell lung carcinoma.

***Key words*:** *non-small cell lung cancer, immunotherapy, Pembrolizumab*

EFEKAT LEČENJA PEMBROLIZUMABOM KOD PACIJENATA SA NESITNOĆELIJSKIM KARCINOMOM PLUĆA

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Pembrolizumab je visokoselektivno anti-PD-1 programmed death ligand 1 (PD-1) monoklonsko antitelo, koje inhibiše aktivnost PD-1 receptora na aktiviranim T-limfocitima. Cilj rada je da kroz slučaj iz kliničke prakse pokažemo efikasnost lečenja pembrolizumabom kod pacijenata sa ekspresijom PD-L1 većom od 50%.

Pacijent star 56 godina javio se lekaru zbog kašlja sa iskašljavanjem beličastog iskašljaja i povišene telesne temperature. Inicijalni MSCT grudnog koša i gornjeg abdomena iz jula 2018. godine opisao je u DB10 eskaviranu tumorsku promenu. Hilarno desno konglomerat limfnih žlezda bio je 33 x 31 mm. Bronhološko ispitivanje sprovedeno je u Kliničkom centru Srbije patohistološkom tipizacijom uzetih biopsata dokazano je da se radi o *Carcinoma bronchogenes squamocellulare non keratodes*. Sprovedeno je testiranje, PD-L1 > 50%, a ECOG PS je bio 0. Konzilijarno je doneta odluka da se lečenje započne imunoterapijom amp. pembrolizumaba 200 mg na tri nedelje. Pacijent je primio 1L C1 25. 7. 2018. godine. Nakon 1L C4 registruje se parcijalni odgovor, MSCT opisuje tumorsku promenu sa centralnom kavitacijom u DB10 27 x 22 mm, medijastinalne limfne noduse do 10 mm, a lečenje je nastavljeno pembrolizumabom. Nakon 1L C20 beleži se kompletan odgovor, MSCT opisuje tumorsku promenu parahilarno desno sa infiltracijom visceralne pleure najšireg dijametra 10 mm, limfni nodusi obostrano traheobronhijalno do 10 mm. Pacijent je primio ukupno 63 ciklusa, a MSCT iz decembra 2022. registruje znake kompletnog odgovora, sve vreme klinički stabilan, održava ECOG PS 0, a toksični efekti nisu ispoljeni.

Opisani slučaj svedoči o novom poglavlju u lečenju pacijenata sa nesitnoćelijskim karcinomom pluća.

Ključne reči: *nesitnoćelijski karcinom pluća, imunoterapija, pembrolizumab*

CHRONIC GRANULOMATOUS INFLAMMATION AS A DIFFERENTIAL DIAGNOSIS DILEMMA IN PULMONOLOGY – A CASE REPORT

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Granulomatous lung disease represents a group of diseases characterized by granuloma formation after exposure to infectious or non-infectious agent with various clinical manifestations. Considering these facts, through a case report from real clinical practice we aimed to point out a wide range of differential diagnosis possibilities that need to be evaluated in the treatment of a patient with a histopathologically confirmed chronic granulomatous lung process.

A 28-year-old patient was hospitalized after scintigraphy for further diagnosis, with the suspicion of a neuroendocrine tumor in the right lung. MSCT exploration confirmed the cavitating lesion of S6, signs of diffuse inflammation were seen endoscopically, while microbiological examinations of the sputum and bronchial aspirate were normal. As the histopathology examinations of transbronchial biopsies were consistent with chronic fibrotic inflammation with a suspicious granulomatous aggregate of Langhans cells, further diagnostic procedures included: QuantiFERON TB Gold Plus test that was negative; angiotensin-converting enzyme levels were within the reference limits; the intraoperative finding of video-assisted thoracoscopy with segmentectomy corresponded to aspergilloma; and the histopathology examinations revealed a chronic granuloma-like inflammation, while there was no presence of fungi. Additional serological analyses verified elevated levels of IgM antibodies to Aspergillus fumigatus and titer monitoring was indicated to decide on further treatment.

Granuloma represents a differential diagnosis challenge, so a multidisciplinary approach is necessary to establish an accurate and precise diagnosis.

Key words: *granuloma, inflammation, aspergillosis*

HRONIČNA GRANULOMATOZNA INFLAMACIJA KAO DIFERENCIJALNO-DIJAGNOSTIČKA DILEMA U PULMOLOGIJI – PRIKAZ SLUČAJA

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Granulomatozna bolest pluća predstavlja grupu oboljenja koja se karakterišu formiranjem granuloma nakon izlaganja infektivnom ili neinfektivnom agensu uz različite kliničke manifestacije. Imajući u vidu navedeno, cilj našeg rada bio je da kroz prikaz slučaja iz realne kliničke prakse ukažemo na širok spektar diferencijalno-dijagnostičkih mogućnosti koje je neophodno evaluirati u tretmanu pacijenta sa patohistološki potvrđenim hroničnim granulomatoznim procesom na plućima.

Pacijentkinja starosti 28 godina hospitalizovana je radi dopunske dijagnostike sa scintigrafskom sumnjom na postojanje neuroendokrinog tumora u desnom plućnom krilu. MSCT eksploracijom se potvđuje kavitirajuća lezija S6, endoskopski se evidentiraju znaci difuzne inflamacije, mikrobiološki i mikobakteriološki pregledi sputuma i fiberbronhoaspirata su urednog nalaza. Kako je nalaz patohistološke analize transbronhijalnih biopsija konzistentan sa hroničnom fibroznom inflamacijom uz suspektan granulomatoliki agregat ćelija tipa *Langhans*, dalji dijagnostički postupak se sprovodi u tom pravcu: QuantiFERON TB Gold Plus test je negativan, nivoi angiotenzin-konvertujućeg enzima su u referentnim granicama, intraoperativni nalaz video-asistirane torakoskopije sa segmentektomijom odgovara aspergilomu, patohistološki nalaz hroničnoj granulomatoznoj inflamaciji, dok prisustvo gljiva nije dokazano. Dopunskim serološkim analizama verifikuju se povišeni nivoi IgM antitela na *Aspergillus fumigatus* te je indikovano praćenje titra radi odluke o daljoj terapiji.

Granulomatozni proces predstavlja diferencijalno-dijagnostički izazov, zbog čega je za postavljanje tačne i precizne dijagnoze neophodan multidisciplinarni pristup.

***Ključne reči*:** *granulom, inflamacija, aspergiloza*

MODERN RESPIRATORY REHABILITATION PROGRAMS – FOR WHOM, HOW, WHERE – FROM EDUCATION TO EMOTIONAL SUPPORT IN ILLNESS

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Respiratory rehabilitation has the greatest positive effect on the course and prognosis of COPD, asthma and pulmonary complications after recovering from Covid 19 infection. Increased exercise capacity and adaptive behavior change are necessary in order to achieve a significant and permanent increase in physical activity in a patient with this symptomatology. In order for the change to happen, at interdisciplinary approach is needed that combines respiratory medicine, rehabilitation, social and behavioral sciences. The purpose of rehabilitation is to restore the patient's well-being, including his physical, psychological, emotional and social status. The most important aspect of rehabilitation is the individual approach. A slight disturbance in the function of the respiratory system is almost imperceptible in everyday activities, so the patient complains of slight fatigue that subsides after a short rest. Anxiety and health concerns appear, with increased dyspnea during exercise, and in a few years dyspnea will accompany daily household activities. Does that progression of the disease indicate a lack of effective treatment? Being unwell, the patients will begin to doubt their diagnosis, medications, rehabilitation and medical team. It is then necessary to reanalyze and update therapeutic treatment and rehabilitation.

***Key words*:** *education, effective treatment, respiratory rehabilitation.*

SAVREMENI PROGRAMI RESPIRATORNE REHABILITACIJE: KOME, KAKO, GDJE – OD EDUKACIJE DO EMOCIONALNE PODRŠKE U BOLESTI

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Resiratorna rehabilitacija ima najveći pozitivan učinak na tok i prognozu HOBP-a, astme i plućnih komplikacija zaostalih nakon COVID-19 infekcije. Povećan kapacitet vježbanja i adaptivna promjena ponašanja neophodni su da bi se postiglo značajno i trajno povećanje fizičke aktivnosti kod pacijenta sa ovom simptomatologijom. Da bi se promjena desila, potreban je interdisciplinarni pristup koji spaja: respiratornu medicinu, rehabilitacijske, društvene i bihevioralne nauke. Svrha rehabilitacije je vraćanje dobrog fizičkog, psihičkog, emocionalnog i socijalnog stanja pacijenta. Najvažniji aspekt rehabilitacije jeste individulani pristup. Blagi poremećaj u funkciji respiratornog sistema je gotovo neprimjetan u svakodnevnim aktivnostima, pa se pacijent žali na lagani umor koji se povlači nakon kraćeg odmora. Anksioznost i zabrinutost za zdravlje pojavljuju se sa pojačanom dispnejom tokom izvođenja vježbi, a za nekoliko godina dispneja će pratiti svakodnevne kućne aktivnosti. Da li napredovanje bolesti ukazuje na nedostatak efikasnog liječenja? Oboljeli pacijenti počinju sumnjati u pravu dijagnozu, lijekove, rehabilitaciju i medicinski tim. Potrebno je ponovo analizirati i ažurirati terapijski tretman i rehabilitaciju.

Ključne reči: *edukacija, efikasno liječenje, respiratorna rehabilitacija.*