



## The 1st Forum of the Academy of Medical Sciences of the Serbian Medical Society

The Academy of Medical Sciences of the Serbian Medical Society (Academy) gathers our most famous scientists and experts from various fields of medicine and dentistry. During the 46 years of its activity, the Academy has held over 850 scientific and educational meetings, a large number of lecture cycles for the general population at the Ilija M. Kolarac Endowment, it has published dozens of monographs and thus contributed to the promotion of the scientific and professional work of distinguished members of the Academy, as well as to the education of doctors and the popularization of science.

On March 24, 2023, the Academy will organize the *1st Forum of the Academy of Medical Sciences of the Serbian Medical Society*. It will be a scientific meeting where the research results of the members of the Academy and their coworkers will be presented and discussed with the aim of promoting their scientific work and realizing their better cooperation in subsequent studies. The topic of the *1st Forum of the Academy* is "Prevention, Diagnosis, Treatment and Control of Mass Infectious and Non-Infectious Diseases." It has been our opinion that such a broad topic would attract experts from various fields and thus illustrate the wide-ranging field of scientific interest and work of the Academy members.

Twenty-four papers have been submitted for the *1st Forum of the Academy*. The greatest attention is paid to COVID-19. The results and experiences of the clinical presentation, course, treatment, and outcome of the disease are presented, as well as the results of experimental research and presentations of various post-COVID disorders. These results and experiences are valuable guideposts for planning measures in future epidemics that infectologists and epidemiologists have been warning us about.

In addition to COVID-19, lectures will also be delivered on some important infectious diseases that are not given enough attention, and which can seriously threaten health and life. These are, above all, tuberculosis and fungal diseases, which will be discussed by our well-known experts.

The meeting dedicated to mass diseases could not but include lectures on malignant diseases. Significant results of the study of modern drugs will be presented, as well as research of insufficiently studied tumors that require additional education of doctors, especially concerning the diagnosis of these diseases.

At the Forum, there will be an opportunity to find out the results of clinical and experimental studies on cardiovascular diseases, such as pharmacogenetic studies and analyses of the results of modern methods of cardiovascular diseases treatment.

Studies from the field of dentistry confirm that modern research requires a multidisciplinary and interdisciplinary approach, which has made it possible to achieve exceptional progress in the treatment of oral and dental diseases.

In addition to the presentation from the aforementioned fields, results from ophthalmology, anesthesiology, and otorhinolaryngology will also be presented. The wide range of topics and the quality of submitted abstracts confirm that Academy members contribute significantly to professional and scientific work and the continuous progress of all fields of medicine.

We hope that at the *1st Forum of the Academy*, doctors from different specialties, as well as experts from other related fields, will gather and that a lively discussion will contribute to the quality of the meeting. We wish to all the participants that the Forum fulfills the expectations of us all – the organizers, the authors of the presented studies, and the audience – and that it will be an incentive for the Academy Forum to become a regular annual scientific meeting of the Academy.

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## ABSTRACTS

# THE 1ST FORUM OF THE ACADEMY OF MEDICAL SCIENCES OF THE SERBIAN MEDICAL SOCIETY

March 24, 2023  
Serbian Medical Society, Belgrade, Serbia\*<sup>#</sup>

## Update on diagnostic criteria for fungal rhinosinusitis and new methods for detection of fungi in sinuses

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**Introduction** The persistent fungal exposure and presence of chronic rhinosinusitis (CRS) are a certain threat for the development of fungal rhinosinusitis (FRS). The aim of this study was to consider the potential diagnostic criteria for FRS, and to evaluate the newly formed methods for detection of fungi in upper parts of respiratory tract.

**Methods** The study is the combination of clinical experiment and a case-series of 218 patients with CRS. We designed new methodological algorithms for detection of fungi in the sinuses: (i) induction of the sinonasal secretion (ISNS) with lavage and aspiration of sinonasal secretions, (ii) processing of nasal polyps (NP) to single cell suspension and (iii) interpretation of the findings of fungi.

**Results** The next prevalence has been found in the group of CRS patients: asthma 130/218 (59.6%), NP 101/218 (46.3%), FRS 50/218 (22.9%), out of whom 24/218 (10.9%) are allergic-FRS (AFRS) and 26/218 (12%) are non-allergic FRS. The results obtained with new methods were evaluated by comparison of 10 predictive criteria for FRS (FRS index) and the mycological findings. The highest specificity and sensitivity are shown in ISNS\_comb method (lavage+aspiration) with nasal pre-treatment (89%; 96%), highest positive and negative predictive value (PPV/NPV) are shown for ISNS\_comb method (94%;93%) and ISNS\_lavage method (93%;87%) with pre-treatment.

**Conclusion** The proposed sampling protocol facilitates extraction of fungi from muco-purulent secretion in patients with FRS and improves fungal detection and isolation rate. Lavage with hypertonic-NaCl should be included in the everyday hygiene routine in an effort to decrease fungal load and antigenic exposure.

**Keywords:** fungal rhinosinusitis; chronic rhinosinusitis; nasal polyps; fungi

**Conflict of interest:** None declared.

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## Clinical presentation, therapy and outcome of COVID-19 patients treated in the temporary COVID hospital “Karaburma”

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**Introduction/Objective** The WHO declared the COVID-19 pandemic on March 11, 2020. The temporary COVID hospital “Karaburma” started operating 19 days later and a total of 4083 COVID patients were treated there until February 22, 2022. The aim of this study was to analyze the first 500 patients and compare the results obtained with the same parameters in all patients treated in COVID hospital „Karaburma”.

**Methods** This study included 4083 COVID patients (65% men, 35% women) average age 59.5 years. Demographic data, clinical picture, treatment and outcome of all patients were analyzed.

**Results** Out of the first 500 patients, 226 (45.2%) had bilateral pneumonia, 23 (4.6%) ARDS, of which 43 (8.6%) were treated in the ICU, compared to 612 (15.0%) of 4083 included in the study. Comorbidities (heart disease, diabetes, etc.) were registered in 235 (47%) of 500 patients. Out of the first 500 patients, 350 (65%) received antibiotics, 214 (42.8%) hydroxychloroquine, 72 (14.4%) oxygen, 150 (30%) anticoagulant therapy, and 64 (12.8%) corticosteroids. Among them, 18 (3.6%) received non-invasive and 21 (4.2%) mechanical ventilation. After the first pandemic wave, all patients received anticoagulant therapy, and dexazone only patients who received oxygen. Out of 4083 patients, 144 (3.52%) received Tocilizumab, and 86 (2.1%) Baricitinib. In the first pandemic wave, 32 (6.4%) of 500 patients died, while mortality in the entire group was 363 (8.9%) patients, of which 262 (72.2%) were men.

**Conclusion** The severity and outcome of COVID-19 depend on the pandemic wave and the patient’s comorbidities. A multidisciplinary approach plays a very important role.

**Keywords:** COVID-19; treatment; outcome

**Conflict of interest:** None declared.

## Invasive fungal infections – analysis of non-neutropenic patients with invasive aspergillosis treated at the Military Medical Academy in the period from 2008 to 2022

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**Introduction/Objective** Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality in patients in intensive care units (ICUs) and after solid organ or hematopoietic stem-cell transplantation (HSCT). Diagnosis of IFIs before death is successfully established in only 12% of patients. The number of patients with invasive aspergillosis (IA) is increasing, especially in ICU, and it is the leading cause of death among IFIs. The aim of this report is to present the clinical characteristics, therapy applied and comorbid conditions in non-neutropenic patients with IA.

**Methods** A total of 57 non-neutropenic patients with IA, of average age 56 years (26 women, 31 men) were treated in the clinic in the period from 2008 to 2022. The diagnosis of IA was established on the basis of radiological procedures, biological material, serology tests and histopathological findings.

**Results** Pulmonary IA was found in 46 (80.7%), rhino-orbital cerebral IA in 4 (7.0%), IA of the paranasal sinuses in 5 (8.7%) and IA of the skin in 2 (3.51%) patients. In these patients various comorbidities were found (tumors, bronchiectasis, IgA immunodeficiency, corticosteroid therapy, diabetes mellitus and others). Treatment was carried out with itraconazole, voriconazole or echinocandins, and 31 (54.4%) patients underwent surgical procedures. By the beginning of 2023, 18 (31.58%) patients had died.

**Conclusion** Diagnosis and therapy of IA in non-neutropenic patients must be accompanied by malignancy and/or immunodeficiency tests. It is possible to increase the survival rates of these patients with regular clinical, microbiological and morphological monitoring.

**Keywords:** invasive aspergillosis; diagnosis; treatment; risk factors

**Conflict of interest:** None declared.

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## Prophylaxis and treatment for viral infections in 355 patients with hematopoietic stem cell transplants treated at the Military Medical Academy

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**Introduction/Objective** Viral infections are a significant cause of morbidity and mortality in patients with allogeneic hematopoietic stem cell transplants (allo-HSCT). Underlying disease, conditioning regimens, source of stem cells, and immunosuppressive therapy after allo-HSCT favor different infections in the post-transplant period. The aim of this work is to present the frequency and type of viral infections in patients with allo-HSCT at the Military Medical Academy and the modalities of treatment.

**Methods** The study included 355 patients (144 women, 211 men) of mean age 29 years, who underwent allo-HSCT at the HSCT Center of the Hematology Clinic of the Military Medical Academy between 1995 and 2017. Allo-HSCT was performed in 130 patients with acute myeloid leukemia, 102 with acute lymphoblastic leukemia, 22 with multiple myeloma and 101 patients with other malignant hemopathies. The type of donor, source of hematopoietic stem cells, type of conditioning regimen and GvHD prophylaxis were analyzed.

**Results** Reactivation of VZV infection was registered in 21 (6.0%) patients, hemorrhagic cystitis associated with BK polyoma virus (BKPyV) in the early phase in 21 (6.0%), in the late phase in 15 (4.2%), influenza in 2 (0.5%) patients, CMV reactivation in 63 (17.3%), reactivation of HBV infection in 6 (1.69%) and HCV infection in 2 (0.56%) patients. Antiviral drugs were used for prophylaxis, pre-emptive and targeted therapy.

**Conclusion** Viral infections are a significant cause of morbidity and mortality in patients after allo-HSCT. This requires monitoring and the application of prophylactic, pre-emptive or direct therapy.

**Keywords:** viral infections; allo-HSCT

**Conflict of interest:** None declared.

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## Antioxidant and free radical species in the aqueous humor of patients with age-related cataract

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**Introduction/Objective** Age-related cataract is a significant cause of visual impairment worldwide. Oxidative damage and the effects of free radical species are considered important in the etiopathogenesis of cataracts. The aim of this study was to evaluate antioxidant capacity and oxidative stress in the aqueous humor of patients with age-related cataracts of different maturity.

**Methods** The clinical and biochemical investigation involved 55 patients with age-related cataract. According to cataract maturity, the patients were classified into incipient (cortical C, 18 pts, nuclear N, 20 pts) and mature (M17 pts) groups. The antioxidant activity of aqueous humor was measured by the reduction power (RP) method and the activity of glutathione peroxidase (Gpx) spectrophotometrically. Changes in the concentrations of hydroxyl and ascorbyl radicals were detected by electron spin resonance spectroscopy.

**Results** Both RP and GPx activity were significantly ( $p < 0.001$ ) reduced in group N compared to group C and in group M compared to group N. Concentrations of hydroxyl ( $29.45 \pm 1.01\%$  in group C,  $38.12 \pm 1.29\%$  in group N and  $74.14 \pm 2.52\%$  in group M) and ascorbyl radicals ( $26.12 \pm 0.89\%$  in group C,  $41.15 \pm 1.39\%$  in group N and  $83.56 \pm 2.84\%$  in group M) increased significantly ( $p < 0.001$ ) with progression of age-related cataract. Significant negative correlation ( $r = -0.759$ ,  $p < 0.001$ ) was detected between the concentrations of hydroxyl radicals and GPx activity.

**Conclusion** Our data support the hypothesis that antioxidant capacity decreases with production of reactive hydroxyl radicals that are involved in the aetiology of age-related cataract.

**Keywords:** cataract; antioxidant enzyme; hydroxyl radical; ascorbyl radical

**Conflict of interest:** None declared.

## Experiences Acquired During the COVID-19 Pandemic for the Future Organization of Work in Medical Education and Scientific Research

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**Introduction/Objective** With the beginning of the pandemic and the announcement of the state of emergency, the healthcare system faced two unfamiliar issues. One was the treatment of the infected people and the timely receipt of protocols for assessment, triage, testing and therapy, and the other one was the protection of healthcare professionals. The aim of this study is to present experiences acquired during the COVID-19 pandemic and emphasize the importance of continuous medical education and multidisciplinary approach for work organization of healthcare professionals.

**Methods** The authors analyze the identified problem comprehensively, from a comparative law perspective, analyzing the legislation of European states and national laws.

**Results** In the first part of the study, we analyze the inclusion of certain medications in the treatment of patients with COVID-19 in EU countries and Serbia, while in the second part we analyze whether the right to safe and healthy working conditions was denied to healthcare professionals in Serbia during the pandemic. Since both of considered issues cause serious disputes between doctors and lawyers, it was necessary to prepare special strategies and protocols for the triage of the most vulnerable patients in case of a new pandemic, and to dedicate special attention to the organization of the work of healthcare professionals. We have determined that the human rights of healthcare workers have been violated and identified in which spheres of human rights violations have occurred in particular.

**Conclusion** Continuing medical education, respecting the rights of healthcare professionals and ensuring working conditions are necessary elements for a successful fight against health-related crises.

**Keywords:** COVID-19; healthcare workers; treatment protocols; the right to safe and healthy work

**Conflict of interest:** None declared.

# Intratemporal facial nerve paralysis: morphologic basis, clinical and microsurgical implications

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**Introduction/Objective** Facial nerve palsies are a common and significant presentation, specifically to ear surgeons, but also in general medical practice. They result from facial nerve dysfunction due to different etiologic factors (trauma, infections, tumors). Inflammatory processes of the middle ear may involve the facial nerve at any point, especially where exposed. The aim of this study is to present our experience with facial nerve paralysis of otitic origin from the anatomical, histopathological and surgical aspects.

**Methods** Anatomical studies were performed on a large collection of temporal bones (2000) to evaluate variations of the facial canal (course, dehiscence, protrusion). The histopathological analysis was done on temporal bones with chronic otitis media to investigate a pathological process involving the facial canal and nerve with and without clinical facial impairment. The clinical studies included 64 patients treated for facial paralysis due to chronic otitis media.

**Results** The most significant anatomical finding in the fallopian canal was the high incidence of dehiscence (defect >0.4 mm) in the tympanic segment close to the oval window (60%). In temporal bones with chronic otitis media, the affected facial nerve showed degenerative changes (demyelination, hypertrophy, proliferation of Schwann cells) and an area with small dark globules resulting from cellular and myelin degeneration. The pathological process was commonly localized in the destroyed tympanic part of the facial canal and the exposed nerve and correlated with clinical and surgical findings.

**Conclusion** Otitis media may be associated with degenerative changes in the facial nerve without clinical impairment of its function, but may have the potential for development of facial paralysis.

**Keywords:** facial nerve paralysis; clinical implication

**Conflict of interest:** None declared.

# The first presenting feature of long COVID 19 infection and acute inflammatory demyelinating polyneuropathy

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**Introduction/Objective** Certain severe neurological illnesses associated with long COVID-19 include immune neuropathies like Guillain-Barré syndrome (GBS) and exacerbation of pre-existing chronic inflammatory demyelinating polyneuropathy (CIDP). The aim of this study was to determine the prevalence of pain in patients with acute inflammatory demyelinating polyneuropathy (AIDP) and to analyze sociodemographic, clinical predictors for the occurrence of pain, clinical phenotype and course of the pain.

**Methods** A total of 124 patients with recently diagnosed long COVID-19 infection presented at the Pain Clinic, UCC of Vojvodina, Novi Sad. The research was conducted with the consent of the Ethics Committee of the Faculty of Medicine, University of Novi Sad. Data were collected monthly for one year.

**Results** The patients had pain, bilateral lower extremity weakness, mute reflexes and sensory loss. Pain was present in 62 patients, 3 months after the onset of symptoms, but only five patients had neuropathic pain. More pronounced deficits, age, female gender, the presence of protein in cerebrospinal fluid, occurrence of sensory symptoms and dysautonomia were recorded as predictors for maintaining pain. When comparing types of pain, non-neuropathic pain was more frequent but less intense and had fewer consequences on the mental health of the sufferer. Musculoskeletal pain persisted for up to 2 years in as many as 1/3 of the patients.

**Conclusion** Neuropathic pain in AIDP was experienced by 3.72% of the total number of patients; 50% of all patients mentioned pain as a symptom. After 3 months, neuropathic pain was recorded in less than 10% of the total number of patients.

**Keywords:** COVID-19; inflammatory demyelinating polyneuropathy; acute; chronic

**Conflict of interest:** None declared.

## Gender difference in the perception of acute postoperative pain in laparoscopic surgery and application of multimodal analgesia

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**Introduction/Objective** Multimodal analgesia consists of nonsteroidal anti-inflammatory drug application 1 hour before surgery, followed by nerve block, skin infiltration with a local anesthetic, use of opioids perioperatively, infusion of the local anesthetic into the peritoneal cavity, and regular fluid and electrolyte therapy. This study was aimed at examining gender differences in the perception of acute postoperative pain after laparoscopic surgery.

**Methods** This prospective, randomized study included 220 patients who underwent laparoscopic surgery between January 2021 and January 2022 at the Clinic for abdominal, endocrine and transplantation surgery (UCC of Vojvodina, Novi Sad). The local anesthetic levobupivacaine (0.25%) was administered in the region of the cholecyst, on the right side of the diaphragm, intraperitoneally and in incisional wounds. The patients were included voluntarily in the study, with written consent. The investigation had the consent of the Ethics Committee of the Faculty of Medicine, University of Novi Sad and the Department of Surgery.

**Results** There were 70 male (31.8%) and 150 female (68.2%) patients in separate groups. A gender difference in pain perception was noted early in the postoperative period and was statistically significant in the first hour ( $t = 1.9$ ;  $p < 0.05$ ) and second hour ( $t = 2.05$ ;  $p < 0.05$ ) postoperatively. Female patients reported greater pain intensity compared to male patients, and they required a higher dose of opioid analgesics postoperatively.

**Conclusion** Intraperitoneal application of the local anesthetic, 0.25% levobupivacaine, during laparoscopic cholecystectomy significantly lowers the intensity and duration of acute postoperative pain. Female patients require a higher dose of this anesthetic due to differences in hormonal status between males and females.

**Keywords:** laparoscopic cholecystectomy; multimodal analgesia; pain

**Conflict of interest:** None declared.

## Physical and biological properties of TiN doped with Ag and Cu by combined methods of cathodic arc evaporation and DC magnetron sputtering

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**Introduction/Objective** Recently, one of the most important complex issues in medicine is the deposition of protective nanocoatings on the surface of medical implants using various plasma procedures. By combining cathodic arc evaporation and magnetron sputtering, a hard TiNx nanocoating can be obtained. This functions by protecting the human body from penetration by any released heavy metal ions present in the composition of different types of implants. In addition, in order to improve the antimicrobial properties of medical implants, an antimicrobial nanocoating is usually applied to their surface, those containing Cu and Ag ions.

**Methods** The methods used for characterization of these coatings include: X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), ellipsometry, inductively coupled plasma (ICP) and a procedure for determination of the wetting angle together with antimicrobial tests.

**Results** TiNx thin films of thickness 29 to 176 nm, were obtained by a combination of cathodic arc deposition and DC magnetron sputtering. The phase composition of the films was determined by a combination of XRD, XPS, FTIR, ellipsometry. Thickness and morphology of the coatings were determined using a combination of ellipsometry and SEM methods. The wetting angles showed that a TiNx nanocoating covered with Cu is superhydrophobic, while that covered with Ag is superhydrophilic. Therefore, rates of release of Cu and Ag ions differ greatly, which leads to differences in their antimicrobial properties.

**Conclusion** TiNx nanocoatings in combination with Cu or Ag nanocoatings possess very important barrier and antimicrobial properties, which are extremely relevant in the development of new medical implants in dentistry and orthopedics.

**Keywords:** cathodic arc evaporation; DC magnetron sputtering; nanocoatings; ellipsometry; XRD

**Conflict of interest:** None declared.

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## Out-of-hospital cardiac arrest before and after the COVID-19 pandemic – a comparison

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**Introduction/Objective** Pandemic coronavirus disease 2019 (COVID-19) caused much disruption in the functioning of health care systems throughout the world. As a consequence, significant deterioration of health of the population was observed. The aim of this study was

to determine if the COVID-19 pandemic affected management of cardiac arrest (CA) and the survival rate of patients with out-of-hospital CA (OHCA) in this area.

**Methods** An observational before-and-after study was carried out to determine the effects of COVID-19 pandemic on the survival of patients with OHCA, who were given cardiopulmonary resuscitation (CPR) by the emergency medical services (EMS) teams. The study was conducted between 1 March 2018 and 1 March 2022, with two equal observation periods: prior to the outbreak of the pandemic (Group I) and after it (Group II).

**Results** A total of 958 patients formed Group I (434 pts; 45.30%) and Group II (524 pts; 54.64%) ( $p < 0.05$ ). No significant difference was found for age, sex, time of arrival of the EMS teams, initial rhythm and adrenaline administration between them. However, patients in Group I were more often intubated ( $\chi^2=8.737$ ;  $df=3$ ;  $p=0.033$ ). Moreover, amiodarone ( $\chi^2=6.508$ ;  $df=1$ ;  $p=0.011$ ) and saline solution ( $\chi^2=5.510$ ;  $df=1$ ;  $p=0.019$ ) were administered to relatively more patients in this group. Return of spontaneous circulation (ROSC) and prehospital survival rates were significantly higher in Group I (18.4%) than in Group II (12.6%) ( $\chi^2=5.685$ ;  $df=1$ ;  $p=0.017$ ).

**Conclusion** The COVID-19 pandemic led to an increase of OHCA. ROSC and prehospital survival rates were higher in the prepandemic period. The management of OHCA by EMS teams may have affected the results.

**Keywords:** coronavirus disease 2019; cardiopulmonary resuscitation; sudden cardiac arrest; survival

**Conflict of interest:** None declared.

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## The first recognized human case of multilocular echinococcosis in Serbia

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**Introduction** *Echinococcus multilocularis*, causes multilocular or alveolar echinococcosis, which differs from infection caused by *Echinococcus granulosus* in clinical presentation in humans. The most common definitive hosts for *E. multilocularis* are foxes and jackals, while domestic mammals like dogs and cats are rare. Humans are rare and accidental intermediate hosts. Cystic echinococcosis in humans is endemic in Serbia, while more severe alveolar echinococcosis has not yet been recorded.

**Case Outline** We present a case of a 67-year-old female from a small village in Sremska Mitrovica municipality. The onset of symptoms began a few years ago. The main one was liver pain which progressed over time. Differential diagnoses included benign liver tumors like haemangioma, cystic echinococcosis and abscess formed in the cystic echinococcal lesion. Left lateral hepatectomy was performed, and S II /III liver segments were removed. Pathological examination clearly showed multilocular echinococcosis with numerous small and empty vesicle spaces with chitin membrane without protoscolices, surrounded by massive fibrosis and infiltrative type of growing into the liver parenchyma. Surgical margins were found positive for echinococcal vesicles showing that echinococcal tissue was not completely removed. Thus albendazole therapy was recommended. Epidemiological interview revealed that the patient lives in an endemic region of multilocular echinococcosis, in a house with two hunting dogs, and back yard where contamination of soil with fox faeces is possible.

**Conclusion** This is the first recorded human case of multilocular echinococcosis in Serbia. Therefore, we must improve prophylactic and diagnostic procedures and surgical techniques to cure this zoonotic disease.

**Keywords:** *Echinococcus multilocularis*; human case; Serbia; Srem region; Mačva region; Vojvodina Province

**Conflict of interest:** None declared.

## Activity of essential oils against the most important endodontic pathogen – *Enterococcus faecalis*

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**Introduction/Objective** In the resistance-growing era, the necessity to modulate oral biofilm with nature-based products including essential oils (EOs) is recognized. The aim of this systematic review is to summarize the antibacterial activity of numerous EOs against the main infected root canal pathogen – *Enterococcus faecalis*.

**Methods** Minimal inhibitory concentrations (MIC) of 56 EOs were determined in the microdilution assay. The data was processed in Microsoft Excel and analyzed in IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

**Results** Among tested EOs, 20 achieved ultrahigh antibacterial effect (MIC < 0.5 mg/mL), nine achieved high effect (MIC ≥ 0.5 mg/mL), nine achieved moderate effect (MIC ≥ 1 mg/mL), while 18 had the weakest potential (MIC ≥ 2 mg/mL). A high abundance of oxygenated monoterpenes was observed in EOs with stronger antibacterial effects (80%, 66.7%, and 77.8% of total content within EOs with ultrahigh, high, and moderate potential, respectively). EOs possessing weak potential had a lower share of oxygenated monoterpenes (44.4%), but the share of monoterpene hydrocarbons (27.8%) was notable. The most dominant constituents in the EO group with ultrahigh effect were 1.8-cineole (4/20), thymol (3/12), and geraniol (2/20), while in the weakest effect oils the most abundant were α-pinene (3/18), 1.8-cineole (2/18), and β-pinene (2/18).

**Conclusion** Although interactions among constituents should not be underestimated, EOs rich in oxygenate monoterpenes and especially thymol (3/12) and geraniol (2/20) seem to have promising antibacterial potential. Further studies are required to estimate to possibility of their implementation in dentistry.

**Keywords:** essential oils; *Enterococcus faecalis*; minimal inhibitory concentration; oral bacteria; oral biofilm

**Conflict of interest:** None declared.

## Clinical presentation, diagnosis and outcome of tuberculous meningitis: our experience in the treatment of 31 patients

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**Introduction/Objective** Tuberculous meningitis (TM) is characterized by a course leading to the emergence of permanent sequelae or death, especially in cases where specific therapy was not started early. The goal of this study was to evaluate the clinical presentation, therapy and outcome of patients with TM treated at our Clinic over a 27-year period.

**Methods** This retrospective study included 31 patients with TM of average age 36.3±17.2 years. Diagnosis was made on the basis of an appropriate clinical presentation, cytological and microbiological findings and the subsequent response to anti-tuberculous therapy (ATT). Disease outcome was defined as recovery, recovery with sequelae and death.

**Results** The time from onset of TM to hospital admission was 15 (2-120) days. The number of lymphocytes in cerebrospinal fluid (CSF) was predominant in 28 (90.3%) patients. The CSF and blood glucose ratio was lower than 0.5 in 28 (90.3%) patients. *M. tuberculosis* was detected in CSF in 4 (12.9%) cases, while this microorganism was isolated in cultures from 12 (38.7%) patients. Continuous ATT was initiated in 29 (93.5%) patients with adverse effects registered in 22 (75.9%) cases. Corticosteroids were given to 23 (74.2%) patients. Complete recovery was recorded in 18 (58.1%) patients. Another 9 (31.0%) patients recovered with permanent neurological sequelae. A fatal outcome was noted in 4 (12.9%) cases, 2 (6.5%) of which occurred before diagnosis of TM.

**Conclusion** Early diagnosis and correct therapy of TM can significantly reduce the high morbidity and mortality associated with this illness.

**Keywords:** tuberculous meningitis; treatment; outcome

**Conflict of interest:** None declared.

## Gender difference in inflammatory and coagulation factors in hospitalized patients with COVID-19

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**Introduction/Objective** Male sex is associated with greater severity and mortality from coronavirus disease 2019 (COVID-19), although infection is equally distributed between men and women. The study aimed at investigating sex differences in the hyperinflammatory immune response to SARS-CoV-2 infection and consequent thrombosis using the linked cytokine profile and blood laboratory data.

**Methods** The observational cohort study involved 99 COVID-19 patients (69 males and 30 females), hospitalized between March 2021 and April 2022. Their clinical/laboratory data were collected to examine sex differences in oxidative stress, neutrophil extracellular traps (NETs) formation and plasma cytokines at hospital admission and up to 5 months of recovery.

**Results** Dihydrotestosterone (DHT) levels were transiently reduced, while sex hormone binding globulin levels decreased continuously in male post-COVID-19 patients after the rise at diagnosis. Pro-inflammatory interleukin-6 (IL-6) and

interferon-gamma were generally increased at diagnosis, while IL-6 level fell in post-COVID-19 patients. Tumor necrosis factor-alpha exhibited a 5-fold increase in females at diagnosis. The chemokines IL-8 and monocyte chemoattractant protein-1 and the coagulation markers intercellular adhesion molecule-1 and E-selectin were consistently upregulated in female COVID-19 and post-COVID-19 patients, in contrast to vascular cell adhesion molecule-1 and P-selectin. DHT increased reactive oxygen species (ROS) in neutrophils of male patients, while estrogen decreased ROS in female patients. NET markers, such as circulating DNA and myeloperoxidase, were significantly increased in the plasma of patients. Sex hormone levels were positively correlated with coagulation markers.

**Conclusion** Markers of chemotaxis, endothelial dysfunction and inflammation are still detectable and partially sex dependent in COVID-19 patients 5 months after hospital admission.

**Keywords:** COVID-19; sex hormones; neutrophil extracellular traps; oxidative stress; cytokines

**Conflict of interest:** None declared.

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## Advanced colorectal adenomas in healthy members of families with Lynch syndrome

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**Introduction/Objective** Lynch syndrome (LS) is an autosomal dominant disorder characterized by early age of onset, the development of cancers in different organs and microsatellite instability. According to Amsterdam criteria at least three relatives may have colorectal or LS-associated cancer. Synchronous and metachronous tumors are common in LS. The aim of our study was to analyze the colonoscopy findings in healthy members of families with LS knowing that colorectal cancer arises from colorectal adenomas.

**Methods** Complete colonoscopies up to the cecum were performed in 68 healthy members of 16 families with LS. All colorectal polyps were removed by snare polypectomy or mucosectomy. Advanced adenomas (AA) were defined by a villous structure and/or high-grade dysplasia and/or a diameter of 10 mm or more.

**Results** In 33 (48.5%) healthy members, 42 adenomas (5-25mm) were detected in all colorectal segments. Thirty (71.4%) adenomas were detected proximal to the splenic flexure. AA were found in 10 (14.7%) healthy members, 6 of them in the cecum and ascending colon, 2 in the transverse and 2 in the descending colon. One healthy member had synchronous AA in different segments of the colon.

**Conclusion** AA are common in healthy members of families with LS. Complete colonoscopy to the cecum is the diagnostic method of choice. Polypectomy or mucosectomy of adenomas, particularly AA breaks the last link in the chain from adenoma to colorectal carcinoma and thus prevents the development of colorectal carcinoma.

**Keywords:** Lynch syndrome; advanced adenoma; colonoscopy

**Conflict of interest:** None declared.

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## Women's oral health as a public health indicator (Case Study Serbia)

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**Introduction/Objective** Prevalence of oral diseases is over 90% and gender also plays an important role. Women show better preventive behavior in oral health than men, but their dentition is often incomplete.

The aim of this study was to examine the state of women's oral health in Vojvodina and the use of dental health care (demographic, socio-economic determinants, dental anxiety) to assess the impact of oral health on women's quality of life.

**Methods** The research was conducted as an epidemiological cross-sectional study. Questionnaires: on general and dental health status, on the impact of oral health on quality of life (OHIP-14), for the assessment of dental anxiety (DAS), and the Modified Oral Health Assessment Form for Adults of the World Health Organization, were used.

**Results** 1900 women aged 16 years and over were included. The results showed that the better dental and periodontal status of women was negatively correlated with age ( $t=24,242$ ;  $p=0,000$ ) and positively correlated with education ( $\chi^2$  test;  $\chi^2=70,919$ ;  $p=0,000$ ), material condition ( $\chi^2$  test;  $\chi^2=67,716$ ;  $p=0,000$ ) and employment status ( $\chi^2$  test;  $\chi^2=30,630$ ;  $p=0,000$ ). The most important predictors of good oral health of women were a high level of education and financial status, employment, the existence of partners and social support. The coverage of women with regular dental examinations was less than 20%.

**Conclusion** This research confirmed the public health importance of women's oral health. Our results are useful for future research and the creation of programs for prevention of oral diseases and improvement of oral health in women.

**Keywords:** oral health; women; public health

**Conflict of interest:** None declared.

## Subacute thyroiditis (De Quervain) during the COVID-19 pandemic

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**Introduction/Objective** Dysfunction of the thyroid gland, usually transient, was observed in approximately 15% of patients with mild to moderate symptoms of COVID-19 since the receptor for ACE2, used by SARS-CoV-2 virion for cell entry, is highly expressed in thyroid tissue. Subacute thyroiditis (SAT) is an inflammatory disorder of the thyroid gland associated with viral infection (direct viral toxicity or an inflammatory response to the virus): mumps, measles, rubella, coxsackie, and adenoviruses. There is increasing evidence that SARS-CoV-2 can also be considered responsible for causing subacute and atypical thyroiditis. The aim of the study was to analyze the effect of COVID-19 infection on appearance and disease course of SAT.

**Methods** In the period 2006–2021, a total of 66 patients were treated for SAT at our clinic. During the COVID-19 pandemic (years 2020 and 2021), seven new patients with SAT were presented. In year 2022 no new patients were registered at our clinic. The diagnosis was made on the basis of the anamnesis (pain in the neck and thyroid gland), high erythrocyte sedimentation rate and CRP, ultrasound, and occasionally thyroid aspiration cytology (epithelioid cell findings).

**Results** In four out of seven patients who previously had COVID-19, SAT had an atypical course: two patients had normal ultrasound findings, one patient had anamnesis of a painful neck, while the palpation findings during the ultrasound examination of the thyroid gland were normal, and one suffered a relapse of SAT after five years.

**Conclusion** SAT after SARS-CoV-2 infection has presented an atypical course in four out of seven patients treated at our institution. More investigation is required in order to associate the atypical course of SAT with SARS-CoV-2 infection.

**Keywords:** COVID-19; thyroid gland; subacute thyroiditis; SARS-CoV-2 infection

**Conflict of interest:** None declared.

## Development of the TAVR program at the Institute for Cardiovascular Diseases of Vojvodina

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**Introduction/Objective** Aortic stenosis is the most common valvular heart disease in elderly patients. In patients with high risk for surgical aortic valve replacement, TAVR (transcatheter aortic valve replacement) is method of choice. Since its introduction in 2002, the number of TAVR has been growing exponentially. We present the results of the TAVR program at the Institute for Cardiovascular Diseases of Vojvodina.

**Methods** During 2022, the procedure was performed in 23 patients with symptomatic severe aortic stenosis and high risk for surgical aortic valve replacement. The decision to perform the TAVR procedure was made by the TAVI team.

**Results** Mean age of the patients was 75.6 years and 57% of patients were men. Medtronic Evolut R valve was implanted in 16 patients (69.5%), the Abbott Portico valve in 7 patients (30.5%). Direct valve implantation was performed in 56.5% of patients. Valve predilatation was performed in 43.5% of patients, while valve postdilatation in 17.4% of patients. In all patients, the procedure was performed through a transfemoral access. Ultrasound-guided puncture was performed in 65.2% of patients, and in 34.8% of patients it was guided by angio-guidewire-ultrasound. Aortic regurgitation was not registered in 52.6% of patients, and mild aortic regurgitation was registered in 47.4% of patients. The average peak to peak gradient is 7 mmHg. The mean value of maxPg was 16.8 mmHg. In one patient, a pacemaker was implanted after the procedure. Vascular complications were noted in 11.8% of patients.

**Conclusion** Results indicate a low percentage of complications with favorable outcome in patients treated with the TAVR procedure.

**Keywords:** aortic stenosis; TAVI; transfemoral access

**Conflict of interest:** None declared.

## Effects of metformin and its combinations with other repurposed drugs on fibrosarcoma in hamsters

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**Introduction/Objective** Many drugs registered for various other indications can act selectively on tumor receptors, signaling pathways, metabolic processes, bioenergetic factors, enzymes, proteins and genes that regulate proliferation, apoptosis and neoangiogenesis of the tumor without affecting these activities in healthy cells. The introduction of new drugs is a very long, complex and expensive process of research. Detecting an anticancer effect in drugs already registered for other indications and forming combinations, may directly reduce the time and cost of such research.

**Methods** The anticancer efficacy of metformin and its combinations with caffeine, itraconazole, nitroglycerin and mebendazole was tested on fibrosarcoma experimentally induced by BHK21/C13 cells in Syrian golden hamsters (6 animals per group, randomly allocated to control and experimental groups, doses equivalent to usual human doses). After animal sacrifice, tumors were excised and their size, biophysical characteristics, histology and immunohistochemistry were assessed. Blood samples were collected for hematological and biochemical analyses and the main organs were toxicologically analyzed. Statistical significance was determined by one-way ANOVA followed by the Student-Newman-Keuls post hoc test.

**Results** Only two-drug combinations of metformin with caffeine or itraconazole or nitroglycerin showed significant antitumor effects on hamster fibrosarcoma compared to control, regarding all tested tumor parameters ( $P < 0.05$ ) without toxicity.

**Conclusion** Administration of metformin in combination with caffeine or itraconazole or nitroglycerin might be an effective and safe approach in novel nontoxic adjuvant anticancer treatment.

**Keywords:** metformin; caffeine; itraconazole; nitroglycerin; hamsters; fibrosarcoma

**Conflict of interest:** None declared.

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## Experimental evaluation of the effects of anticancer modulation therapy on MAPK/PI3K/AKT/mTOR/NF-kB signaling with non-toxic drugs

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**Introduction/Objective** The large diversity in molecular mechanisms of cancer regulation allows some marketed pleiotropic non-oncological non-toxic pharmaceuticals to be used in oncology, which may reduce the duration and cost of research on novel anticancer treatment. At present, there are no published results *in vivo* on the anticancer effects of certain combinations of non-oncological pleiotropic drugs (disulfiram, diclofenac, nitroglycerin, metformin, deoxycholic acid, mebendazole) that influence MAPK/PI3K/AKT/mTOR/NF-kB signaling.

**Methods** The anticancer effects of the aforementioned repurposed drug combinations at 20-50% LD<sub>50</sub> (equivalent to the usual human dose) were assessed by fibrosarcoma growth kinetics (measured daily *in vivo* with calipers) and tumor apoptosis markers (COX4, cytochrome C) in hamsters, randomly allocated to control and experimental groups (6 animals per group). The animals were sacrificed 15-18 days after BHK-21/C13 tumor inoculation. Tumors were excised, measured and blood collected. Biophysical, pathohistological, toxicological, hematological, biochemical and statistical analyses were performed.

**Results** Disulfiram with metformin, disulfiram with deoxycholic acid and deoxycholic acid with metformin were combinations that showed significant antitumor effects on fibrosarcoma growth kinetics and tumor apoptosis markers in hamsters ( $P < 0.05$ ). All examined drugs in efficacious combinations could inhibit MAPK/PI3K/AKT/mTOR/NF-kB signaling. Addition of the NF-kB stimulator, mebendazole, to effective two-drug combinations rescued cancer growth, indicating that these pathways may be responsible for the antitumor action.

**Conclusion** The combinations of non-oncological drugs: disulfiram with metformin, disulfiram with deoxycholic acid and deoxycholic acid with metformin have the potential to be used as effective non-toxic adjuvant anticancer therapy in oncology.

**Keywords:** disulfiram; deoxycholic acid; metformin; hamsters; BHK-21/C13; fibrosarcoma; signal pathway

**Conflict of interest:** None declared.

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## Cardiovascular precision medicine – the role of pharmacogenetic testing

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**Introduction/Objective** Dual antiplatelet therapy (DAPT) with aspirin plus a P2Y<sub>12</sub> R inhibitor (clopidogrel or 3<sup>rd</sup> generation drugs such as ticagrelor or prasugrel) is the standard of care after percutaneous coronary intervention (PCI) to reduce the risk of major adverse cardiovascular events (MACEs). Clopidogrel is a prodrug that requires CYP2C19-catalyzed metabolism to its active form. The gene for the enzyme CYP2C19 is highly polymorphic, so we may distinguish normal metabolizers (NM), intermediate metabolizers (IM) and poor metabolizers (PM). The main objective of our study was to identify IM and PM patients who should be treated with ticagrelor or prasugrel and NM patients, who should receive clopidogrel after PCI for prevention of MACEs.

**Methods** Using the PCR method in DNA from whole blood of patients after PCI, we analyzed the genotype of 70 patients of average age 66.89 years.

**Results** The results of our study are as follows: among female patients 71.43% were NM and 28.57% were PM; among male patients 80% were NM, 17.14% were IM and 2.86% (one patient) PM.

**Conclusion** According to our results that are compatible with genotyping data from other studies on the European population, we may conclude that more than 70% of our patients ≥65 years old are NM and may receive genotype-guided long-term clopidogrel therapy for prevention of MACEs after PCI. This pharmacogenetic testing enables a precision approach in cardiovascular medicine, as for older patients clopidogrel shows a safer profile (lower rate of bleeding events) in comparison with prasugrel and ticagrelor.

**Keywords:** dual antiplatelet therapy; pharmacogenetic testing; percutaneous coronary intervention; clopidogrel; precision medicine

**Conflict of interest:** None declared.

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