

CROATIAN INTERNATIONAL PUBLICATIONS

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Klarica M, Radoš M, Erceg G, Petošić A, Jurjević I, Orešković D. The influence of body position on cerebrospinal fluid pressure gradient and movement in cats with normal and impaired craniospinal communication. PLoS One. 2014;9(4):e95229.

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Intracranial hypertension is a severe therapeutic problem, as there is insufficient knowledge about the physiology of cerebrospinal fluid (CSF) pressure. In this paper a new CSF pressure regulation hypothesis is proposed. According to this hypothesis, the CSF pressure depends on the laws of fluid mechanics and on the anatomical characteristics inside the cranial and spinal space, and not, as is today generally believed, on CSF secretion, circulation and absorption. The volume and pressure changes in the newly developed CSF model, which by its anatomical dimensions and basic biophysical features imitates the craniospinal system in cats, are compared to those obtained on cats with and without the blockade of craniospinal communication in different body positions. During verticalization, a long-lasting occurrence of negative CSF pressure inside the cranium in animals with normal cranio-spinal communication was observed. CSF pressure gradients change depending on the body position, but those gradients do not enable unidirectional CSF circulation from the hypothetical site of secretion to the site of absorption in any of them. Thus, our results indicate the existence of new physiologi-

cal/pathophysiological correlations between intracranial fluids, which opens up the possibility of new therapeutic approaches to intracranial hypertension.

Matković Puljić V, Kosanović Ličina ML, Kavić M, Nemeth Blažić T. Repeat HIV Testing at Voluntary Testing and Counseling Centers in Croatia: Successful HIV Prevention or Failure to Modify Risk Behaviors? PLoS One. 2014;9(4):e93734.

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HIV testing plays a critical role in preventing the spread of the virus and identifying infected individuals in need of care. Voluntary counseling and testing centers (VCTs) not only conduct testing but they also provide counseling. Since a proportion of people who test negative for HIV on their previous visit will return for retesting, the frequency of retesting and the characteristics of those who retest may provide insights into the efficacy of testing and counseling strategies. In this cross-sectional, retrospective study of 1,482 VCT clients in Croatia in 2010, 44.3% had been tested for HIV before. The rate of repeat HIV testing is lower in Croatia than in other countries. Men who have sex with men (MSM) clients, those with three or more sexual partners in the last 12 months, consistent condom users with steady partners, and intravenous drug users were more likely to be repeat testers. This finding suggests that clients presenting for repeat HIV testing are those who self-identify as being at a higher risk of infection. Our data showed that testing positive for HIV was not associated with

repeat testing. However, the effects of repeat testing on HIV epidemiology needs to be explored.

Bilic P, Jukic V, Vilibic M, Savic A, Bozina N. Treatment-resistant schizophrenia and DAT and SERT polymorphisms. *Gene*. 2014;543(1):125-32.

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One fifth to one third of all patients diagnosed with schizophrenia are resistant to drug treatment, which makes it a major clinical challenge. Genetic studies have focused on the association between treatment resistant schizophrenia (TRS) and a number of candidate genes, including serotonin and dopamine system genes. We explored associations between carefully characterized TRS and DAT-VNTR, SERT-PR and SERT-in2 polymorphisms. There were 173 patients enrolled in the study that were clinically evaluated using Positive and Negative Syndrome Scale and Clinical Global Impressions Scales and divided into two groups based on treatment resistance (92 patients in TRS group). Patients with a combination of SERT-in2 II and DAT 9/10, 9/11, 9/9 and 6/6 genotypes were more likely to have TRS, compared to those with 10/10 or 10/12 genotype (OR=5.1; 95% CI=1.6-16.8). In the group of patients with DAT 10/10 or 10/12 genotype, those who also shared SERT-in2 I or ss genotype were more likely to have TRS, compared to II genotype carriers (OR=2.7; 95% CI=1.0-7.0). The model in which interaction between SERT-in2 and DAT polymorphisms is linked to TRS can possibly explain contradictory previous results regarding role of DAT and SERT in TRS, but further research is needed.

Oreskovic Z, Bicanic G, Hrabac P, Tripkovic B, Delimar D. Treatment of postoperative pain after total hip arthroplasty: comparison between metamizol and paracetamol as adjunctive to opioid analgesics-prospective, double-blind, randomised study. *Arch Orthop Trauma Surg*. 2014;134(5):631-6.

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INTRODUCTION: Metamizole use has been limited because of its risk of agranulocytosis. However, more recent literature seems to support its safety. This prospective, randomised, double-blind study was conducted to

compare the analgesic effects of intravenous metamizole or intravenous paracetamol in combination with morphine PCA during the first 24 h following total hip arthroplasty. **MATERIALS AND METHODS:** One hundred ten consecutive patients were selected for study. The two study groups were (A) metamizole, (B) paracetamol. Postoperative pain therapy was provided by Morphine PCA pump. In the first treatment group (A group), all patients received intravenous metamizole 1.5 g every 8 h during the first 24 postoperative hours. In the second treatment group (B group), all patients received intravenous paracetamol 1 g every 8 h during the first 24 postoperative hours. Postoperative pain intensity was measured 1, 2, 3, 4, 6, 8, 10, 14, 18, 22 h after the end of surgery by a VAS. **RESULTS:** Statistically significant differences in VAS pain values favoring metamizole were reported at 6-h ($p = 0.038$), 8-h ($p = 0.036$), 14-h ($p = 0.011$), 18-h ($p < 0.001$) and 22-h ($p = 0.025$) post-baseline. Mean cumulative pain values were 17.9 for metamizole and 30.6 for paracetamol. **CONCLUSIONS:** In this study, we have also shown excellent efficacy of paracetamol and metamizole combined with opioids, but metamizole proved to be a better analgesic than paracetamol. It is also necessary to mention the financial aspect considering that intravenous paracetamol is about ten times more expensive than an equivalent analgesic doses of intravenous metamizole.

Tafra R, Brakus SM, Vukojevic K, Kablar B, Colovic Z, Saraga-Babic M. Interplay of proliferation and proapoptotic and antiapoptotic factors is revealed in the early human inner ear development. *Otol Neurotol*. 2014;35(4):695-703.

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HYPOTHESIS: Spatiotemporal interplay of factors controlling proliferation, differentiation and apoptosis within the developing human inner ear is essential for labyrinth morphogenesis and development of vestibular and cochlear functions. **BACKGROUND:** Studies on the early human inner ear development are scarce and insufficient. **METHODS:** The immunolocalization of Ki-67, Bcl-2, caspase-3, and IGF-1 was analyzed in 6 human inner ears, 5 to 10 gestational weeks old. Statistical data were analyzed using the Kruskal-Wallis test. **RESULTS:** During the analyzed period, the otocyst has transformed into cochlear duct and

sacculle ventrally and semicircular canals and utricle dorsally. Initial differentiation of sensorineural fields characterized organ of Corti, maculae, and cristae ampullares. Intense (50%) and evenly distributed proliferation Ki-67 in the otocyst decreased to 24% to 30% and became spatially restricted within the membranous labyrinth epithelium. Simultaneously, expression of antiapoptotic Bcl-2 protein increased in sensorineural fields of organ of Corti, macula, and crista ampullaris. Throughout the investigated period, apoptotic caspase-3 positive cells were mainly distributed at the luminal and basal surfaces of labyrinth epithelium. An inhibitor of apoptosis IGF-1 co-expressed with Bcl-2 and increased in the sensorineural fields with advancing development. CONCLUSION: The described expression pattern indicates roles for cell proliferation in the growth of the inner ear and Bcl-2 in differentiation of sensorineural fields and protection from apoptosis. Both IGF-1 and caspase-3-mediated apoptosis seem to contribute to proper morphogenesis, differentiation, and innervations of sensorineural fields within the cochlea, semicircular canals, sacculle, and utricle. Alterations in spatiotemporal interplay of investigated factors might lead to disturbances of vestibular and cochlear function.

Ljubičić N, Budimir I, Pavić T, Biščanin A, Puljiz Z, Bratanić A, Troškot B, Zekanović D. Mortality in high-risk patients with bleeding Mallory-Weiss syndrome is similar to that of peptic ulcer bleeding. Results of a prospective database study. Scand J Gastroenterol. 2014;49(4):458-64.

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Abstract Objective. The aim of this study was to identify the predictive factors influencing mortality in patients with bleeding Mallory-Weiss syndrome in comparison with peptic ulcer bleeding. **Material and methods.** Between January 2005 and December 2009, 281 patients with endoscopically confirmed Mallory-Weiss syndrome and 1530 patients with peptic ulcer bleeding were consecutively evaluated. The 30-day mortality and clinical outcome were related to the patients' demographic data, endoscopic, and clinical characteristics. **Results.** The one-year cumulative incidence for bleeding Mallory-Weiss syndrome was 7.3 cases/100,000 people and for peptic ulcer bleeding 40.4 cases/100,000 people. The age-standardized incidence for both bleeding Mallory-Weiss syndrome and peptic

ulcer bleeding remained unchanged during the observational five-year period. The majority of patients with bleeding Mallory-Weiss syndrome were male patients with significant overall comorbidities (ASA class 3-4). Overall 30-day mortality rate was 5.3% for patients with bleeding Mallory-Weiss syndrome and 4.6% for patients with peptic ulcer bleeding ($p = 0.578$). In both patients with bleeding Mallory-Weiss syndrome and peptic ulcer bleeding, mortality was significantly higher in patients over 65 years of age and those with significant overall comorbidities (ASA class 3-4). **Conclusion.** The incidence of bleeding Mallory-Weiss syndrome and peptic ulcer bleeding has not changed over a five-year observational period. The overall 30-day mortality was almost equal for both bleeding Mallory-Weiss syndrome and peptic ulcer bleeding and was positively correlated to older age and underlying comorbid illnesses.

Matanović SM, Vlahović-Palčevski V. Potentially inappropriate prescribing to the elderly: comparison of new protocol to Beers criteria with relation to hospitalizations for ADRs. Eur J Clin Pharmacol. 2014;70(4):483-90.

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PURPOSE: Screening tools for detecting potentially inappropriate medications (PIMs) represent an important way to assess drug prescribing in the elderly. Recently, we introduced a new comprehensive tool to detect both PIMs and clinically important drug-drug interactions (DDI). The aim of the study was to assess the applicability of the new tool. **METHODS:** The new tool was used to detect PIMs and DDI and to assess their relation to morbidity and hospital admissions. It was also compared to the widely used Beers criteria. The study population included 454 consecutive patients aged ≥ 65 years who were acutely admitted to the Department of Internal Medicine of the University Hospital of Osijek. The Naranjo protocol was used to analyze the causal relationship between a drug and an adverse event. **RESULTS:** According to the new protocol, 44 % patients were taking PIMs, while 33 % patients were taking drugs with potentially serious DDIs. In 11 % of the overall number of patients, the cause of admission was adverse drug reaction (ADR), and among contributing drugs, 44 % were potentially inappropriate according to our protocol. Gastrointestinal bleeding was the most common diagnosis causing ADR-associated admission, and in 72 % cases, either PIM or a potentially serious DDI was involved. **CONCLUSION:** The new Croatian tool detected a high number of patients taking PIMs and/or having potentially impor-

tant drug-drug interactions. The tool also detected almost half of the drugs contributing to ADR-associated admission. We expect the tool to be useful in prescription evaluation for the elderly inpatient and outpatient population.

Lukšić I, Suton P, Macan D, Dinjar K. Intraoral adenoid cystic carcinoma: is the presence of perineural invasion associated with the size of the primary tumour, local extension, surgical margins, distant metastases, and outcome? Br J Oral Maxillofac Surg. 2014;52(3):214-8.

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Adenoid cystic carcinoma is the most common malignancy of the minor salivary glands, and its biological behaviour is characterised by slow and indolent growth; rare involvement of regional lymph nodes; a high propensity for perineural invasion; multiple or delayed recurrences, or both;

and a high incidence of distant metastases. Our aim was to find out the relation between the presence of perineural invasion and these factors. Between 1 January 1984 and 1 May 2008, 26 cases of adenoid cystic carcinoma of the intraoral salivary glands, which had initially been treated surgically, were reviewed retrospectively. The most common site was the palate, and perineural invasion was reported in 13 of the 26 resected specimens. There was no significant association between it and the size of the primary tumour (OR=1.0; p=1.00), invasion of the surgical margins (OR=2.08; p=0.4), the presence of distant metastases (OR=3.43; p=0.197), or local control (p=0.76). It was exclusively present in patients with local extension, and was significantly associated with outcome (p=0.04). Resection with clear margins is the gold standard of care for patients with intraoral adenoid cystic carcinoma, and the role of adjuvant irradiation remains controversial. Given its paradoxical and complex biological behaviour, large studies with long term follow-up are needed to define the clinicopathological and immunohistochemical variables associated with outcome, as well as the optimal treatment.