

## CROATIAN INTERNATIONAL PUBLICATIONS

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**Bojanic A<sup>1</sup>, Bojanic K<sup>2</sup>, Likic R<sup>3</sup>. Brain drain: final year medical students' intentions of training abroad. *Postgrad Med J.* 2015;91(1076):315-21.**

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**BACKGROUND:** In Croatia, a new European Union (EU) member state since July 2013, there is already a shortage of around 3280 doctors to reach the European average. **OBJECTIVES:** To investigate the emigration intentions of the current cohort of final year medical students at Zagreb School of Medicine. **METHODS:** An electronic questionnaire was used in June 2013 to assess the attitudes of 232 final year medical students towards working conditions abroad and expectations for career opportunities in Croatia following accession to the EU. **RESULTS:** With an overall response rate of 87%, more than half of the surveyed students (106/202, 53%) intended to travel abroad, either for specialty (52/202, 26%) or subspecialty (54/202, 27%) training. More female students (58/135, 43%) than male students (17/62, 27%) indicated they would not emigrate. Most attractive emigration destinations were: Germany (34/121, 28%), USA (19/121, 16%), the UK (19/121, 16%), Switzerland (16/121, 13%) and Canada (11/121, 9%). The most important goals that respondents aimed to achieve through training abroad were to excel professionally (45/120, 38%), to prosper financially (20/120, 17%) and to acquire new experiences and international exposure (31/120, 26%). **CONCLUSIONS:** Students' motivating factors, goals for and positive beliefs about training abroad, as well as negative expectations regarding career opportunities in Croatia, may point towards actions that could be taken to help make Croatia a country that facilitates

medical education and professional career development of young doctors.

**Dolenec P, Pilipović K, Rajič J, Župan G. Temporal pattern of neurodegeneration, programmed cell death, and neuroplastic responses in the thalamus after lateral fluid percussion brain injury in the rat. *J Neuropathol Exp Neurol.* 2015;74(6):512-26.**

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The effects of traumatic brain injury (TBI) on the thalamus are not well characterized. We analyzed neuronal degeneration and loss, apoptosis, programmed cell death-executing pathways, and neuroplastic responses in the rat thalamus during the first week after lateral fluid percussion injury (LFPI). The most prominent neurodegenerative and neuroplastic changes were observed in the region containing the posterior thalamic nuclear group and ventral posteromedial and posterolateral thalamic nuclei ipsilateral to the LFPI. There was progressive neurodegeneration in these regions, with maximal neuronal loss on Day 7. Increases in numbers of apoptotic cells were detected on Day 1 and were enhanced on Days 3 and 7 after TBI. There was unchanged expression of active caspase-3 at all postinjury time points, but there was increased expression of apoptosis-inducing factor (AIF) on Day 7. The AIF nuclear translocation was detected on Day 1 and was maximal on Day 7. Total thalamic synaptophysin expression was unchanged, but immunostaining intensities were increased at all time points after TBI. Decreased growth-associated protein-43 expression and signal intensity were observed on Day 1. Our results suggest that progressive neuronal damage and

loss, AIF signaling pathway-dependent programmed cell death, and limited neuroplastic changes occur in the rat thalamus during the first week after LFPI induction.

**Hauser G<sup>1</sup>, Salkic N<sup>2</sup>, Vukelic K<sup>3</sup>, Jajac Knez A<sup>3</sup>, Stimac D<sup>1</sup>. Probiotics for Standard Triple Helicobacter pylori Eradication: A Randomized, Double-blind, Placebo-controlled Trial. *Medicine (Baltimore)*. 2015;94(17):e685.**

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The primary objective in the study is determination of efficacy of probiotic preparation as a supportive therapy in eradication of *Helicobacter pylori*. The study was multicenter, prospective, randomized, placebo controlled, and double-blind. The subjects first filled out a specially designed questionnaire to assess the severity of the 10 symptoms, which can be related to eradication therapy to be monitored during the trial. Each subject then received 28 capsules of probiotic preparation or matching placebo capsules, which they were supposed to take over the following 14 days, twice a day, at least 2 hours prior to or after the antibiotic therapy administration. A total of 804 patients were enrolled in the trial, of which 650 (80.85%) were included in the analysis. The results show a significantly larger share of cured subjects in the probiotic arm versus the placebo arm (87.38% vs 72.55%;  $P < 0.001$ ). Additionally, presence and intensity of epigastric pain, bloating, flatulence, taste disturbance, loss of appetite, nausea, vomiting, heartburn, rash, and diarrhea were monitored over the study period. At 15 days postinclusion, probiotic treatment was found superior to placebo in 7 of 10 mentioned symptoms. Average intensity for symptoms potentially related to antibiotic therapy was significantly higher in the placebo group, 0.76 vs 0.55 ( $P < 0.001$ ). Adding probiotics to the standard triple therapy for *H. pylori* eradication significantly contributes to treatment efficacy and distinctly decreases the adverse effects of therapy and the symptoms of the underlying disease.

**Vučina VV<sup>1</sup>, Filipović SK<sup>2</sup>, Kožnjak N<sup>3</sup>, Stamenić V<sup>4</sup>, Clark AD<sup>5</sup>, Mounaud B<sup>6</sup>, Blau J<sup>6</sup>, Hoestlandt C<sup>6</sup>, Kaić B<sup>2</sup>. Cost-effectiveness of pneumococcal conjugate vaccination in Croatia. *Vaccine*. 2015;33 Suppl 1:A209-18.**

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**OBJECTIVE:** Pneumococcus is a known cause of meningitis, pneumonia, sepsis, and acute otitis media in children and adults globally. Two new vaccines for children have the potential to prevent illness, disability, and death, but these vaccines are expensive. The Croatian Ministry of Health has considered introducing the vaccine in the past, but requires economic evidence to ensure that the limited funds available for health care will be used in the most effective way. **METHODOLOGY:** Croatia appointed a multidisciplinary team of experts to evaluate the cost-effectiveness of introducing pneumococcal conjugate vaccination (PCV) into the national routine child immunization program. Both 10-valent and 13-valent PCV (PCV10 and PCV13) were compared to a scenario assuming no vaccination. The TRIVAC decision-support model was used to estimate cost-effectiveness over the period 2014-2033. We used national evidence on demographics, pneumococcal disease incidence and mortality, the age distribution of disease in children, health service utilization, vaccine coverage, vaccine timeliness, and serotype coverage. Vaccine effectiveness was based on evidence from the scientific literature. Detailed health care costs were not available from the Croatian Institute for Health Insurance at the time of the analysis so assumptions and World Health Organization (WHO) estimates for Croatia were used. We assumed a three-dose primary vaccination schedule, and an initial price of US\$ 30 per dose for PCV10 and US\$ 35 per dose for PCV13. We ran univariate sensitivity analyses and multivariate scenario analyses. **RESULTS:** Either vaccine is estimated to prevent approximately 100 hospital admissions and one death each year in children younger than five in Croatia. Compared to no vaccine, the discounted cost-effectiveness of either vaccine is estimated to be around US\$ 69,000-77,000 per disability-adjusted life-years (DALYs) averted over the period 2014-2033 (from the government or societal perspective). Only two alternative scenarios were borderline cost-effective (US\$ per DALY averted less than 3×GDP per capita of approximately US\$ 40,000). The first was a scenario based primarily on the WHO 2008 pneumococcal disease burden estimates for Croatia. The second was a scenario that assumed a fairly dramatic drop in the price of the vaccine over the period. Both vaccines

would need to be priced at approximately US\$ 20 per dose or less to be considered cost-effective under base-case assumptions. PCV10 would be more cost-effective than PCV13 with base-case assumptions, but this is sensitive to the price of each vaccine. CONCLUSION: Based on estimated health and economic benefits in children alone, PCV is unlikely to be cost-effective in Croatia. Both vaccines would need to be priced at less than US\$ 20 per dose to be considered cost-effective for children. Further analyses should be conducted to estimate the health and economic burden of pneumococcal disease in older age groups, and to assess the influence on cost-effectiveness results when short-term and long-term indirect effects are included for older individuals. While there are important uncertainties around the price and effectiveness of both vaccines, our analysis suggests there is insufficient evidence to warrant a significant difference in the price of the two vaccines.

**Markeljjevic J<sup>1</sup>, Sarac H<sup>2</sup>, Bozina N<sup>3</sup>, Henigsberg N<sup>4</sup>, Simic M<sup>5</sup>, Cicin Sain L<sup>6</sup>. Serotonin transporter gene polymorphisms: Relation with platelet serotonin level in patients with primary Sjogren's syndrome. J Neuroimmunol. 2015;282:104-9.**

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Significantly lower platelet serotonin level (PSL) in patients with primary Sjogren's syndrome (pSS) than in healthy controls has been reported in our prior studies. In the present report, we demonstrated effect of functional polymorphisms in the serotonin transporter gene (5-HTT) on PSL. We describe a group of 61 pSS patients and 100 healthy individuals subjects, who received PSL measurement in our prior study. All subjects were genotyped for the promoter

5-HTTLPR (L/S), rs25531 (A/G) and intronic 5-HTTVNTRin2 (l/s) polymorphisms. Overall, the presence of 5-HTTVNTRin2 ss genotype was associated with significantly lower PSL in pSS patients, not in healthy controls. Reduced PSL in pSS patients is in line with hypothesis of association between chronic immunoinflammation and 5-HT system dysregulation, identifying additional mechanisms such as altered 5-HT transport as potential genetic factor contributing to PSL depletion.

**Bergovec M<sup>1</sup>, Kubat O<sup>2</sup>, Smerdelj M<sup>2</sup>, Seiwerth S<sup>3</sup>, Bonevski A<sup>4</sup>, Orlic D<sup>2</sup>. Epidemiology of musculoskeletal tumors in a national referral orthopedic department. A study of 3482 cases. Cancer Epidemiol. 2015;39(3):298-302.**

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AIM OF THE STUDY: Musculoskeletal tumors are relatively rare, and their geographic distribution varies greatly around the world. In this study, we present the incidence, age distribution and localization of musculoskeletal tumors diagnosed and/or treated at a tertiary referral orthopedic department, catering to an entire Southeastern European country. METHODS: This was a retrospective study of prospectively collected data, in which all patients diagnosed and/or treated for musculoskeletal tumors at our Department in the period of 30 years (1981-2010) were included. RESULTS: Data of a total of 3482 patients with musculoskeletal tumors were collected. Average age of patients was 33.5 years (range, 2 months-88 years), with even distribution according to sex. Malignant tumors were seen in 20.7% of patients, more often in men (56.9%). Most common malignant tumors were osteosarcoma (estimated incidence: 1.68/million/year), chondrosarcoma (0.79/million/year) and Ewing sarcoma (0.76/million/year). Benign tumors and tumor-like lesions were found in 79.3% of patients, with slight female predominance. Most common benign bone

lesions were osteochondroma (5.81/million/year), simple bone cyst (2.13/million/year), and enchondroma (2.05/million/year). CONCLUSION: This report represents a first of its kind in our region, and gives representative results to be compared to other middle and south European countries. Further nationwide studies are needed to improve strategies in bone tumor diagnosis and treatment.

**Čavar S, Jelašić D, Seiwerth S, Milošević M, Hutinec Z, Mišić M. Endoglin (CD 105) as a potential prognostic factor in neuroblastoma. *Pediatr Blood Cancer*. 2015;62(5):770-5.**

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**BACKGROUND:** Endoglin (CD105) is a cytokine that modulates angiogenesis by regulating different cellular functions, including endothelial proliferation, differentiation, migration and formation of microvessels. CD105 is expressed strongly in the tumor vasculature, and intratumoral microvessel density (IMVD), as determined by the use of antibodies to CD105, it has been found to be an important prognostic indicator for outcome in various malignancies. This study aims to determine if the clinical outcome of children with neuroblastoma is correlated with IMVD, as determined by CD105 staining and other prognostic factors. **PROCEDURE:** Tumor tissue specimens from 38 patients with peripheral neuroblastic tumors who underwent surgical resection or biopsy of their primary tumor without any preoperative therapy were retrospectively reviewed. IMVD was identified immunohistochemically using monoclonal antibodies against CD105. Prognostic factors, such as the MYCN oncogene, disease stage, histopathology and age, were correlated with outcome. **RESULTS:** Among 38 examined specimens, the median IMVD value was 23.2 (15.1-28.4). The IMVD identified by CD105 was significantly higher in patients with unfavorable histology, metastatic disease, MYCN amplification and COG high risk group. ROC analysis was used to find significant IMVD level regarding EFS. The cut-off >18 was selected according to the greatest sensitivity (100%) and specificity (68.42%). The multivariate Cox proportional hazards analysis demonstrated that MYCN amplification and IMVD were significant prognostic factors in predicting EFS (hazard ratio for MYCN amplification: 3.61; 95% CI: 1.20-10.90; P = 0.023 and for IMVD: 1.05; 95% CI: 1.00-1.09; P = 0.037). **CONCLUSION:** IMVD determined by CD105 appeared to be an independent prognostic factor for neuroblastoma.

**Tomičić M, Petric D, Rumboldt M, Carević V, Rumboldt Z. Deep breathing: A simple test for white coat effect detection in primary care. *Blood Press*. 2015;24(3):158-63.**

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**AIM:** White coat hypertension (WCH) is hard to differentiate from sustained hypertension without the use of 24-h ambulatory blood pressure monitoring (ABPM). This invaluable procedure is nevertheless cumbersome and expensive. A simple test of deep breathing over 30 s (DBT) was proposed as a method to unveil WCH. **METHODS:** Two hundred and fourteen outpatients referred for the evaluation of uncontrolled hypertension (blood pressure, BP > 140/90 mmHg despite therapy) were enrolled in a controlled clinical trial. The examinees were randomly divided in two groups: control (n = 108; sequential standard BP measurement only) and intervention (n = 106; the same+DBT), using ABPM as the reference standard. **RESULTS:** The relative decrease in BP was significantly larger in the intervention group than in the control group, by 15/4 mmHg (p = 0.005). The best detection of WCH was obtained at ≥ 15% systolic BP reduction following DBT, with a positive predictive value of 94.0% (95% CI 72.0-100.0). BP reduction of ≤ 8% may rule WCH out with a negative predictive value of 78.4% (95% CI 64.0 - 85.9). **CONCLUSION:** DBT is a reliable, inexpensive and fast test for the detection of WCH in primary care.