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TEACHING INSTITUTE
OF PUBLIC HEALTH

Creating a Healthier Future

REVIEW 2019

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in Current Contents and other indexed journals

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Zagreb, 2020

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Miljenko Grbić

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FOREWORD

The *2019 Review of Scientific articles in Current Contents and other indexed journals* is an annual report on scientific papers by the employees of the Andrija Stampar Teaching Institute of Public Health published in *Current Contents* journals and other indexed journals. The first chapter brings 25 abstracts of original scientific papers and reviews published in *Current Contents* journals (there were 18 such papers in 2018) and the second one – five papers published in other indexed journals.

In 2019, there were 53 scientists in the Teaching Institute: 38 with doctoral degrees and 15 with master's degrees. The percentage of female scientists dominates (4 in 5) the overall number: 43 female scientists versus 10 male scientists.

The number of papers in *2019 Review* reveals that 2019 was even more successful than 2018 for the Teaching Institute in terms of scientific work. So we congratulate the employees of the Institute and their external associates for any scientific contribution.

Institute Head
Zvonimir Šostar

1. ORIGINAL SCIENTIFIC AND REVIEW ARTICLES IN CURRENT CONTENTS

1.1. A “PATHOGENIC NEEDLE” IN A “COMMENSAL HAYSTACK”: GENETIC VIRULENCE SIGNATURES OF *CORYNEBACTERIUM GLUCURONOLYTICUM* THAT MAY DRIVE ITS INFECTIOUS PROPENSITY FOR THE MALE UROGENITAL SYSTEM

Medical Hypotheses. 2019;126:38-41

Impact factor: 1.322

Meštrović T^{1,2}, Wilson J³, Ljubin Sternak S^{4,5}, Sviben M^{4,6}, Bedenić B^{4,7}, Barać A^{8,9}, Neuberg M², Drenjančević D^{10,11}, Ribić R², Kozina G²

¹ Polyclinic “Dr. Zora Profozić”, Zagreb, Croatia

² University Centre Varaždin, University North, Varaždin, Croatia

³ Sint Maarten Medical Center, Sint Maarten

⁴ University of Zagreb School of Medicine, University of Zagreb, Zagreb, Croatia

⁵ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁶ Croatian National Institute of Public Health, Zagreb, Croatia

⁷ University Hospital Centre Zagreb, Zagreb, Croatia

⁸ Clinical Centre of Serbia, Belgrade, Serbia

⁹ Faculty of Medicine, University of Belgrade, Belgrade, Serbia

¹⁰ Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

¹¹ University Hospital Centre, Osijek, Croatia

tomislav.mestrovic@gmail.com

Abstract

The predominance of the genus *Corynebacterium* in the healthy male urogenital system contributes to the resident microbiome of not only the distal urethra, but potentially the proximal urethra and urinary bladder as well. However, for certain species in this genus, pathogenic potential was described, and the salient representative is *Corynebacterium glucuronolyticum* (*C. glucuronolyticum*) implicated in cases of urethritis and prostatitis in men. Nonetheless, some still question whether *C. glucuronolyticum* can actually be considered pathogenic or rather just a commensal species fortuitously isolated in patients with urogenital symptoms and/or syndromes. Although pathogen/commensal dichotomy is not always clear-cut, we hypothesize that specific genetic markers may expose *C. glucuronolyticum* as a convincingly pathogenic *Corynebacterium*. More specifically, characteristic pathogenic gene constellation inherent to this species (most notably the presence of specific sortase/SpaA-type pili gene clusters, but also the augmentative role of type VII secretion system) may significantly facilitate host tissue adhesion, with subsequent suppression/evasion of the immune response and acquisition of vitally important nutrients. Consequently, these genetic markers differentiate *C. glucuronolyticum* from its commensal counterparts, and give this species a pathogenic facet, which can be even further influenced by the Allee effect. In this paper we also propose a specific methodological approach on how to analyze *C. glucuronolyticum* epithelial colonization capacity and explore inceptive host cell-pathogen interactions that manipulate host environment and immune responses. This entails moving from approaches based primarily on overall homology of primary sequences towards specific structure-function studies to precisely evaluate all stakeholders involved in pili assemblage, cell adhesion and the expression of other virulence traits. In the era of high precision medicine, the hypothesized roles of *C. glucuronolyticum* adhesion systems in both virulence and nutrient acquisition may also reveal promising targets for future drug developments.

Keywords: *Corynebacterium glucuronolyticum*, pathogenesis, urogenital infections

1.2. AN OUTBREAK OF HUMAN PARAINFLUENZA VIRUS 3 (PHYLOGENETIC SUBCLUSTER C5) INFECTION AMONG ADULTS AT A RESIDENTIAL CARE FACILITY FOR THE DISABLED IN CROATIA, 2018

Intervirology. 2019;doi: 10.1159/000503630 Epub

Impact factor: 0.873

Čivljak R^{1,2}, Košutić Gulija T³, Slović A³, Huljev E^{1,2}, Turčić N⁴, Meštrović T^{5,6}, Vraneš J^{2,7}, Ljubin Sternak S^{2,7}

¹ Dr. Fran Mihaljevic University Hospital for Infectious Diseases, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Center of Excellence for Virus Immunology and Vaccines, Center for Research and Knowledge Transfer in Biotechnology, University of Zagreb, Zagreb, Croatia

⁴ Zagreb County Institute of Public Health, Dugo Selo, Croatia

⁵ Dr. Zora Profozic Polyclinic, Zagreb, Croatia

⁶ University Centre Varaždin, University North, Varaždin, Croatia

⁷ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

sljsternak@stampar.hr

Abstract

Introduction: Although highly pertinent for children, outbreaks of human parainfluenza virus (HPIV) may cause up to 15% of all respiratory illnesses in adults and predispose them to serious adverse outcomes, with HPIV serotype 3 (HPIV3) being the most common. This study represents the first report of an HPIV3 outbreak among adults at a long-term health-care facility in Croatia.

Methods: A retrospective study was conducted to investigate an outbreak of acute respiratory infection (ARI) at a single residential care facility for the disabled in Croatia. Demographic, epidemiological, and clinical data were collected for all

residents, while hospitalized patients were appraised in detail by laboratory/radiological methods. Multiplex PCR for respiratory viruses and sequencing was performed. Partial HPIV3 HN 581 nt sequences were aligned with HPIV3 sequences from the GenBank database to conduct a phylogenetic analysis, where different bioinformatic approaches were employed.

Results: In late June 2018, 5 of the 10 units at the facility were affected by the outbreak. Among the 106 residents, 23 (21.7%) developed ARI, and 6 (26.1%) of them were hospitalized. HPIV3 was identified in 18 (73%) of the residents and 5 (83%) of the hospitalized individuals. Isolated HPIV3 strains were classified within the phylogenetic subcluster C5 but grouped on 2 separate branches of the phylogenetic tree. During the entire outbreak period, none of the institution's employees reported symptoms of ARI.

Conclusions: Our study has shown that this health care-associated outbreak of HPIV3 infection could have been linked to multiple importation events. Preventive measures in curbing such incidents should be enforced vigorously.

Keywords: community residential care home, human parainfluenza virus 3, multiplex PCR, pneumonia, sequencing

1.3. ASSOCIATION AMONG CLOPIDOGREL CESSATION, PLATELET FUNCTION, AND BLEEDING IN CORONARY BYPASS SURGERY: AN OBSERVATIONAL TRIAL

The Thoracic and Cardiovascular Surgeon. 2019;doi:10.1055/s-0039-1693122
Epub

Petričević M^{1,2}, Knežević J^{3,4}, Biočina B^{1,2}, Mikuš M^{1,2}, Konosić L^{1,2}, Rašić M^{1,2}, Milošević M², Rotim C⁵, Madžar T⁶, Rotim A⁶, Gašparović H^{1,2}, Goerlinger K^{7,8}

¹ University Hospital Center Zagreb, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ University Hospital Center Mostar, Mostar, Bosnia and Herzegovina

⁴ School of Medicine, University of Mostar, Mostar, Bosnia and Herzegovina

⁵ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁶ School of Medicine, University of Osijek, Osijek, Croatia

⁷ Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Germany

⁸ TEM International GmbH, Munich, Germany

petricevic.mate@gmail.com

Abstract

Objectives: This study sought to determine (1) the association between the length of preoperative clopidogrel discontinuation, blood loss, and transfusion requirements and (2) whether preoperative platelet function testing predicts excessive postoperative bleeding in patients undergoing coronary artery bypass grafting (CABG) surgery.

Methods: In this retrospective analysis, patients undergoing CABG were divided into three groups with regard to the period between preoperative clopidogrel cessation and surgery: group 1 (n=94, ≤3 days), group 2 (n=100, 4-5 days), and

group 3 (n=83, 6-7 days), respectively. Impedance aggregometry (Multiplate) with arachidonic acid (ASPI) test assay (used for platelets stimulation) and adenosine diphosphate (ADP) test (used for platelets stimulation) was performed before the surgery. Primary outcome was 24 hours chest tube output (CTO) and transfusion requirements (red blood cell concentrate [RBCC], platelet concentrate [PC], fibrinogen concentrate [FC], and fresh-frozen plasma [FFP]) were considered as secondary outcomes.

Results: CTO during 24 hours was significantly higher in group 1 as compared with groups 2 and 3, respectively ($p=0.003$). Considering secondary outcomes, RBCC ($p=0.043$), PC ($p=0.001$), FC ($p=0.003$), and FFP ($p=0.010$) were more frequently transfused in group 1 as compared with groups 2 and 3, respectively. Multiple electrode aggregometry ASPI and ADP tests were significantly correlated with the 24-hour CTO (ASPI test— $\rho=-0.258$, $p<0.001$; ADP test— $\rho=-0.164$, $p=0.007$). A significant correlation was observed between clopidogrel-free interval and 24-hour CTO ($\rho=-0.200$, $p<0.001$). Receiver-operating characteristics (ROC) curve analysis revealed cutoff values to delineate bleeding tendency (ASPI test ≤ 25 area under the aggregation curve [AUC], ADP test ≤ 63 AUC, and clopidogrel-free interval ≤ 3 days).

Conclusion: Excessive postoperative bleeding occurred less frequently if the period between clopidogrel discontinuation and surgery was longer than 3 days, as compared with shorter waiting time. Inadequate recovery of the platelets function following clopidogrel cessation in preoperative period was associated with increased bleeding risk. Platelet function testing was found to be a useful tool for postoperative bleeding management in our hands.

Keywords: coronary artery bypass grafting, multiple electrode aggregometry, antiplatelet, drugs, clopidogrel, transfusion

1.4. ASSOCIATION BETWEEN BLOOD GROUP AND NONMELANOMA SKIN CANCERS (BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA)

International Journal of Environmental Research and Public Health. 2019;16(13):e2267

Impact factor: 2.468

Celić D¹, Lipozenčić J², Kolarić B^{3,4}, Ferencak G¹, Rajković JK¹, Borlinić T⁵

¹ Medikol Polyclinic, Čakovec, Croatia

² Croatian Academy of Medical Sciences, Zagreb, Croatia

³ Faculty of Medicine, University of Rijeka, Rijeka, Croatia

⁴ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁵ Čakovec County Hospital, Čakovec, Croatia

dijana.celic@medikol.hr

Abstract

Background: Development of nonmelanoma skin cancers (NMSCs) has been associated with certain risk factors, but studies of the association between ABO blood group and NMSCs have been rare and inconclusive. The aim of this study was to assess the association of the previously known risk factors and blood group as a new potential risk factor in NMSCs.

Methods: The study included 401 patients, 202 men, and 199 women, which included 367 diagnosed cases of basal cell carcinoma and 148 diagnosed cases of squamous cell carcinoma. The control group consisted of 438 subjects, 198 men, and 240 women. A standardized questionnaire adapted for this targeted study was used. The relation between the dependent variable (NMSCs) and independent variables was investigated by logistic regression.

Results: Compared to the non AB blood group, the risk of developing NMSCs was significantly higher in the AB blood group (MOR = 2.28; 95% CI = 1.41-3.69). We

established a logistic model that could best describe the probability of NMSCs development.

Conclusion: Study results are expected to instigate basic research into the role of A and B antigens in normal skin epithelium, NMSCs etiopathogenesis, possible effect on metastatic potential and disease prognosis, potential tumor immunotherapy, and targeted detection and prevention in subjects at an increased risk of NMSCs development.

Keywords: ABO blood groups, basal cell carcinoma, nonmelanoma skin cancers, squamous cell carcinoma

1.5. ASSOCIATION OF POOR SELF-PERCEIVED HEALTH WITH DEMOGRAPHIC, SOCIOECONOMIC AND LIFESTYLE FACTORS IN THE CROATIAN ADULT POPULATION

Društvena istraživanja. 2019;28(2):229-248

Impact factor: 0.271

Ivičević Uhernik A¹, Skoko Poljak D², Dečković Vukres V¹, Jelavić M³, Mihel S¹, Benjak T¹, Štefančić V¹, Draušnik Ž¹, Stevanović R¹

¹ Croatian Institute of Public Health, Zagreb, Croatia

² Ministry of Health of the Republic of Croatia, Zagreb, Croatia

³ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

ana.ivicevic@hzjz.hr

Abstract

The aim of this study was to analyse the association of poor self-perceived health with demographic, socioeconomic and lifestyle factors using data from the European Health Interview Survey. When applying the multiple logistic regression model, two demographic (male sex, older age), all four socioeconomic (low education level, unemployed and retired, living in households with lowest income, poor social support) and only one lifestyle factor (no alcohol consumption) were revealed as associated with poor self-perceived health. The association of socioeconomic factors with self-perceived health among the adult population in Croatia is direct and not mediated exclusively through lifestyle factors.

Keywords: self-perceived health, European Health Interview Survey, socioeconomic factors, lifestyle factors

1.6. COMPARATIVE PROTEOMIC STUDY OF PHYTOTOXIC EFFECTS OF SILVER NANOPARTICLES AND SILVER IONS ON TOBACCO PLANTS

Environmental Science and Pollution Research. 2019;26(22):22529-22550

Impact factor: 2.914

Peharec Štefanić P¹, Jarnević M¹, Cvjetko P¹, Biba R¹, Šikić S², Tkalec M¹, Cindrić M³, Letofsky Papst I⁴, Balen B¹

¹ Faculty of Science, University of Zagreb, Zagreb, Croatia

² Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

³ Ruđer Bošković Institute, Zagreb, Croatia

⁴ Institute of Electron Microscopy and Nanoanalysis (FELMI), Graz University of Technology, Graz Centre for Electron Microscopy (ZFE), Austrian Cooperative Research (ACR), Graz, Austria

bbalen@biol.pmf.hr

Abstract

Widespread application of silver nanoparticles (AgNPs), due to their antibacterial and antifungal properties, increases their release into the environment and potential detrimental impact on living organisms. Plants may serve as a potential pathway for AgNPs bioaccumulation and a route into the food chain, hence investigation of AgNP phytotoxic effects are of particular importance. Since proteins are directly involved in stress response, studies of their abundance changes can help elucidate the mechanism of the AgNP-mediated phytotoxicity. In this study, we investigated proteomic changes in tobacco (*Nicotiana tabacum*) exposed to AgNPs and ionic silver (AgNO₃). A high overlap of differently abundant proteins was found in root after exposure to both treatments, while in leaf, almost a half of the proteins exhibited different abundance level between treatments, indicating tissue-specific responses. Majority of the identified proteins were down-regulated in both tissues after exposure to either AgNPs or

AgNO₃; in roots, the most affected proteins were those involved in response to abiotic and biotic stimuli and oxidative stress, while in leaf, both treatments had the most prominent effect on photosynthesis-related proteins. However, since AgNPs induced higher suppression of protein abundance than AgNO₃, we conclude that AgNP effects can, at least partially, be attributed to nanoparticle form.

Keywords: silver nanoparticles, silver nitrate, *Nicotiana tabacum*, two-dimensional electrophoresis, proteomics, phytotoxicity

1.7. COMPARATIVE STUDY OF RAGWEED POLLEN SEASONS (2008–2017) IN THE AIR OF CROATIAN TOURIST CITIES OF ZAGREB (CONTINENTAL AREA) AND ZADAR (MEDITERRANEAN AREA)

Aerobiologia. 2019;35:765-770

Impact factor: 1.931

Vucić A¹, Večenaj A², Hrga I², Peroš Pucar D¹, Stjepanović B², Hruševar D³, Mitić B³

¹ Institute of Public Health Zadar, Zadar, Croatia

² Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

³ Faculty of Science, University of Zagreb, Zagreb, Croatia

bozena.mitic@biol.pmf.hr

Abstract

The majority of tourists visit Croatia during the summer months, which overlaps with the ragweed pollination season, and this might be the main health issue, which could affect Croatian tourism. Therefore, the aim of this research was to perform the preliminary analyses of ragweed pollen seasons in two different Croatian tourist cities – continental Zagreb and Mediterranean Zadar, and to define researched areas according to the allergenic risk assessment. The research was performed during a 10-year period (2008-2017), and aerobiological samplings, as well as qualitative and quantitative analyses, were carried out by standard methodology recommended by EAN/REA. The results showed differences between cities in the seasonal pollen integral (SPI_n) and intradiurnal variations index (IDI) of ragweed pollen, and similarities in the features of the main pollen seasons (MPS). The SPI_n was higher in the air of Zagreb during the whole studied period; it was on average 2899 pg/m³ in Zagreb and 579 pg/m³ in Zadar. The MPS in both cities were similar (from the first half of August until the mid-September) and relatively short, around 40 days. The IDI indicates that *Ambrosia* pollen in Zagreb derives from local sources, whilst in Zadar is probably

a result of long-range transport. According to the allergenic risk assessment, Zagreb is placed in the intermediate-risk area and Zadar in the low-risk area. Relatively short exposure times during the summer periods enable both cities to be favourable tourist destinations even during the ragweed seasons, especially Zadar, with its low ragweed pollen concentrations.

Keywords: allergenic pollen, *Ambrosia artemisiifolia* L., tourism, Lowland Croatia, Mediterranean Croatia

1.8. DETECTING STYRENE WITH SPECTRAL FLUORESCENCE SIGNATURE ANALYSIS

Journal of Environmental Health. 2019;81(9):24-30

Impact factor: 0.36

Cvetković B¹, Kolarić B^{1,2}, Cvetković Ž¹, Pintarić S³

¹ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

² Faculty of Medicine, University of Rijeka, Rijeka, Croatia

³ First School of Economics, Zagreb, Croatia

branko.kolaric@medri.uniri.hr

Abstract

The large global production of plastics and their presence everywhere in society and the environment have created a need for assessing chemical hazards and risks associated with plastic products. Plastics from polystyrene can release potentially toxic products (including styrene), particularly when heated. In this study we used a Fluo-Imager Analyser with software for spectral fluorescence signature (SFS) analysis. The objective of this study was to evaluate and compare the amount of styrene released into food and beverages by using SFS on a Fluo-Imager Analyser. Our results showed that concentrations of released styrene were in the range of 1.45–9.95 µg/L for hot water and 0.10–2.78 µg/L for room temperature water. The results indicate that this fluorescence diagnostic method is an effective tool for analysis of styrene released into food and beverages from polystyrene containers and cups, and could be useful in further investigations of styrene toxicity.

Keywords: expanded polystyrene, gas chromatography, organic compounds, drinking water, migration, monomer, toxicity, food, microextraction, phytoplankton

1.9. DETERMINATION OF URANIUM CONCENTRATIONS IN SOIL, WATER, VEGETABLES AND BIOLOGICAL SAMPLES FROM INHABITANTS OF WAR AFFECTED AREAS IN EASTERN CROATIA (ICP-MS METHOD)

Journal of Environmental Radioactivity. 2019;203:147-153

Impact factor: 2.179

Venus M¹, Puntarić D², Gvozdić V³, Vidosavljević D¹, Bijelić L¹, Puntarić A⁴, Puntarić E⁵, Vidosavljević M⁶, Jergović M⁷, Šabarić J⁷

¹ Faculty of Medicine, J.J. Strossmayer University of Osijek, Osijek, Croatia

² Croatian Catholic University Zagreb, Zagreb, Croatia

³ J.J. Strossmayer University of Osijek, Osijek, Croatia

⁴ Faculty of Food Technology and Biotechnology, University of Zagreb, Zagreb, Croatia

⁵ Croatian Agency for Environment and Nature, Zagreb, Croatia

⁶ Vinkovci County General Hospital, Vinkovci, Croatia

⁷ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

domagoj.vidosavljevic@gmail.com

Abstract

The occurrence of elevated uranium levels in post-war areas raise concerns among populations, especially in areas affected by heavy bombardment and potential use of depleted uranium weapons. The aim of this study was to assess public exposure to the uranium water, soil, vegetables, urine, serum and hair samples were collected for the first time in eastern Croatia and analysed using an inductively coupled plasma mass spectrometry (ICP-MS) method, in order to try to explain the possible origins of uranium in the population and environment. Urine, serum and hair samples were collected from 389 inhabitants. A large

variation of uranium concentrations in urine, serum and hair samples was found in this study. The majority of urine, serum and hair samples from our study had uranium concentrations below the reference literature values. A higher uranium concentration in the hair of 4% of inhabitants, mostly from rural areas, could not be explained at this stage of research. A further, extended epidemiological study should be made of uranium in the region.

Keywords: uranium, ICP-MS, environment, biomonitoring, eastern Croatia

1.10. EFFECTS OF IN-FEED CLINOPTILOLITE TREATMENT ON SERUM METABOLIC AND ANTIOXIDATIVE BIOMARKERS AND ACUTE PHASE RESPONSE IN DAIRY COWS DURING PREGNANCY AND EARLY LACTATION

Research in Veterinary Science. 2019;127:57-64

Impact factor: 1.751

Folnožić I¹, Samardžija M¹, Đuričić D², Vince S¹, Perkov S³, Jelušić S⁴, Valpotić H¹, Ljubić Beer B¹, Lojkić M¹, Gračner D¹, Žura Žaja I¹, Maćešić N¹, Grizelj J¹, Dobranić T¹, Redžepi G⁵, Šostar Z⁴, Turk R¹

¹ Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia.

² Veterinary Practice Đurđevac, Đurđevac, Croatia

³ Merkur University Hospital, Zagreb, Croatia

⁴ Andrija Stampar Teaching Institute for Public Health, Zagreb, Croatia

⁵ University Hospital Centre Jordanovac, Zagreb, Croatia

smarko@vef.hr

Abstract

The objective of this study was to evaluate the effects of in-feed clinoptilolite (CPL) on serum metabolic and antioxidative biomarkers, acute phase proteins and reproductive performance in cows during pregnancy and lactation. A total of 78 Holstein-Friesian cows were randomly assigned into two groups: the treatment group, cows fed CPL ($n = 38$) which received 50 g of powdered CPL twice a day from day 180 before parturition to day 60 postpartum; and the control group ($n = 40$). Blood samples were taken on days 180, 90, 60, 30 and 10 before parturition, on day of calving and on days 5, 12, 19, 26, 33, 40 and 60 postpartum, and were analysed for metabolic biomarkers: glucose, triglycerides, total cholesterol, high density lipoprotein cholesterol, non-esterified fatty acids, beta-hydroxybutyrate (BHB), antioxidative biomarkers and acute phase proteins:

paraoxonase-1 (PON1), apolipoprotein A-I, haptoglobin (Hp) and serum amyloid A (SAA). CPL supplementation increased concentration of glucose and significantly decreased ($P < .05$) level of BHB during puerperium. The SAA concentration in CPL-fed cows was significantly decreased ($P < .05$) on days 33, 40 and 60 postpartum as well as Hp concentration on days 0 and 12 postpartum. The results of this study suggest that the CPL-fed cows may have improved metabolic status due to the tendency of greater glucose levels and decreased BHB values during early lactation. In addition, acute phase response was lower ($P < .05$) in CPL-fed cows. Such an outcome might be attributed to the effect of dietary CPL on intensity and severity of the negative energy balance and inflammatory response in dairy cows.

Keywords: acute phase proteins, antioxidative enzymes, cattle, metabolic biomarkers, zeolite

1.11. EFFECTS OF INDUSTRIAL EFFLUENTS CONTAINING MODERATE LEVELS OF ANTIBIOTIC MIXTURES ON THE ABUNDANCE OF ANTIBIOTIC RESISTANCE GENES AND BACTERIAL COMMUNITY COMPOSITION IN EXPOSED CREEK SEDIMENTS

Science of The Total Environment. 2019;706. Epub 9 December 2019

Impact Factor: 5.589

Milaković M¹, Vestergaard G^{2,3}, González Plaza JJ¹, Petrić I¹, Kosić Vukšić J⁴, Senta I¹, Kublik S², Schloter M², Udiković Kolić N¹

¹ Ruđer Bošković Institute, Zagreb, Croatia

² Helmholtz Zentrum München, Neuherberg, Germany

³ Technical University of Denmark, Lyngby, Denmark

⁴ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

nudikov@irb.hr

Abstract

Environmental discharges of very high (mg/L) antibiotic levels from pharmaceutical production contributed to the selection, spread and persistence of antibiotic resistance. However, the effects of less antibiotic-polluted effluents (µg/L) from drug-formulation on exposed aquatic microbial communities are still scarce. Here we analyzed formulation effluents and sediments from the receiving creek collected at the discharge site (DW0), upstream (UP) and 3000 m downstream of discharge (DW3000) during winter and summer season. Chemical analyses indicated the largest amounts of trimethoprim (up to 5.08 mg/kg) and azithromycin (up to 0.39 mg/kg) at DW0, but sulfonamides accumulated at DW3000 (total up to 1.17 mg/kg). Quantitative PCR revealed significantly increased relative abundance of various antibiotic resistance genes (ARGs) against β-lactams, macrolides, sulfonamides, trimethoprim and tetracyclines in sediments from DW0, despite relatively high background levels of some ARGs already at UP site. However, only sulfonamide (*su12*) and macrolide ARG subtypes

(*mphG* and *msrE*) were still elevated at DW3000 compared to UP. Sequencing of 16S rRNA genes revealed pronounced changes in the sediment bacterial community composition from both DW sites compared to UP site, regardless of the season. Numerous taxa with increased relative abundance at DW0 decreased to background levels at DW3000, suggesting die-off or lack of transport of effluent-originating bacteria. In contrast, various taxa that were more abundant in sediments than in effluents increased in relative abundance at DW3000 but not at DW0, possibly due to selection imposed by high sulfonamide levels. Network analysis revealed strong correlation between some clinically relevant ARGs (e.g. *bla_{GES}*, *bla_{OXA}*, *ermB*, *tet39*, *sul2*) and taxa with elevated abundance at DW sites, and known to harbour opportunistic pathogens, such as *Acinetobacter*, *Arcobacter*, *Aeromonas* and *Shewanella*. Our results demonstrate the necessity for improved management of pharmaceutical and rural waste disposal for mitigating the increasing problems with antibiotic resistance.

Keywords: antibiotic manufacturing, sediment, pollution, bacterial community, antibiotic resistance genes

1.12. EMERGING TRENDS IN THE EPIDEMIOLOGY OF WEST NILE AND USUTU VIRUS INFECTIONS IN SOUTHERN EUROPE

Frontiers in Veterinary Science. 2019;6(6):437. Epub

Impact Factor: 2.029

Vilibić Čavlek T^{1,2}, Savić V³, Petrović T⁴, Toplak I⁵, Barbić Lj⁶, Dušan Petrić D⁷, Tabain I¹, Hrnjaković Cvjetković I^{8,9}, Bogdanić M¹, Klobučar A¹⁰, Mrzljak A^{2,11}, Stevanović V⁶, Dinjar Kujundžić P¹¹, Radmanić L⁶, Monaco F¹², Listeš E¹³, Savini G¹²

¹ Croatian Institute of Public Health, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Croatian Veterinary Institute, Zagreb, Croatia

⁴ Scientific Veterinary Institute, Novi Sad, Serbia

⁵ Veterinary Faculty, University of Ljubljana, Ljubljana, Slovenia

⁶ Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia

⁷ Faculty of Agriculture, University of Novi Sad, Novi Sad, Serbia

⁸ Institute of Public Health Vojvodina, Novi Sad, Serbia

⁹ Medical Faculty, University of Novi Sad, Novi Sad, Serbia

¹⁰ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

¹¹ Merkur University Hospital, Zagreb, Croatia

¹² OIE Reference Center for West Nile Disease, Istituto Zooprofilattico Sperimentale "G. Caporale", Teramo, Italy

¹³ Croatian Veterinary Institute, Regional Institute Split, Split, Croatia

tatjana.vilibic-cavlek@hzjz.hr

Abstract

The epidemiology of West Nile (WNV) and Usutu virus (USUV) has changed dramatically over the past two decades. Since 1999, there have been regular reports of WNV outbreaks and the virus has expanded its area of circulation in many Southern European countries. After emerging in Italy in 1996, USUV has spread to other countries causing mortality in several bird species. In 2009, USUV seroconversion in horses was reported in Italy. Co-circulation of both viruses was detected in humans, horses and birds. The main vector of WNV and USUV in Europe is *Culex pipiens*, however, both viruses were found in native *Culex* mosquito species (*Cx. modestus*, *Cx. perexiguus*). Experimental competence to transmit the WNV was also proven for native and invasive mosquitoes of *Aedes* and *Culex* genera (*Ae. albopictus*, *Ae. detritus*, *Cx. torrentium*). Recently, *Ae. albopictus* and *Ae. japonicus* naturally-infected with USUV were reported. While neuroinvasive human WNV infections are well-documented, USUV infections are sporadically detected. However, there is increasing evidence of a role of USUV in human disease. Seroepidemiological studies showed that USUV circulation is more common than WNV in some endemic regions. Recent data showed that WNV strains detected in humans, horses, birds, and mosquitoes mainly belong to lineage 2. In addition to European USUV lineages, some reports indicate the presence of African USUV lineages as well. The trends in WNV/USUV range and vector expansion are likely to continue in future years. This mini-review provides an update on the epidemiology of WNV and USUV infections in Southern Europe within a multidisciplinary “One Health” context.

Keywords: West Nile virus, Usutu virus, epidemiology, “One Health”, Southern Europe

1.13. FROM PERUVIAN MUMMIES TO LIVING HUMANS: FIRST CASE OF PULMONARY TUBERCULOSIS CAUSED BY *MYCOBACTERIUM PINNIPEDII*

The International Journal of Tuberculosis and Lung Disease. 2019;23(12):1283-1285

Impact factor: 2.024

Zmak L^{1,2}, Obrovac M², Janković Makek M^{2,3}, Perko G⁴, Tekavec Trkanjec J^{2,5}

¹ Croatian Institute of Public Health, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ University Hospital Centre Zagreb, Zagreb, Croatia

⁴ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁵ University Hospital Dubrava, Zagreb, Croatia

Abstract

The zoonotic potential of *Mycobacterium tuberculosis* complex species is well known. However, *M. pinnipedii*, the causative agent of tuberculosis (TB) predominantly in seals and sea lions, has never been isolated from a respiratory specimen in humans. Here we describe the first known human case of pulmonary TB caused by *M. pinnipedii* in a 79-year-old female patient with rheumatoid arthritis and chronic respiratory disease. The epidemiological data did not explain where the patient was exposed to *M. pinnipedii*, thus leaving the source of transmission unknown.

Keywords: rheumatoid arthritis, transmission link, zoonotic TB

1.14. GLOBAL MONITORING OF ANTIMICROBIAL RESISTANCE BASED ON METAGENOMICS ANALYSES OF URBAN SEWAGE

Nature Communications. 2019;10:1124

Impact Factor: 11.878

Hendriksen RS¹, Munk P¹, Njage P¹, van Bunnik B², McNally L³, Lukjancenko O¹, Röder T¹, Nieuwenhuijse D⁴, Pedersen SK¹, Kjeldgaard J¹, Kaas RS¹, Clausen PTLC¹, Vogt JK¹, Leekitcharoenphon P¹, van de Schans MGM⁵, Zuidema T⁵, de Roda Husman AM⁶, Rasmussen S⁷, Petersen B⁷, Amid C⁸, Cochrane G⁸, Sicheritz Ponten T⁹, Schmitt H⁶, Alvarez JRM¹⁰, Aidara Kane A¹⁰, Pamp SJ¹, Lund O⁷, Hald T¹, Woolhouse M², Koopmans MP⁴, Vigre H¹, Petersen TN¹, Aarestrup FM¹, Jergović M^{11,12} et al¹²

¹ National Food Institute, Technical University of Denmark, Kgs. Lyngby, Denmark

² Usher Institute, University of Edinburgh, Edinburgh, United Kingdom

³ School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom

⁴ Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands

⁵ RIKILT Wageningen University and Research, Wageningen, The Netherlands

⁶ National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

⁷ Technical University of Denmark, Kgs. Lyngby, Denmark

⁸ European Molecular Biology Laboratory, European Bioinformatics Institute, Hinxton, United Kingdom

⁹ Centre of Excellence for Omics-Driven Computational Biodiscovery, AIMST University, Kedah, Malaysia

¹⁰ World Health Organization, Geneva, Switzerland

¹¹ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

¹² The Global Sewage Surveillance Project Consortium

fmaa@food.dtu.dk

Abstract

Antimicrobial resistance (AMR) is a serious threat to global public health, but obtaining representative data on AMR for healthy human populations is difficult. Here, we use metagenomics analysis of untreated sewage to characterize the bacterial resistome from 79 sites in 60 countries. We find systematic differences in abundance and diversity of AMR genes between Europe/North-America/Oceania and Africa/Asia/South-America. Antimicrobial use data and bacterial taxonomy only explains a minor part of the AMR variation that we observe. We find no evidence for cross-selection between antimicrobial classes, or for effect of air travel between sites. However, AMR gene abundance strongly correlates with socioeconomic, health and environmental factors, which we use to predict AMR gene abundances in all countries in the world. Our findings suggest that global AMR gene diversity and abundance vary by region, and that improving sanitation and health could potentially limit the global burden of AMR. We propose metagenomic analysis of sewage as an ethically acceptable and economically feasible approach for continuous global surveillance and prediction of AMR.

Keywords: global surveillance, antimicrobial resistance, AMR, wastewater, sewage, metagenomics, resistome, machine learning, prediction

1.15. GLUCONOBACTER OXYDANS – POTENTIAL BIOLOGICAL AGENT FOR BINDING OR BIOTRANSFORMATION OF MYCOTOXINS

World Mycotoxin Journal. 2019;12(2):153-161

Impact Factor: 2.406

Markov K¹, Frece J¹, Pleadin J², Bevardi M³, Barišić L¹, Gajdoš Kljusurić J¹, Vulić A², Jakopović Ž¹, Mrvčić J¹

¹ Faculty of Food Technology and Biotechnology, University of Zagreb, Zagreb, Croatia

² Croatian Veterinary Institute, Zagreb, Croatia

³ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

kmarko@pbf.hr

Abstract

The potential application of viable and heat-treated cells of *Gluconobacter oxydans* for binding or degradation of aflatoxin B₁ (AFB₁), citrinin (CIT), ochratoxin A (OTA) and patulin (PAT) in liquid matrix was investigated. Experiments were conducted using uncontaminated and toxin-containing YPM (yeast-peptone-mannitol) medium and inoculated with a bacterium suspension of either viable or heat-treated cells (10⁸ cfu/ml) and incubated at 28 °C for 24 h. The unbound AFB₁ and OTA were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS), whereas CIT and PAT were quantified by high performance liquid chromatography (HPLC). Obtained results suggest that *G. oxydans* is able to bind various mycotoxins by 26 to 94%. Viable cells showed the best binding ability towards OTA and PAT (80.8 and 93.8%, respectively), while heat-treated cells bound less than 50% of tested mycotoxins. Fourier transform infrared spectroscopy (FTIR) showed that partial removal of mycotoxins involves physical binding of the toxin to the proteins and polysaccharides constituting the bacterial cell wall. Since mycotoxins contain numerous functional groups that multiply the IR spectra upon binding to bacteria, the precision of FTIR monitoring of bacteria-mycotoxin interactions is limited.

Keywords: *Gluconobacter oxydans*, mycotoxins, IR-spectra, cell wall components, PCA

1.16. HEPATITIS E SEROPREVALENCE AND ASSOCIATED RISK FACTORS IN CROATIAN LIVER TRANSPLANT RECIPIENTS

The Journal of the Brazilian Society of Tropical Medicine. 2019;52:e20190302

Impact factor: 1.498

Mrzljak A^{1,2}, Dinjar Kujundžić P¹, Vilibić Čavlek T^{2,3}, Jemeršić L⁴, Prpić J⁴, Đaković Rode O^{5,6}, Kolarić B^{7,8}, Vince A^{2,5}

¹ Merkur University Hospital, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Croatian Institute of Public Health, Zagreb, Croatia

⁴ Croatian Veterinary Institute, Zagreb, Croatia

⁵ University Hospital for Infectious Diseases “Dr Fran Mihaljević”, Zagreb, Croatia

⁶ School of Dental Medicine, University of Zagreb, Zagreb, Croatia

⁷ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁸ Faculty of Medicine, University of Rijeka, Rijeka, Croatia

anna.mrzljak@mef.hr

Abstract

Introduction: Solid-organ transplant recipients are at risk of hepatitis E virus (HEV) infection. We analyzed the seroprevalence/risk factors of HEV in Croatian liver transplant recipients.

Methods: Two hundred forty-two serum samples were tested for HEV immunoglobuline IgG/IgM and HEV RNA. Sociodemographic data and risk factors were collected using a questionnaire.

Results: HEV IgG seroprevalence rate was 24.4%. Positive/equivocal HEV IgM were found in two patients. HEV RNA was not detected. Logistic regression

showed that older age, female gender, rural area/farm, water well, and septic tank were associated with HEV seropositivity.

Conclusions: This study revealed a high exposure rate to HEV in Croatian liver recipients.

Keywords: hepatitis E virus, seroprevalence, risk factors, liver transplant recipients, Croatia

1.17. HIGH DETECTION RATES OF HUMAN BOCAVIRUS IN INFANTS AND SMALL CHILDREN WITH LOWER RESPIRATORY TRACT INFECTION FROM CROATIA

Clinical Laboratory. 2019;65(1)

Impact factor: 0.955

Ljubin Sternak S^{1,2}, Meštrović T^{3,4}, Ivković Jureković I^{5,6}, Tešović G⁷, Mlinarić Galinović G², Lukšić I¹, Tabain I⁸, Tot T⁹, Mijač M¹, Vraneš J^{1,2}

¹ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Polyclinic "Dr. Zora Profozić", Zagreb, Croatia

⁴ University Centre Varaždin, University North, Varaždin, Croatia

⁵ Children's Hospital Zagreb, Zagreb, Croatia

⁶ Faculty for Dental Medicine and Healthcare/School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

⁷ University Hospital for Infectious Diseases, Zagreb, Croatia

⁸ Croatian Institute of Public Health, Zagreb, Croatia

⁹ General Hospital Karlovac, Karlovac, Croatia

suncanica.ljubinsternak@stampar.hr

Abstract

Background: Human bocavirus (HBoV) is known to cause lower respiratory tract infections (LRTI) in children and may result in substantial morbidity and mortality. The aim of this study was to determine HBoV prevalence among hospitalized infants and small children with acute LRTI in Zagreb, Croatia, as well as to evaluate HBoV DNA quantity in samples in relation to the patients' age and co-infection with other respiratory viruses.

Methods: During winter season 2016/2017, a total of 295 children younger than three years of age who were admitted to hospitals with LRTI were tested for the presence of HBoV, respiratory syncytial virus (RSV), adenovirus (ADV), parainfluenza virus (PIV) types 1 to 3, and human metapneumovirus (HMPV). HBoV was detected with a real-time PCR method, and the other viruses were diagnosed using monoclonal antibodies in direct fluorescence assay.

Results: Viral etiology was proven in 225/295 (76.3%) of patients. The most commonly diagnosed virus was RSV (59.3%), followed by HBoV (23.1%), PIVs (4.4%), ADV (3.1%), and HMPV (1.4%). HBoV-infected children were older than RSV-infected children; likewise, detection rates of HBoV infection increased with age, while RSV infection rates decreased with age. In 51% of HBoV-positive samples an additional respiratory virus was also detected. There was no difference in HBoV DNA quantity between samples with single virus detection and those with multiple virus detection ($p = 0.056$), although samples positive only for HBoV showed higher cycle threshold values. There was no difference in HBoV DNA quantity in samples of different age groups ($p > 0.05$).

Conclusions: Frequent detection of HBoV in small children with LRTI, even in combination with other viruses, highlights its role in the pathogenesis of respiratory disease.

Keywords: human bocavirus, respiratory syncytial virus, real-time PCR, Croatia

1.18. INFLUENCE OF GERONTOLOGY SERVICES ON THE PHYSICAL AND PSYCHOLOGICAL HEALTH OF ELDERLY IN THE CITY OF ZAGREB

Psychiatria Danubina. 2019;31(Suppl. 1):S99-S104

Impact factor: 1.341

Živoder I^{1,2}, Kolarić B^{3,4}, Županić M⁵

¹ Alma Mater Europaea – ECM, Maribor, Slovenia

² University North, Varazdin, Croatia

³ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁴ Faculty of Medicine, University of Rijeka, Rijeka, Croatia

⁵ University of Applied Health Sciences, Zagreb, Croatia

branko.kolaric@stampar.hr

Abstract

Background: The World Health Organization (WHO) defines the quality of life as an individual perception of personal position in the cultural and social system within an individual's environment. Elderly people, in general, prefer to live in their own home as much as possible, and moving means for them losing social relationships, changing routines and lifestyles and losing independence. The research aimed to gain insight into the use of gerontology services for the elderly people, their availability, diversity of information, a range of services they provide, and impact of these services on quality of life.

Subjects and methods: The study population is defined as persons residing in Zagreb, 65 years of age or older, with no physical disability or severe bodily, cognitive or mental illnesses who are users of the gerontology center. The survey was conducted using a customized questionnaire survey on a total sample of 103 respondents.

Results: The most significant number of respondents, since they use the facilities, feel satisfied (68%) and very satisfied (28.2%) in their life. More than half of the participants (52.4%) rated their quality of life as very good and excellent, 46.6% of respondents rated their quality of life as good. Issues that effect on quality of life point to the dissatisfaction of the respondents are their financial resources, inadequate health services, and the lack of a positive social network.

Conclusions: Community services, such as gerontology centers, enable social network development, new learning, physical activity, which have an impact on physical and psychological health and thus on the quality of life of elderly people. The satisfaction of the respondents using these services was rated above the average (3.71), which indicates that the society is moving in the right direction, encouraging this form of care for the elderly.

Keywords: quality of life, non-institutional care, gerontology center, community services

1.19. MOLECULAR EPIDEMIOLOGY OF HUMAN RESPIRATORY SYNCYTIAL VIRUS AND HUMAN METAPNEUMOVIRUS IN HOSPITALIZED CHILDREN WITH ACUTE RESPIRATORY INFECTIONS IN CROATIA, 2014–2017

Infection, Genetics and Evolution. 2019;76:104039

Impact factor: 2.611

Jagušić M^{1,2}, Slović A^{1,2}, Ivančić Jelečki J^{1,2}, Ljubin Sternak S^{3,4}, Vilibić Čavlek T^{4,5}, Tabain I⁵, Forčić D^{1,2}

¹ Centre for Research and Knowledge Transfer in Biotechnology, University of Zagreb, Zagreb, Croatia

² Center of Excellence for Viral Immunology and Vaccines – CERVirVac, Zagreb, Croatia

³ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁴ School of Medicine, University of Zagreb, Zagreb, Croatia

⁵ Croatian National Institute of Public Health, Zagreb, Croatia

aslovic@unizg.hr

Abstract

Acute respiratory infection (ARI) is the most common infection in children under 5 years of age and it is frequently caused by two pneumoviruses, human respiratory syncytial virus (HRSV) and human metapneumovirus (HMPV). Epidemic seasons of these viruses overlap and disease manifestations are highly similar, including severe lower ARI such as bronchiolitis or pneumonia. Reinfections with pneumoviruses are frequent and limited prevention treatment is available. Genetic diversity of HRSV and HMPV strains circulating in Croatia was monitored during four consecutive years (2014–2017). Co-circulation of multiple lineages was observed for both viruses. Within HRSV group A, ON1 strains gained strong predominance during the 4-year period, while previously dominant

genotype NA1 was detected only sporadically. Similarly, newly occurring HMPV genotype A2c gained predominance over genotype A2b during this period, resulting in all infection in 2017 being caused by A2c. Along with phylogenetic analysis based on the commonly used fragments for detection and genotyping of these viruses, full length G and SH genes were also analysed. Evolutionary dynamics showed that inferred substitution rates of HRSV and HMPV are between 2.51×10^{-3} and 3.61×10^{-3} substitutions/site/year. This study established presence of recently described HMPV strains containing large duplications in the G gene in Croatia. Viruses with either of the two duplications belong to a subcluster A2c, which has completely replaced all other group A subclusters in 2017.

Keywords: human respiratory syncytial virus, human metapneumovirus, small hydrophobic protein, glycoprotein, epidemiology, evolution

1.20. PREVALENCE AND MOLECULAR EPIDEMIOLOGY OF WEST NILE AND USUTU VIRUS INFECTIONS IN CROATIA IN THE “ONE HEALTH” CONTEXT, 2018

Transboundary and Emerging Diseases. 2019;66(5):1946-1957

Impact factor: 3.554

Vilibić Čavlek T^{1,2}, Savić V³, Sabadi D^{4,5}, Perić Lj^{4,5}, Barbić Lj⁶, Klobučar A⁷, Miklaušić B⁸, Tabain I¹, Santini M^{2,8}, Vucelja M⁹, Dvorski E¹⁰, Butigan T¹⁰, Kolaric Sviben G¹¹, Potočnik Hunjadi T¹², Balenović M³, Bogdanić M¹, Andrić Z¹³, Stevanović V⁶, Capak K¹, Baličević M¹⁴, Listeš E¹⁵, Savini G¹⁶

¹ Croatian Institute of Public Health, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Croatian Veterinary Institute, Zagreb, Croatia

⁴ Clinical Hospital Center Osijek, Osijek, Croatia

⁵ Medical Faculty, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

⁶ Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia

⁷ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁸ University Hospital for Infectious Diseases “Dr Fran Mihaljevic”, Zagreb, Croatia

⁹ Faculty of Forestry, University of Zagreb, Zagreb, Croatia

¹⁰ General Hospital Varazdin, Varazdin, Croatia

¹¹ General Hospital "Dr Tomislav Bardek", Koprivnica, Croatia

¹² County Hospital Cakovec, Cakovec, Croatia

¹³ General County Hospital Pozega, Pozega, Croatia

¹⁴ General Hospital “Dr Josip Bencevic”, Slavonski Brod, Croatia

¹⁵ Croatian Veterinary Institute, Regional Institute Split, Split, Croatia

¹⁶ OIE Reference Center for West Nile Disease, Istituto Zooprofilattico Sperimentale “G. Caporale”, Teramo, Italy

tatjana.vilibic-cavlek@hzjz.hr

Abstract

In 2018, Croatia reported the largest outbreak of West Nile virus (WNV) infections as well as the re-occurrence of human Usutu virus (USUV) infections. For the first time, fatal WNV and USUV infections were detected in wild birds. We analysed epidemiological characteristics and molecular epidemiology of WNV and USUV infections detected during 2018 transmission season. From April to November, 178 patients with neuroinvasive disease and 68 patients with febrile disease were tested for WNV and USUV. Viral RNA was detected in cerebrospinal fluid (CSF) and urine samples using a real-time RT-PCR. Positive samples were tested by nested RT-PCR and nucleotide sequencing. IgM/IgG antibodies were detected in serum/CSF samples using ELISA with confirmation of cross-reactive samples by virus neutralization test (VNT). WNV neuroinvasive disease was confirmed in 54 and WNV fever in seven patients from 10 continental Croatian counties. Areas affected in 2018 were those in which cases occurred in previous seasons, while in three areas human cases were reported for the first time. Phylogenetic analysis of six strains from patients residing in different geographic areas showed circulation of WNV lineage 2. In three patients, neuroinvasive USUV infection was confirmed by RT-PCR or VNT. Sequence analysis of one detected strain revealed USUV Europe 2 lineage. During the same period, a total of 2,574 horse and 1,069 poultry serum samples were tested for WNV antibodies using ELISA. Acute asymptomatic WNV infection (IgM antibodies) was documented in 20/0.7% horses. WNV IgG antibodies were found in 307/11.9% horses and in 125/12.7% poultry. WNV RNA was detected in two goshawks and USUV RNA was detected in one blackbird from north-western Croatia. In the Zagreb area, 3,670 female mosquitoes were collected. One *Culex pipiens* pool collected in July tested positive for USUV RNA. Our results highlight the importance of continuous multidisciplinary ‘One health’ surveillance of these emerging arboviruses.

Keywords: West Nile virus, Usutu virus, prevalence, molecular epidemiology, Croatia

1.21. RESOURCE UTILISATION AND COST OF CERVICAL CANCER AND DYSPLASIA IN CROATIA

European Journal of Gynaecological Oncology. 2019;XL(1):40-47

Impact Factor: 0.245

Ivičević Uhernik A¹, Vajagić M², Jelavić M³, Cesarec A², Lučić A², Jovanović M², Lovrić Z¹, Šekerija M¹

¹ Croatian Institute of Public Health, Zagreb, Croatia

² Croatian Health Insurance Fund, Zagreb, Croatia

³ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

ana.ivicevic@hzjz.hr

Abstract

Purpose of investigation: To analyse resource utilisation and costs due to cervical cancer and dysplasia in Croatia.

Materials and Methods: Patients diagnosed with cervical cancer were identified from the Croatian National Cancer Registry. Resource utilisation and costs of cervical cancer treatment for the period of five years after the date of diagnosis were retrieved from the Croatian Health Insurance Fund Claims Database. Patients diagnosed with cervical dysplasia were identified and their resource utilisation and treatment costs during one year following diagnosis were obtained from the Croatian Health Insurance Fund Claims Database. Results were calculated for different healthcare services and disease stages.

Results: There were 346 patients diagnosed with cervical cancer in 2008. Total costs of treatment in the five-year period were 2,177,071 Euros, while average cost of treatment per patient was 6,403 Euros. The largest shares of total costs were costs for hospitalisations (73%), followed by outpatient healthcare (17%), and personal sick leave (7%). There were also 14,913 patients with cervical

dysplasia diagnosed in 2012. Total costs of their treatment during one year after the diagnosis were 1,609,073 Euros, with average costs per patient of 108 Euros. Outpatient care (48%), followed by hospitalisations (45%), and prescribed medicines (6%) had the greatest share of total costs.

Conclusion: Treatment of cervical cancer and dysplasia in Croatia is associated with significant costs and healthcare resource utilisation.

Keywords: cervical cancer, cervical dysplasia, resource utilisation, cost of illness

1.22. THE APPLICATION OF A NEURAL NETWORK-BASED RAGWEED POLLEN FORECAST BY THE RAGWEED POLLEN ALARM SYSTEM IN THE PANNONIAN BIOGEOGRAPHICAL REGION

Aerobiologia. 2019;doi:10.1007/s10453-019-09615-w Epub

Impact factor: 1.931

Csépe Z¹, Leelőssy Á¹, Mányoki G¹, Kajtor Apatini D¹, Udvardy O¹, Péter B¹, Páldy A¹, Gelybó G¹, Szigeti T¹, Pándics T¹, Kofol Seliger A², Simčič A², Leru PM³, Eftimie AM³, Šikoparija B⁴, Radišić P⁴, Stjepanović B⁵, Hrga I⁵, Večenaj A⁵, Vucić A⁶, Peroš Pucar D⁶, Škorić T⁷, Ščevková J⁸, Bastl M⁹, Berger U⁹, Magyar D¹

¹ National Public Health Center, Budapest, Hungary

² National Laboratory of Health, Environment and Food, Ljubljana, Slovenia

³ Colentina Clinical Hospital, Bucharest, Romania

⁴ BioSenseInstitute – Research Institute for Information Technologies in Biosystems, University of Novi Sad, Novi Sad, Serbia

⁵ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁶ Institute of Public Health Zadar, Zadar, Croatia

⁷ Public Health Institute Subotica, Subotica, Serbia

⁸ Faculty of Natural Sciences, Comenius University, Bratislava, Slovak Republic

⁹ Medical University of Vienna, Vienna, Austria

magyar.donat@gmail.com

Abstract

Ragweed Pollen Alarm System (R-PAS) has been running since 2014 to provide pollen information for countries in the Pannonian biogeographical region (PBR). The aim of this study was to develop forecast models of the representative aerobiological monitoring stations, identified by analysis based on a neural

network computation. Monitoring stations with 7-day Hirst-type pollen trap having 10-year long validated data set of ragweed pollen were selected for the study from the PBR. Variables including forecasted meteorological data, pollen data of the previous days and nearby monitoring stations were used as input of the model. We used the multilayer perceptron model to forecast the pollen concentration. The multilayer perceptron (MLP) is a feedforward artificial neural network. MLP is a data-driven method to forecast the behaviour of complex systems. In our case, it has three layers, one of which is hidden. MLP utilizes a supervised learning technique called backpropagation for training to get better performance. By testing the neural network, we selected different sets of variables to predict pollen levels for the next 3 days in each of the monitoring stations. The predicted pollen level categories (low – medium – high – very high) are shown on isarithmic map. We used the mean square error, mean absolute error and correlation coefficient metrics to show the forecasting system's performance. The average of the Pearson correlations is around 0.6 but shows big variability (0.13-0.88) among different locations. Model uncertainty is mainly caused by the limitation of the available input data and the variability in ragweed season patterns. Visualization of the results of the neural network forecast on isarithmic maps is a good tool to communicate pollen information to general public in the PBR.

Keywords: ragweed, pollen, forecast, neural network, MLP

1.23. TOXICITY AND SAFETY STUDY OF SILVER AND GOLD NANOPARTICLES FUNCTIONALIZED WITH CYSTEINE AND GLUTATHIONE

Beilstein Journal of Nanotechnology. 2019;10:1802-1817

Impact Factor: 2.269

Pem B¹, Pongrac IM², Ulm L³, Pavičić I¹, Vrčec V⁴, Domazet Jurašin D⁵, Ljubojević M¹, Krivohlavek A³, Vinković Vrček I¹

¹ Institute for Medical Research and Occupational Health, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁴ Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia

⁵ Rudjer Boskovic Institute, Zagreb, Croatia

ivinkovic@imi.hr

Abstract

This study was designed to evaluate the nano–bio interactions between endogenous biothiols (cysteine and glutathione) with biomedically relevant, metallic nanoparticles (silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs)), in order to assess the biocompatibility and fate of nanoparticles in biological systems. A systematic and comprehensive analysis revealed that the preparation of AgNPs and AuNPs in the presence of biothiols leads to nanoparticles stabilized with oxidized forms of biothiols. Their safety was tested by evaluation of cell viability, reactive oxygen species (ROS) production, apoptosis induction and DNA damage in murine fibroblast cells (L929), while ecotoxicity was tested using the aquatic model organism *Daphnia magna*. The toxicity of these nanoparticles was considerably lower compared to their ionic metal forms (i.e., Ag⁺ and Au³⁺). The comparison with data published on polymer-coated nanoparticles evidenced that surface modification with biothiols made them

safer for the biological environment. In vitro evaluation on human cells demonstrated that the toxicity of AgNPs and AuNPs prepared in the presence of cysteine was similar to the polymer-based nanoparticles with the same core material, while the use of glutathione for nanoparticle stabilization was considerably less toxic. These results represent a significant contribution to understanding the role of biothiols on the fate and behavior of metal-based nanomaterials.

Keywords: biocompatibility, cysteine, ecotoxicity, glutathione, nano-bio interactions, nanosafety, nanotoxicity

1.24. TOXICITY OF NANOSILVER AND FUMONISIN B₁ AND THEIR INTERACTIONS ON DUCKWEED (*LEMNA MINOR* L.)

Chemosphere. 2019;229:86-93

Impact factor: 5.108

Radić S¹, Domijan AM², Glavaš Ljubimir K³, Maldini K³, Ivešić M⁴, Peharec Štefanić P¹, Krivohlavek A⁴

¹ Faculty of Science, University of Zagreb, Zagreb, Croatia

² Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia

³ Croatian Waters, Zagreb, Croatia

⁴ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

sandra@biol.pmf.hr

Abstract

In the environment co-contamination of several toxicants commonly occurs. However, toxicological studies usually are focused on only one toxicant. The aim of this study was to investigate toxicity of silver nanoparticles (AgNP) and mycotoxin fumonisin B₁ (FB₁) and their possible interactions as well as to explore tentative mechanism of their toxic effect. Duckweed (*Lemna minor* L.) was treated with AgNP or FB₁ (at concentrations 0.5 and 1.0 mg L⁻¹) or with their combination at same concentrations for 3 days. Both AgNP and FB₁, applied individually significantly affected levels of certain nutrients, reduced growth rate and the levels of photosynthetic pigments though AgNP at a much greater extent compared to FB₁. Furthermore, AgNP induced ROS generation, lipid peroxidation and increase of antioxidative enzymes activities, while FB₁ induced changes only in the activities of antioxidative enzymes. Those results implicate that phytotoxicity of both AgNP and FB₁ can be associated with imbalance of mineral and cell redox status. However, toxic actions of AgNP singly applied were more pronounced. Combined treatment with AgNP and FB₁ produced higher degree of

changes in all parameters than corresponding concentrations of AgNP or FB₁ alone implying their additive effects. Additionally, higher level of FB₁ found in medium, and higher level of intracellular Ag following combined treatment indicates interaction of two toxicants at the transport level/uptake in the cell which resulted in higher accumulation of Ag in duckweed cells. The latter in turn exerted higher toxicity to duckweed compared to single treatment of AgNP.

Keywords: mycotoxins, nanosilver, oxidative stress, photosynthetic pigments, plant

1.25. VIRAL PATHOGENS ASSOCIATED WITH ACUTE RESPIRATORY ILLNESS IN HOSPITALIZED ADULTS AND ELDERLY FROM ZAGREB, CROATIA, 2016 TO 2018

Journal of Medical Virology. 2019;91(7):1202-1209

Impact factor: 2.049

Čivljak R^{1,2}, Tot T³, Falsey AR⁴, Huljev E^{1,2}, Vraneš J^{1,5}, Ljubin Sternak S^{1,5}

¹ Dr Fran Mihaljevic University Hospital for Infectious Diseases, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ General Hospital Karlovac, Karlovac, Croatia

⁴ Rochester General Hospital and University of Rochester School of Medicine and Dentistry, Rochester, New York, United States of America

⁵ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

sljsternak@stampar.hr

Abstract

Aims: To investigate the viral etiology of acute respiratory infection (ARI) in hospitalized adults and elderly patients in Croatia, compare the prevalence of detected viruses, and to determine clinical characteristics and seasonal occurrence of investigated infections.

Methods: From January 2016 to June 2018, a total of 182 adult patients presented with symptoms of ARI and admitted to the hospital were tested for 15 respiratory viruses by multiplex reverse-transcription polymerase chain reaction. Clinical data were collected by retrospective analysis of the patient's chart.

Results: A virus was identified in 106 (58.5%) of the patients. The most commonly detected virus was influenza virus (41.5%), followed by respiratory syncytial virus (13.8%), human metapneumovirus (13.0%), parainfluenza viruses (12.2%),

rhinoviruses (11.4%), adenovirus and coronaviruses with equal frequencies (3.3%), and enterovirus (1.6%). The serum level of C-reactive protein and white blood cell count were significantly lower in patients with respiratory viruses identified when compared with those in whom no virus was detected ($P < 0.001$ and $P = 0.007$, respectively). There were no differences in clinical symptoms according to the type of the detected virus, except for more frequent illness exposure recall for influenza infection ($P = 0.010$). Influenza, parainfluenza, and pneumoviruses were detected mostly in winter months, while rhinoviruses in autumn and spring.

Conclusions: In addition to influenza, pneumoviruses, rhinoviruses, and parainfluenza viruses play an important role in etiology of ARIs in adults. Fast and accurate laboratory diagnosis for respiratory viruses in routine practice is needed for clinicians optimally manage patients with ARI and potentially avoid the unnecessary use of antimicrobial drugs.

Keywords: human metapneumovirus, influenza, multiplex reverse-transcription polymerase chain reaction, respiratory syncytial virus

2. ORIGINAL SCIENTIFIC AND REVIEW ARTICLES IN OTHER INDEXED JOURNALS

2.1. ADAPTATION AND VALIDATION OF THE CAMBRIDGE PULMONARY HYPERTENSION OUTCOME REVIEW (CAMPHOR) FOR CROATIA

Acta clinica Croatica. 2019; 58(1):3-11

Impact Factor: 0.403

Hećimović A¹, Heaney A², McKenna SP², Basara L¹, Jakopović M^{1,3}, Vukić Dugac A^{1,3}, Redžepi G¹, Rotim C⁴, Samaržija M^{1,3}, Jokić-Begić N⁵, Popović Grle S^{1,3}

¹ Zagreb University Hospital Centre, Zagreb, Croatia

² Galen Research, Manchester, UK

³ School of Medicine, University of Zagreb, Zagreb, Croatia

⁴ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁵ Faculty of Humanities and Social Science, University of Zagreb, Zagreb, Croatia

anahecimovic1978@gmail.com

Abstract

Pulmonary hypertension (PH) is a chronic disease which severely impairs quality of life (QoL). The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is the first disease-specific tool to assess patient-reported symptoms, functioning and QoL in PH patients. The aim of this study was to adapt and validate the CAMPHOR for use in Croatia. The adaptation process involved three stages: translation (bilingual and lay panel), cognitive debriefing interviews with patients and psychometric validation. For the latter stage, a postal survey was conducted with 50 patients to examine the reliability and validity of the adapted scale. All three scales of the Croatian CAMPHOR demonstrated excellent internal consistency (Symptoms = 0.93; Activity limitations = 0.94; QoL = 0.92) and test-retest reliability correlations (Symptoms = 0.90; Activity limitations = 0.95; QoL = 0.90). Predicted correlations with the SF-36 scales provided evidence for construct validity of the CAMPHOR scales. Evidence for known group validity

was shown by the ability of the scales to distinguish between participants based on patient-perceived general health and disease severity. The Croatian version of the CAMPHOR is a valid and reliable tool for use in clinical routine and clinical research.

Keywords: hypertension, pulmonary, quality of life, Croatia, reproducibility of results, surveys and questionnaires

2.2. INFERTILITY AND SEXUAL DYSFUNCTIONS: A SYSTEMATIC LITERATURE REVIEW

Acta clinica Croatica. 2019; 58(3):508-515

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Starc A¹, Trampuš M², Pavan Jukić D³, Rotim C⁴, Jukić T³, Polona Mivšek A⁵

¹ Faculty of Health Sciences, University of Ljubljana, Ljubljana, Slovenia

² Jesenice General Hospital, Jesenice, Slovenia

³ Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

⁴ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁵ Faculty of Health Sciences, University of Ljubljana, Ljubljana, Slovenia

andrej.starc@guest.arnes.si

Abstract

This study aimed to investigate whether infertility and its treatment affect couple sexuality. A systematic literature review was performed, focusing on female and male sexual dysfunctions due to infertility. The method was descriptive, using a meta-synthesis of scientific research published between 2012 and 2017 in the English language. The search for suitable studies was carried out with the research databases Medline, CINAHL, PubMed and ScienceDirect using the following keywords: infertility, sexual dysfunctions, couple. It can be concluded that infertility negatively affects the sexuality of an infertile couple, which is further proven by a high percentage of sexual dysfunctions (43%-90% among women and 48%-58% among men). Couples report less satisfaction with sexuality. Since lower satisfaction and dysfunctions are closely connected with infertility and its treatment, couples might benefit from sexual therapy and support during the process of infertility treatment. Further research should focus

on the evaluation of different psychological interventions that would address sexuality in couples when diagnosed and treated for infertility.

Keywords: infertility, sexuality, erectile dysfunction, sexual dysfunctions, psychological

2.3. SERUM ADIPOCYTOKINES ARE ASSOCIATED WITH MICROALBUMINURIA IN PATIENTS WITH TYPE 1 DIABETES AND INCIPIENT CHRONIC COMPLICATIONS

Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2019; 13(1):496-499

Impact factor: 1.942

Bulum T^{1,2}, Vučić Lovrenčić M¹, Tomić M¹, Vučković Rebrina S¹, Roso V¹, Kolarić B^{3,4}, Vuksan V^{5,6}, Duvnjak L^{1,2}

¹ Merkur University Hospital, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

⁴ Faculty of Medicine, University of Rijeka, Rijeka, Croatia

⁵ Medical School, University of Toronto, Toronto, Canada

⁶ St. Michael's Hospital, Toronto, Canada

tbulum@idb.hr

Abstract

Aims: Recent studies have implicated possible contribution of adipocytokines in development and progression of microvascular complications in patients with type 1 diabetes (T1DM). The aim of our study was to investigate relationship between adipocytokines, namely leptin, resistin, adiponectin and dipeptidyl peptidase-4 (DPP-4) activity, with albuminuria in T1DM.

Methods: This study included 202 T1DM without or with incipient microvascular complications. Urinary albumin excretion rate (UAE) was measured from at least two 24-h urine samples. Serum DPP-4 activity was measured by a colorimetric assay, and the level of adiponectin, leptin, and resistin was determined by the ELISA method.

Results: Serum DPP-4 activity and adiponectin were significantly higher in patients with normoalbuminuria compared to patients with microalbuminuria (47 vs 36 U/L, and 10.9 vs 7.3 $\mu\text{g}/\text{mL}$, respectively, $p \leq 0.02$). In multivariate logistic regression analysis adiponectin and serum DPP-4 activity were significantly associated with risk of microalbuminuria in our subjects ($p \leq 0.04$), with odds ratios of 0.72-0.99. However, after adjustment for age, sex, HbA1c, duration of diabetes and BMI, only serum DPP-4 activity was significantly associated with risk of microalbuminuria ($p = 0.008$).

Conclusion: The results of our study suggest that serum DPP-4 activity is lower in T1DM with microalbuminuria. Prospective studies are warranted to evaluate the relationship between serum DPP-4 activity and progression and development of albuminuria and nephropathy in T1DM.

Keywords: adipocytokines, albuminuria, dipeptidyl peptidase-4, type 1 diabetes

2.4. THE EMERGING ROLE OF RHINOVIRUSES IN LOWER RESPIRATORY TRACT INFECTIONS IN CHILDREN – CLINICAL AND MOLECULAR EPIDEMIOLOGICAL STUDY FROM CROATIA, 2017–2019

Frontiers in Microbiology. 2019;10:2737

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Ljubin Sternak S^{1,2}, Meštrović T^{3,4}, Ivković Jureković I^{5,6}, Kolarić B^{1,7}, Slović A⁸, Forčić D⁸, Tot T⁹, Mijač M^{1,2}, Vraneš J^{1,2}

¹ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Polyclinic “Dr. Zora Profozić”, Zagreb, Croatia

⁴ University Centre Varaždin, University North, Varaždin, Croatia

⁵ Children’s Hospital Zagreb, Zagreb, Croatia

⁶ Faculty for Dental Medicine and Healthcare/School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

⁷ Faculty of Medicine, University of Rijeka, Rijeka, Croatia

⁸ Center of Excellence for Virus Immunology and Vaccines, Center for Research and Knowledge Transfer in Biotechnology, University of Zagreb, Zagreb, Croatia

⁹ General Hospital Karlovac, Karlovac, Croatia

tmestrovic@unin.hr

Abstract

Rhinoviruses (RVs) are increasingly implicated not only in mild upper respiratory tract infections, but also in more severe lower respiratory tract infections; however, little is known about species diversity and viral epidemiology of RVs among the infected children. Therefore, we investigated the rhinovirus (RV) infection prevalence over a 2-year period, compared it with prevalence patterns

of other common respiratory viruses, and explored clinical and molecular epidemiology of RV infections among 590 children hospitalized with acute respiratory infection in north-western and central parts of Croatia. For respiratory virus detection, nasopharyngeal and pharyngeal flocked swabs were taken from each patient and subsequently analyzed with multiplex RT-PCR. To determine the RV species in a subset of positive children, 5'UTR in RV-positive samples has been sequenced. Nucleotide sequences of referent RV strains were retrieved by searching the database with Basic Local Alignment Tool, and used to construct alignments and phylogenetic trees using MAFFT multiple sequence alignment tool and the maximum likelihood method, respectively. In our study population RV was the most frequently detected virus, diagnosed in 197 patients (33.4%), of which 60.4% was detected as a mono-infection. Median age of RV-infected children was 2.25 years, and more than half of children infected with RV (55.8%) presented with lower respiratory tract infections. Most RV cases were detected from September to December, and all three species co-circulated during the analyzed period (2017–2019). Sequence analysis based on 5'UTR region yielded 69 distinct strains; the most prevalent was RV-C (47.4%) followed by RV-A (44.7%) and RV-B (7.9%). Most of RV-A sequences formed a distinct phylogenetic group; only strains RI/HR409-18 (along with a reference strain MF978777) clustered with RV-C strains. Strains belonging to the group C were the most diverse (41.6% identity among strains), while group B was the most conserved (71.5% identity among strains). Despite such differences in strain groups (hitherto undescribed in Croatia), clinical presentation of infected children was rather similar. Our results are consistent with newer studies that investigated the etiology of acute respiratory infections, especially those focused on children with lower respiratory tract infections, where RVs should always be considered as potentially serious pathogens.

Keywords: rhinovirus, species, epidemiology, phylogenetic analysis, children, lower respiratory tract infection

2.5. VERIFICATION OF AUTHENTICITY OF *GINKGO BILOBA* L. LEAF EXTRACT AND ITS PRODUCTS PRESENT ON THE CROATIAN MARKET BY ANALYSIS OF QUANTITY AND RATIO OF GINKGO FLAVONE GLYCOSIDES (QUERCETIN, KAEMPFEROL AND ISORHAMNETIN) OVER TERPENE TRILACTONES TO THE EFFECT OF UNMASKING COUNTERFEIT DRUGS ENDANGERING PATIENT HEALTH

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Impact Factor: 0.403

Budeč M¹, Bošnjir J^{1,2}, Racz A², Lasić D¹, Brkić D¹, Mosović Ćuić A², Kuharić Ž¹, Jurak G¹, Barušić L¹

¹ Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

² University of Applied Health Studies, Zagreb, Croatia

maja.budec@stampar.hr

Abstract

Ginkgo biloba L. is the eldest plant growing on the Earth; preparations made of its leaves and seeds represent an integral part of the Chinese medicine for over a millennium. The plant species was first discovered by Linnaeus in 1771, its name thereby originating from the Latin words *bis* (two) and *lobus* (lobe), which duly illustrate the specific shape of its leaf. Contemporary *Ginkgo biloba* L. plant based pharmaceuticals mostly comprise extracts recovered from leaves harvested during fall, when the concentration of active components reaches its peak. Recent investigations have managed to establish the chemical composition of the plant leaf, together with the mechanisms underlying its beneficial effects on rheological profile of the blood and acceleration of its flow. High price of these preparations and their vast popularity have soon become an incentive for counterfeiting *Ginkgo biloba* L. extracts and the release of bogus drugs comprising cheaper extracts coming from other plants. Namely, modern *Ginkgo biloba* L.-based medicinal products and food supplements comprise extracts

recovered from the plant leaf that get to be standardized according to its key pharmacological active components, most often flavone glycosides (represented in the share of 22%-27%) and terpene trilactones (represented in the share of 6%-7%). The flavonoids that predominate such preparations and are most relevant from the pharmacological standpoint are quercetin, kaempferol and isorhamnetin, their total amount and mutual ratios, thereby being an unquestionable indicator of the extract authenticity. Therefore, most of the analyses aiming at verifying the authenticity of a given *Ginkgo biloba* L.-based product boil down to the analysis of these parameters. Counterfeiting involves partial or full replacement of the *Ginkgo biloba* L. extract (GBE) with a cheaper plant extract of a similar composition, the latter occasionally being enriched with an additional amount of flavonoids, most often quercetin, not originating from the *Ginkgo biloba* L. plant. The aim of this study was to verify the authenticity and quality of *Ginkgo biloba* L.-based products circulating on the Croatian market. To that effect, 10 samples of products produced by various manufactures were analyzed in a certified laboratory. The parameters based on which the authenticity of the preparations was assessed were the shares of aglycones of typical ginkgo flavone glycosides, that is to say, quercetin, kaempferol and isorhamnetin, and mutual ratios of the established quantities of quercetin over kaempferol as the key clues to unmasking *Ginkgo* extracts counterfeiting. The amount of ginkgo flavone glycosides was established using high performance liquid chromatography. The analysis proved 80% of the samples analyzed to be conformant to the label statements as regards the total amount of flavone glycosides and their mutual ratios. In 20% of the samples, the ratio of quercetin over kaempferol deviated from normal values; on top of that, the presence of the phytoestrogen genistein, one of the components typically comprised by the *Sophora japonica* L. plant, was also proven, documenting counterfeiting of the GBE and its replacement by the *Sophora japonica* L. extracts in the samples under consideration. Due to the untrue label statements descriptive of these products, the information on the presence of pharmacologically active genistein was neglected to be mentioned despite of its unfavorable health impact that can be expected in some consumer groups. The results of this study indicated the frequency of counterfeiting the *Ginkgo biloba* L.-based products found on the Croatian market to be deemed substantial. Therefore, a more rigorous and more thorough control over these products and sanctioning of irresponsible

manufacturers and distributors is proposed, so as to contribute to a higher market representation of high quality products, as well as to avoid health risks and downsize the rate of their counterfeiting.

Keywords: *Ginkgo biloba* L., quercetin, kaempferol, isorhamnetin, ginkgo flavone glycosides, terpene trilactones, counterfeit drugs

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