

## CROATIAN INTERNATIONAL PUBLICATIONS

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Tomlinson M, Swartz L, Officer A, Chan KY, Rudan I\*, Saxena S. Research priorities for health of people with disabilities: an expert opinion exercise. *Lancet*. 2009;374:1857-62.

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International evidence shows that people with disabilities have many unmet health and rehabilitation needs, face barriers in accessing mainstream health-care services, and consequently have poor health. Inadequate specific information is available about the prevalence and patterns of health conditions of people with disabilities, effective interventions, and policy-relevant research about what works to improve health and functioning of people with disabilities. In view of the urgency of the issues at stake and scarcity of resources, research contributing to improvement of health of people with disabilities needs to be prioritised. We invited 82 stakeholders to list and score research options, with the priority-setting method of the Child Health and Nutrition Research Initiative. 83 research questions were assessed for answerability, applicability, sensitivity, support within the context, and equity. The leading research priority was identification of barriers that people with disabilities have in accessing health services at different levels, and finding the best possible strategies to integrate their needs into primary health-care systems and ensure local delivery. Results showed that addressing specific impairments is secondary to ensuring that health systems provide adequately for all people with disabilities. Our findings are a call for urgent attention to the issue of access to appropriate health care for people with disabilities, especially in low-income and middle-income countries.

Ilić I, Mitrović Z, Aurer I, Basić-Kinda S, Radman I, Ajduković R, Labar B, Dotlić S, Nola M. Lack of prognostic significance of the germinal-center phenotype in diffuse large B-cell lymphoma patients

treated with CHOP-like chemotherapy with and without rituximab. *Int J Hematol*. 2009;90:74-80.

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The influence of the germinal-center B-cell (GCB) and the non-GCB phenotypes of diffuse large B-cell lymphoma (DLBCL) on the outcome of 92 patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy, with or without rituximab was determined in this study. The differentiation between the GCB and non-GCB types was arrived at by immunohistochemistry using previously published criteria. Thirty-nine patients had the GCB and 53 had the non-GCB type of DLBCL. Forty-nine patients were treated with rituximab and chemotherapy; 43 were treated with chemotherapy alone. The GCB and non-GCB group did not differ in their international prognostic index factors and score, presence of bulky disease, or frequency of rituximab treatment. Median follow-up of the surviving patients was carried out for 37 months. There was no difference between the GCB and non-GCB groups in both overall response rates (67 vs. 70%, respectively) and estimated rates of 3-year event-free (46 vs. 49%, respectively) and overall (54 vs. 56%, respectively) survival. In addition, no differences of the outcomes were observed between the subgroups treated with or without rituximab. The patients of this study with immunohistochemically determined GCB-type DLBCL did not have an improved prognosis, irrespective of whether they had received rituximab or not.

Mejstříková E, Fronková E, Kalina T, Omelka M, Batinić D\*, Dubravčić K\*, et al. Detection of residual B precursor lymphoblastic leukemia by uniform gating flow cytometry. *Pediatr Blood Cancer*. 2010;54:62-70.

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**BACKGROUND:** Residual disease (RD) is an important prognostic factor in acute lymphoblastic leukemia (ALL). Flow cytometry (FC)-based RD detection is easy to perform, but interpretation requires expert analysis due to individual differences among patients. **PROCEDURE:** We focused at the design of standardized and reproducible RD monitoring in ALL. RD was investigated by a uniform gating strategy, which was designed internationally and tested in one center by Ig/TCR rearrangements. **RESULTS:** For each gate, positivity cutoff value was assigned using quantification of non-leukemic background. Comparing to Ig/TCR at 0.1% level, 80 of 103 specimens were correctly diagnosed by FC. The predictive value of FC RD at day 15 was then analyzed. In B lineage ALL, day 15 FC significantly correlated with Ig/TCR results at day 33 and/or week 12 ( $P < 0.01$ ). No significant correlation was found in T lineage ALL. **CONCLUSIONS:** Thus, FC with preset uniform gating at day 15 predicts PCR-detectable MRD in B precursor ALL. Presented data may be used to define new polychromatic cytometric diagnostics of MRD including semiautomatic assessment.

**Vuković J, Modun D, Budimir D, Sutlović D, Salamunić I, Žaja I, et al. Acute, food-induced moderate elevation of plasma uric acid protects against hyperoxia-induced oxidative stress and increase in arterial stiffness in healthy humans. *Atherosclerosis*. 2009;207:255-60**

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We examined the effects of acute, food-induced moderate increase of plasma uric acid (UA) on arterial stiffness and markers of oxidative damage in plasma in healthy males exposed to 100% normobaric oxygen. Acute elevation of plasma UA was induced by consumption of red wine, combination of ethanol and glycerol, or fructose. By using these beverages we were able to separate the effects of UA, wine polyphenols and ethanol. Water was used as a control beverage. Ten males randomly consumed test beverages in a cross-over design over the period of 4 weeks, one beverage per week. They breathed 100% O<sub>2</sub> between 60(th) and 90(th)min of the 4-h study protocol. Pulse wave augmentation index (AIx) at brachial and radial arteries, plasma antioxidant capacity (AOC), thiobarbituric acid-reactive substances (TBARS), lipid hydroperoxides (LOOH) assessed by xylenol orange method, UA and blood ethanol concentrations were determined before and 60, 90, 120, 150 and 240 min after beverage consumption. Consumption of the beverages did not affect the AIx, TBARS or LOOH values during 60 min before exposure to hyperoxia, while AOC

and plasma UA increased except in the water group. Significant increase of AIx, plasma TBARS and LOOH, which occurred during 30 min of hyperoxia in the water group, was largely prevented in the groups that consumed red wine, glycerol+ethanol or fructose. In contrast to chronic hyperuricemia, generally considered as a risk factor for cardiovascular diseases and metabolic syndrome, acute increase of UA acts protectively against hyperoxia-induced oxidative stress and related increase of arterial stiffness in large peripheral arteries.

**Stanietsky N, Šimić H\*, Arapović J\*, Toporik A, Levy O, Novik A, et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. *Proc Natl Acad Sci U S A*. 2009;106:17858-63**

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NK cell cytotoxicity is controlled by numerous NK inhibitory and activating receptors. Most of the inhibitory receptors bind MHC class I proteins and are expressed in a variegated fashion. It was recently shown that TIGIT, a new protein expressed by T and NK cells binds to PVR and PVR-like receptors and inhibits T cell activity indirectly through the manipulation of DC activity. Here, we show that TIGIT is expressed by all human NK cells, that it binds PVR and PVRL2 but not PVRL3 and that it inhibits NK cytotoxicity directly through its ITIM. Finally, we show that TIGIT counter inhibits the NK-mediated killing of tumor cells and protects normal cells from NK-mediated cytotoxicity thus providing an "alternative self" mechanism for MHC class I inhibition.

**Kojundžić SL, Puljak L, Hogan Q, Sapunar D. Depression of Ca(2+)/calmodulin-dependent protein kinase II in dorsal root ganglion neurons after spinal nerve ligation. *J Comp Neurol*. 2010;518:64-74.**

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The enzyme calcium/calmodulin-dependent protein kinase II (CaMKII) is associated with memory and its alpha isoform is critical for development of activity-induced synaptic changes. Therefore, we hypothesized that CaMKII is involved in altered function of dorsal root ganglion (DRG) neurons after neuronal injury. To test this hypothesis, Sprague-Dawley rats were made hyperalgesic by L5 and L6 spinal nerve ligation (SNL), and changes in total phosphorylated and unphosphorylated CaM-

KII (tCaMKII) and phosphorylated form of its alpha isoform (pCaMKIIalpha) were analyzed using immunochemistry in different subpopulations of DRG. SNL did not induce any changes in tCaMKII between experimental groups, while the overall percentage of pCaMKIIalpha-positive neurons in injured L5 DRG SNL (24.8%) decreased significantly when compared to control (41.7%). SNL did not change the percentage of pCaMKIIalpha/N52 colabeled neurons but decreased the percentage of N52-negative nonmyelinated neurons that expressed pCaMKIIalpha from 27% in control animals to 11% after axotomy. We also observed a significant decrease in the percentage of small nonpeptidergic neurons labeled with IB4 (37.6% in control vs. 4.0% in L5 SNL DRG), as well as a decrease in the percentage of pCaMKIIalpha/IB4 colabeled neurons in injured L5 DRGs (27% in control vs. 1% in L5 DRG of SNL group). Our results show that reduction in pCaMKIIalpha levels following peripheral injury is due to the loss of IB4-positive neurons. These results indicate that diminished afferent activity after axotomy may lead to decreased phosphorylation of CaMKIIalpha.

**Dujić Z, Uglešić L, Brešković T, Valić Z, Heusser K, Marinović J, Ljubković M, Palada I. Involuntary breathing movements improve cerebral oxygenation during apnea struggle phase in elite divers. J Appl Physiol. 2009;107:1840-6**

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We investigated whether the involuntary breathing movements (IBM) during the struggle phase of breath holding, together with peripheral vasoconstriction and progressive hypercapnia, have a positive effect in maintaining cerebral blood volume. The central hemodynamics, arterial oxygen saturation, brain regional oxyhemoglobin (bHbO<sub>2</sub>), deoxyhemoglobin, and total hemoglobin changes and IBM were monitored during maximal dry breath holds in eight elite divers. The frequency of IBM increased (by approximately 100%), and their duration decreased (approximately 30%), toward the end of the struggle phase, whereas the amplitude was unchanged (compared with the beginning of the struggle phase). In all subjects, a consistent increase in brain regional deoxyhemoglobin and total hemoglobin was also found during struggle phase, whereas bHbO<sub>2</sub> changed biphasically: it initially increased until the middle of the struggle phase, with the subsequent relative decline at the end of the breath hold. Mean arterial pressure was elevated during the struggle phase, al-

though there was no further rise in the peripheral resistance, suggesting unchanged peripheral vasoconstriction and implying the beneficial influence of the IBM on the cardiac output recovery (primarily by restoration of the stroke volume). The IBM-induced short-lasting, sudden increases in mean arterial pressure were followed by similar oscillations in bHbO<sub>2</sub>. These results suggest that an increase in the cerebral blood volume observed during the struggle phase of dry apnea is most likely caused by the IBM at the time of the hypercapnia-induced cerebral vasodilatation and peripheral vasoconstriction.

**Bojanić I, Bergovec M, Smoljanović T. Combined anterior and posterior arthroscopic portals for loose body removal and synovectomy for synovial chondromatosis. Foot Ankle Int. 2009;30:1120-3**

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**BACKGROUND:** Synovial chondromatosis is a rare disorder characterized by formation of cartilaginous bodies within the synovia of joints, tendon sheaths, and bursae secondary to a synovial metaplastic process. Recent literature has described using only an anterior approach to the ankle for these patients. It is unclear how well, if at all, synovectomy of the posterior part of the ankle joint was performed. Most recurrences occur years after surgery, as a result of incomplete synovectomy. **MATERIALS AND METHODS:** We treated five patients (mean age 31.6 years; range, 21 to 63; four male, one female) with synovial chondromatosis of the ankle. We performed arthroscopic loose body removal and total synovectomy using both posterior and anterior ankle arthroscopic portals. At latest followup of a mean of 34.2 (range, 13 to 58) months, the functional result was assessed with the AOFAS score. **RESULTS:** The AOFAS score improved from a mean of 67 (range, 58 to 77) points to a mean of 94 (range, 77 to 100) points. Overall patient satisfaction was good to excellent. We noted only one minor complication when a loose body was lost in the subcutaneous tissue, and was removed two weeks after the arthroscopy. **CONCLUSION:** Our experience in this small group of patients seems to indicate that a 2 portal approach with total synovectomy and removal of loose bodies gives the best result and minimizes the risk of recurrence.