

CROATIAN INTERNATIONAL PUBLICATIONS

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Eterović M¹, Medved V², Bilić V², Kozarić-Kovačić D³, Žarković N⁴. Poor Agreement Between Two Commonly Used Measures of Shame- and Guilt-Proneness. *J Pers Assess.* 2019 Apr 23:1-9. doi: 10.1080/00223891.2019.1585361.

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This study sought to assess the agreement between commonly used measures of shame- and guilt-proneness, the Test of Self-Conscious Affect-3 (TOSCA-3), representing scenario measures, and the Personal Feelings Questionnaire-2 (PFQ-2), representing checklist measures. To overcome the limitations of the widely used correlation analysis, the 2 measures were compared by the Bland-Altman method. We administered both measures at once to the same sample of 138 graduate students (67.39% were female; median age = 27 years). A randomly selected sample of 46 students repeated the procedure 8 weeks later. We tested how well our data fit the hypothesized measurement models, analyzed internal consistency of measures, evaluated their repeatability, and analyzed the agreement between them. To account for the different ranges, both measures' scores were expressed as the percentages of their maxima. The observed data fit the proposed models well. Both measures showed good internal consistency and repeatability. In the shame domain, TOSCA-3 exceeded PFQ-2 scores by 22.32% on average (49.81, -5.13%; 95% limits of agreement), and even more in the guilt domain, by 38.4% (67.75, 8.20%). Our results question the often-assumed congruence of the shame domains assessed by scenario and checklist measures.

Rosic Despalatovic B¹, Bratanic A², Puljiz Z², Bozickovic J¹. Esophageal Stenosis in a Patient with Lichen Planus. *Case Rep Gastroenterol.* 2019 Mar 7;13(1):134-139. doi: 10.1159/000498907. eCollection 2019 Jan-Apr.

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Lichen planus is a chronic, idiopathic disorder which usually affects skin and mucosal surfaces. While oral mucosa is frequently involved, esophageal localization is uncommon, and it usually manifests with dysphagia. It has also been associated with squamous cell carcinoma. Underdiagnosing of esophageal lichen planus often leads to a delay in treatment. There are also no clear recommendations for treatment of this disorder. Systemic corticosteroids are usually the first-line therapy, but different other therapeutic approaches are also used, with a various rate of response. We present the case of a patient with esophageal lichen planus complicated with esophageal stenosis, who was rather resistant to treatment.

Kopjar N¹, Fuchs N², Žunec S¹, Mikolić A¹, Micek V¹, Kozina G³, Lucić Vrdoljak A¹, Brčić Karačonji I¹. DNA Damaging Effects, Oxidative Stress Responses and Cholinesterase Activity in Blood and Brain of Wistar Rats Exposed to Δ^9 -Tetrahydrocannabinol. *Molecules.* 2019 Apr 19;24(8). pii: E1560. doi: 10.3390/molecules24081560.

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Currently we are faced with an ever-growing use of Δ^9 -tetrahydrocannabinol (THC) preparations, often

used as supportive therapies for various malignancies and neurological disorders. As some of illegally distributed forms of such preparations, like cannabis oils and butane hash oil, might contain over 80% of THC, their consumers can become intoxicated or experience various detrimental effects. This fact motivated us for the assessments of THC toxicity in vivo on a Wistar rat model, at a daily oral dose of 7 mg/kg which is comparable to those found in illicit preparations. The main objective of the present study was to establish the magnitude and dynamics of DNA breakage associated with THC exposure in white blood and brain cells of treated rats using the alkaline comet assay. The extent of oxidative stress after acute 24 h exposure to THC was also determined as well as changes in activities of plasma and brain cholinesterases (ChE) in THC-treated and control rats. The DNA of brain cells was more prone to breakage after THC treatment compared to DNA in white blood cells. Even though DNA damage quantified by the alkaline comet assay is subject to repair, its elevated level detected in the brain cells of THC-treated rats was reason for concern. Since neurons do not proliferate, increased levels of DNA damage present threats to these cells in terms of both viability and genome stability, while inefficient DNA repair might lead to their progressive loss. The present study contributes to existing knowledge with evidence that acute exposure to a high THC dose led to low-level DNA damage in white blood cells and brain cells of rats and induced oxidative stress in brain, but did not disturb ChE activities.

Saric F¹, Barcot O², Puljak L³. Risk of bias assessments for selective reporting were inadequate in the majority of Cochrane reviews. *J Clin Epidemiol*. 2019 Apr 19. pii: S0895-4356(18)31135-1. doi: 10.1016/j.jclinepi.2019.04.007.

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OBJECTIVE: To analyze adequacy of risk of bias (RoB) judgments for selective reporting in Cochrane systematic reviews. **STUDY DESIGN AND SETTING :** We extracted RoB assessments, including judgment (low, high or unclear risk) and supporting comment from Cochrane reviews of randomized controlled trials using computer parser. We analyzed sources of information mentioned in supporting comments. We compared judgments of Cochrane authors with guidance from the Cochrane

Handbook for Systematic Reviews of Interventions (Cochrane Handbook) and categorized them into adequate or inadequate. **RESULTS:** At least 60% of judgments for risk of selective reporting bias of trials in analyzed Cochrane reviews were not in line with the Cochrane Handbook. Few Cochrane authors mentioned the trial protocol as a source of data for assessing selective reporting. Most of the inadequate judgments were made among trials that were judged with low risk of selective reporting bias; more than 90%. In 9% of analyzed RoB tables, Cochrane authors did not use this RoB domain at all. **CONCLUSIONS:** Cochrane authors frequently make RoB judgments about selective reporting that are not in line with Cochrane Handbook and not mentioning trial protocol. Interventions aimed at helping Cochrane authors to make adequate RoB assessments in Cochrane reviews would be beneficial.

Skokauskas N¹, Fung D², Flaherty LT³, von Klitzing K⁴, Pūras D⁵, Servili C⁶, Dua T⁷, Falissard B⁸, Vostanis P⁹, Moyano MB¹⁰, Feldman I¹¹, Clark C¹², Boričević V¹³, Patton G¹⁴, Leventhal B¹⁵, Guerrero A¹⁶. Shaping the future of child and adolescent psychiatry. *Child Adolesc Psychiatry Ment Health*. 2019 Apr 11;13:19. doi: 10.1186/s13034-019-0279-y. eCollection 2019.

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Child and adolescent psychiatry is in a unique position to respond to the growing public health challenges associated with the large number of mental disorders arising early in life, but some changes may be necessary to meet these challenges. In this context, the future of child and adolescent psychiatry was considered by the Section on Child and Adolescent Psychiatry of the World Psychiatric Association (WPA CAP), the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP), the World Association for Infant Mental Health (WAIMH), the International Society for Adolescent Psychiatry and Psychology (ISAPP), the UN Special Rapporteur on the Right to Health, representatives of the WHO Department of Mental Health and Substance Abuse, and other experts. We take this opportunity to outline four consensus priorities for child and adolescent psychiatry over the next decade: increase the workforce necessary for providing care for children, adolescents and families facing mental disorders; reorienting child and adolescent mental health services to be more responsive to broader public health needs; increasing research and research training while also integrating new research finding promptly and efficiently into clinical practice and research training; Increasing efforts in advocacy.

Krajcar N¹, Marić LS^{1,2}, Šarić D³, Milić N⁴, Tešović G^{1,5}. Cefpodoxime proxetil as a therapeutic option in switching therapy for infective endocarditis in children: case reports and literature review. J Chemother. 2019 Apr 22:1-5. doi: 10.1080/1120009X.2019.1603797.

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Infective endocarditis (IE) is uncommon in children, affecting predominantly subjects with congenital heart disease (CHD) and patients with indwelling central lines. The principles of antibiotic treatment in paediatric population are similar to those in adults. Prolonged intravenous administration of bactericidal rather than bacteriostatic agents is preferred. Outpatient intravenous therapy after initial treatment in the hospital may be considered only in selected patients. Partial oral treatment has been described in cases of left-sided, uncomplicated IE caused by common pathogens in adult patients. There are no guidelines or trials in paediatric population regarding switching therapy from

intravenous to oral route. We present two cases of IE in children caused by uncommon pathogenic bacteria (*Abiotrophia defectiva* and *Haemophilus parainfluenzae*) successfully treated with oral third-generation cephalosporin-cefpodoxime proxetil after initial intravenous therapy. This paper provides observations on different therapeutic approach for IE in children as well as another potential use of cefpodoxime proxetil.

Krecak I¹, Medic MG², Gveric-Krecak V¹, Roncevic P³, Bašić Kinda S³, Babel J², Radonic R^{2,4}. Coombs-positive refractory acquired thrombotic thrombocytopenic purpura in a patient with chronic myelomonocytic leukemia successfully treated with rituximab. Acta Clin Belg. 2019 Apr 22:1-5. doi: 10.1080/17843286.2019.1608395.

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OBJECTIVES: Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare autoimmune disorder characterized by auto-antibodies to Willebrand factor (vWF) cleaving enzyme (ADAMTS13), resulting in unusually large vWF multimers that lead to platelet aggregation, microthrombi formation and microangiopathic hemolytic anemia. Hemolysis in aTTP is mechanical; thus, direct antiglobulin test (Coombs test) is usually negative. Multiple autoimmune conditions and various auto-antibodies have been described in the context of chronic myelomonocytic leukemia (CMML). In this paper, we describe the first case of CMML with auto-antibodies to ADAMTS13, presenting initially as plasmapheresis-refractory Coombs-positive aTTP. **RESULTS:** Although our patient was not treated for CMML, a complete remission of aTTP was eventually achieved with rituximab. **Conclusion;** We propose that aTTP should be in the differential diagnosis of CMML patients with thrombocytopenia and anemia (Coombs positive or not) who develop signs of thrombotic microangiopathy. Further studies are much needed to decipher the immune-mediated processes in CMML.

Stupin A^{1,2}, Stupin M^{1,3}, Baric L¹, Matic A¹, Kolar L¹, Drenjancevic I¹. Sex-related differences in forearm skin microvascular reactivity of young healthy

subjects. *Clin Hemorheol Microcirc.* 2019 Apr 19. doi: 10.3233/CH-180483.

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OBJECTIVE: To assess sex-related differences in forearm skin microvascular reactivity to vascular occlusion and cardiovascular health in young healthy women and men. **METHODS:** 203 young healthy individuals (67 men/136 women) participated in this study. Post-occlusive reactive hyperemia (PORH) in skin microcirculation following 1', 2' and 3' vascular occlusion period was assessed using laser Doppler flowmetry. Anthropometric parameters, body composition, blood pressure, heart rate and biochemical parameters were measured in all participants. Correlations between PORH and measured parameters were determined by using corresponding tests. **RESULTS:** Women had significantly higher forearm PORH following 1', 2' and 3' vascular occlusion than men. Women had lower body mass index and waist-to-hip ratio, but higher fat mass than men. Men had significantly higher blood pressure and lower heart rate than women. Also, women had lower hemoglobin, urea, creatinine and serum uric acid, but higher HDL cholesterol level than men. PORH was negatively associated with waist-to-hip ratio and systolic blood pressure only in women. **CONCLUSIONS:** Young healthy women exhibit higher skin microvascular reactivity to vascular occlusion compared to age-matched men. Increased systolic blood pressure or central obesity (waist-to-hip ratio) may pose greater risk to young healthy women than men by adversely affecting peripheral microvascular function.

Dohrmann DD¹, Putnik P², Bursać Kovačević D³, Simal-Gandara J⁴, Lorenzo JM⁵, Barba FJ⁶. Japanese, Mediterranean and Argentinean diets and their potential roles in neurodegenerative diseases. *Food Res Int.* 2019 Jun;120:464-477. doi: 10.1016/j.foodres.2018.10.090. Epub 2018 Nov 10.

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Environmental factors are responsible of cellular senescence and processes found in the development of cognitive disorders. The aim of this paper is to compare benefits of the Japanese, Mediterranean, and Argentinian Diet on the onset or prevention of senile dementia (SD) and Alzheimer's Disease (AD). Special focus was on the effects of specific compounds such as polyunsaturated fatty acids (PUFAs), antioxidants, and saturated and trans fatty acids. A high adherence to diets rich in PUFAs, monounsaturated fatty acids (MUFAs) and antioxidants may decrease the risk of developing neurodegenerative diseases; while the predominance of saturated and trans fatty acids possibly rises it.

Pallmer K¹, Barnstorf I¹, Baumann NS¹, Borsari M¹, Jonjic S², Oxenius A¹. NK cells negatively regulate CD8 T cells via natural cytotoxicity receptor (NCR) 1 during LCMV infection. *PLoS Pathog.* 2019 Apr 17;15(4):e1007725. doi: 10.1371/journal.ppat.1007725. eCollection 2019 Apr.

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Besides their function in recognizing cancerous and virally infected cells, natural killer (NK) cells have the potential to shape adaptive immune responses. However, the mechanisms employed by NK cells to negatively regulate virus-specific CD8 T cell responses remain to be fully defined. Using activating receptor natural cytotoxicity receptor (NCR) 1 deficient (NCR1gfp/gfp) mice, we found increased numbers of virus-specific CD8 T cells, leading to enhanced virus control during acute LCMV infection. Furthermore, vi-

rus-specific CD8 T cells were more activated in the absence of NCR1, resulting in exacerbated immunopathology, documented by weight loss, and superior virus control early during chronic LCMV infection. Transfer experiments of virus-specific CD8 T cells into NCR1 deficient hosts revealed a direct cross talk between NK and CD8 T cells. Studies on the splenic microarchitecture revealed pronounced disorganization of T cells in infected NCR1gfp/gfp mice, resulting in enhanced immunopathology and disruption of the T cell niche upon chronic LCMV infection. Our data show a novel pathway employed by NK cells to regulate antiviral CD8 T cell responses, namely direct recognition and elimination of activated CD8 T cells via NCR1 early during infection to protect the host from an overshooting T cell response.

Campbell MD^{1,2}, Babic D³, Bolcina U³, Smirčić-Duvnjak L⁴, Tankova T⁵, Mitrakou A⁶, Kempler P⁷, Janez A⁷. High level of clinical inertia in insulin initiation in type 2 diabetes across Central and South-Eastern Europe: insights from SITIP study. *Acta Diabetol.* 2019 Apr 16. doi: 10.1007/s00592-019-01346-1.

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AIMS: Little is known regarding initiation of insulin therapy in type 2 diabetes (T2D) in Central and South-Eastern European countries. Therefore, we conducted a survey to characterise the prescribing practices of specialist diabetes healthcare professionals in this region and assessed factors that influence clinical decision-making regarding insulin initiation in T2D. **METHODS:** A cross-sectional survey sampled 211 specialist diabetes healthcare prescribers from five Central and South-Eastern European countries (Bulgaria, Croatia, Greece, Hungary, and Slovenia). A structured questionnaire was developed which surveyed current clinical practices and influencing factors, barriers to insulin initiation, and combination therapy prescribing preferences. **RESULT:** Only 9.4% (20 of out of 211 respondents)

of healthcare professionals would initiate insulin therapy in T2D patients at the recommended HbA1c threshold of 7-7.9% [53-63 mmol/mol]. Large regional differences were evident in insulin initiation thresholds ($\geq 9.0\%$ [≥ 75 mmol/mol]: Bulgaria 80.8% vs. Slovenia 13.3%). Psychological distress was recorded as the major barrier to insulin initiation. Health insurance regulations were ranked more important than personal clinical experience and clinical guidelines in clinical decision-making. Information from peers was more influential than manufacturer information, clinical experience, and continuous medical education, respectively, for insulin initiation. **CONCLUSIONS:** Despite large regional variation, there is widespread delay of insulin initiation from specialist diabetes healthcare professionals in Central and South-Eastern Europe.

Ferri-Certić J¹, ZavrI-Džananović D², Ležaić L³, Žižek D⁴. Impact of left ventricular pacing threshold on ventricular arrhythmia occurrence in cardiac resynchronization therapy. *J Cardiol.* 2019 Apr 13. pii: S0914-5087(19)30087-5. doi: 10.1016/j.jjcc.2019.03.015.

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BACKGROUND: Cardiac resynchronization therapy (CRT) is an established heart failure (HF) treatment option, however its effect on ventricular arrhythmias (VAs) is controversial. Regional scar burden and high left ventricular (LV) pacing threshold (PT) are associated with poor outcome in CRT patients. The aim of our study was to analyze the impact of intraoperative LVPT on VA occurrence. **METHODS:** Eighty consecutive patients with advanced HF scheduled for a CRT defibrillator device [aged 63.3±10.9 years; New York Heart Association II-III 86.2%; 52 males (65%); 34 ischemic etiology (42.5%); 71 sinus rhythm (88.7%); QRS duration 168±25.7ms] were evaluated using single-photon emission computed tomography myocardial perfusion imaging. Regional myocardial viability was calculated as the mean tracer activity in the corresponding segments at the LV lead pacing site. Fluoroscopic position and intraoperative LVPT were determined at implant after the final LV lead position was determined. **RESULTS:** LVPT was inversely associated with regional myocardial viability ($p = -0.785$, $p < 0.001$). After a median follow-up of 36 months (24-57) months VAs were registered in

27 patients (33.7%). Patients with VAs had higher median intraoperative LVPT compared to those without VAs [2.2V (1.9-2.8) vs. 0.8V (0.6-1.2), $p < 0.001$]. In a multivariate logistic regression model intraoperative LVPT was identified as a strong independent predictor of VAs. **CONCLUSION:** Increased intraoperative LVPT during CRT could be associated with lower regional myocardial viability at LV lead location. CRT patients with higher LVPT could have an increased risk of VA occurrence.

Phelps R¹, Winston JA², Wynn D³, Habek M⁴, Hartung HP⁵, Havrdová EK⁶, Markowitz GS⁷, Margolin DH⁸, Rodriguez CE⁹, Baker DP¹⁰, Coles AJ¹¹. **Incidence, management, and outcomes of autoimmune nephropathies following alemtuzumab treatment in patients with multiple sclerosis.** *Mult Scler.* 2019 Apr 15:1352458519841829. doi: 10.1177/1352458519841829.

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BACKGROUND: Autoimmune disorders including nephropathies have been reported more frequently in alemtuzumab-treated multiple sclerosis (MS) patients than in the general population. **OBJECTIVE:** Describe instances of autoimmune nephropathy in alemtuzumab-treated MS patients. **METHODS:** Cases were identified from safety monitoring within the alemtuzumab relapsing-remitting multiple sclerosis (RRMS) clinical development program (CDP) or post-marketing, or following off-label use. **RESULTS:** As of 16 June 2017, 16 autoimmune nephropathies have occurred following alemtuzumab treatment for MS. The incidence of autoimmune nephropathies was 0.34% within the CDP (5/1485 patients). The five CDP cases (one of anti-glomerular basement membrane (anti-GBM) disease, two of membranous glomerulonephropathy, and two of serum anti-GBM antibody without typical anti-GBM disease) were identified early, responded to conventional therapy (where needed), and had favorable outcomes. Three of 11 cases outside the CDP occurred following off-label alemtuzumab use prior to approval for RRMS and were all anti-GBM disease. Diagnosis was delayed in one of these three cases and another did not receive appropriate treatment; all three cases resulted in end-stage renal failure. All anti-GBM disease cases with documented urinalysis demonstrated prior microscopic hematuria. **CONCLUSION:** Close monitoring of alemtuzumab-treated MS patients facilitates diagnosis and treatment early in the nephropathy course when preservation of renal function is more likely.