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SERVICIO ANATOMÍA PATOLÓGICA

BIOCHIM BIOPHYS ACTA MOL CELL BIOL L. 2021 JUN;1866(6):158909. DOI: 10.1016/J.BBALIP.2021.158909.

LIPOPROTEIN RECEPTOR SR-B1 DEFICIENCY ENHANCES ADIPOSE TISSUE INFLAMMATION AND REDUCES SUSCEPTIBILITY TO HEPATIC STEATOSIS DURING DIET-INDUCED OBESITY IN MICE

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Scavenger receptor class B type 1 (SR-B1) is a membrane lipoprotein receptor/lipid transporter involved in the pathogenesis of atherosclerosis, but its role in obesity and fatty liver development is unclear. Here, we determined the effects of SR-B1 deficiency on plasma metabolic and inflammatory parameters as well as fat deposition in adipose tissue and liver during obesity. To induce obesity, we performed high-fat diet (HFD) exposure for 12 weeks in male SR-B1 knock-out (SR-B1^{-/-}, n = 14) and wild-type (WT, n = 12) mice. Compared to HFD-fed WT mice, plasma from HFD-fed SR-B1^{-/-} animals exhibited increased total cholesterol, triglycerides (TG) and tumor necrosis factor- α (TNF- α) levels. In addition, hypertrophied adipocytes and macrophage-containing crown-like structures (CLS) were observed in adipose tissue from HFD-fed SR-B1 deficient mice. Remarkably, liver from obese SR-B1^{-/-} mice showed attenuated TG content, dysregulation in hepatic peroxisome proliferator-activated receptors (PPARs) expression, increased hepatic TG secretion, and altered hepatic fatty acid (FA) composition. In conclusion, we show that SR-B1 deficiency alters the metabolic environment of obese mice through modulation of liver and adipose tissue lipid accumulation. Our findings provide the basis for further elucidation of SR-B1's role in obesity and fatty liver, two major public health issues that increase the risk of advanced chronic diseases and overall mortality.

HEPATOLOGY. 2021 JUN;73(6):2293-2310. DOI: 10.1002/HEP.31585.

EPIGENOME-WIDE ANALYSIS OF METHYLATION CHANGES IN THE SEQUENCE OF GALLSTONE DISEASE, DYSPLASIA, AND GALLBLADDER CANCER

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Background and Aims. Gallbladder cancer (GBC) is a highly aggressive malignancy of the biliary tract. Most cases of GBC are diagnosed in low-income and middle-income countries, and research into this disease has long been limited. In this study we therefore investigate the epigenetic changes along the model of GBC carcinogenesis represented by the sequence gallstone disease \rightarrow dysplasia \rightarrow GBC in Chile, the country with the highest incidence of GBC worldwide. Approach and Results. To perform epigenome-wide methylation profiling, genomic DNA extracted from sections of formalin-fixed, paraffin-embedded gallbladder tissue was analyzed using Illumina Infinium MethylationEPIC BeadChips. Preprocessed, quality-controlled data from 82 samples (gallstones n = 32, low-grade dysplasia n = 13, high-grade dysplasia n = 9, GBC n = 28) were available to identify differentially methylated markers, regions, and pathways as well as changes in copy number variations (CNVs). The number and magnitude of epigenetic changes increased with disease development and predominantly involved the hypermethylation of cytosine-guanine dinucleotide islands and gene promoter regions. The methylation of genes implicated in Wnt signaling, Hedgehog signaling, and tumor suppression increased with tumor grade. CNVs also increased with GBC development and affected cyclin-dependent kinase inhibitor 2A, MDM2 proto-oncogene, tumor protein P53, and cyclin D1 genes. Gains in the targetable ErbB2 receptor tyrosine kinase 2 gene were detected in 14% of GBC samples. Conclusions. Our results indicate that GBC carcinogenesis comprises three main methylation stages: early (gallstone disease and low-grade dysplasia), intermediate (high-grade dysplasia), and late (GBC). The identified gradual changes in methylation and CNVs may help to enhance our understanding of the mechanisms underlying this aggressive disease and eventually lead to improved treatment and early diagnosis of GBC.

DEPARTAMENTO DE ANESTESIOLOGÍA Y MEDICINA PERIOPERATORIA

J CLIN ANESTH. 2021 FEB;68:110063. DOI: 10.1016/J.JCLINANE.2020.110063.

ERECTOR SPINAE PLANE BLOCK: A NARRATIVE REVIEW WITH SYSTEMATIC ANALYSIS OF THE EVIDENCE PERTAINING TO CLINICAL INDICATIONS AND ALTERNATIVE TRUNCAL BLOCKS

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Study objective: This narrative review discusses the anatomy, mechanism of action, techniques, pharmacology, indications, complications and substitutes for erector spinae plane (ESP) blocks. Interventions: The Medline, Embase and Google Scholar databases (inception-last week of April 2020) were searched. For indications and alternative blocks, a systematic analysis of the available evidence was carried out. In order to highlight the best evidence available, only randomized trials with prospective registration, blinded assessment and sample size justification were retained for analysis. Main results: The collective body of anatomical studies suggests that ESP block may work through a combination of different mechanisms (e.g., local anesthetic spread to the thoracic paravertebral space, epidural space, and dorsal ramus). Compared to control, the available evidence suggests that ESP block results in decreased postoperative pain and opioid requirement for a wide array of thoracic and abdominal surgical interventions. Erector spinae plane blocks and thoracic paravertebral blocks seem to provide comparable benefits for thoracoscopic and breast cancer surgery when performed with a similar number of injections. Currently, ESP blocks should be favored over intercostal blocks since, at best, the latter provide similar analgesia to ESP blocks despite requiring multiple-level injections. Conclusions: In recent years, ESP blocks have become the topic of considerable clinical interest. Future trials are required to investigate their optimal technique, dose of local anesthetic and perineural adjuvants. Moreover, additional investigation should compare ESP blocks with robust multimodal analgesic regimens as well as truncal blocks such as thoracic epidural block, midpoint transverse process to pleura block, PECS block, quadratus lumborum block, and transversus abdominis plane block.

J CLIN ANESTH. 2021 FEB;68:110076. DOI: 10.1016/J.JCLINANE.2020.110076.

MOTOR-SPARING NERVE BLOCKS FOR TOTAL KNEE REPLACEMENT: A SCOPING REVIEW

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Study objective: This scoping review investigates the optimal combination of motor-sparing analgesic interventions for patients undergoing total knee replacement (TKR). Design: Scoping review. Intervention: MEDLINE, EMBASE and CINAHL databases were searched (inception-last week of May 2020). Only trials including motor-sparing interventions were included. Randomized controlled trials lacking prospective registration and blinded assessment were excluded. Main results: The cumulative evidence suggests that femoral triangle blocks outperform placebo and periarticular infiltration. When combined with the latter, femoral triangle blocks are associated with improved pain control, higher patient satisfaction and decreased opioid consumption. Continuous femoral triangle blocks provide superior postoperative analgesia compared with their single-injection counterparts. However, these benefits seem less pronounced when perineural adjuvants are used. Combined femoral triangle-obturator blocks result in improved analgesia and swifter discharge compared with femoral triangle blocks alone. Conclusions: The optimal analgesic strategy for TKR may include a combination of different analgesic modalities (periarticular infiltration, femoral triangle blocks, obturator nerve block). Future trials are required to investigate the incremental benefits provided by local anesthetic infiltration between the popliteal artery and the capsule of the knee (IPACK), popliteal plexus block and genicular nerve block.

EUR J ANAESTHESIOL. 2021 JAN;38(1):49-57. DOI: 10.1097/EJA.0000000000001356.

EFFECTS ON CEREBRAL BLOOD FLOW OF POSITION CHANGES, HYPEROXIA, CO₂ PARTIAL PRESSURE VARIATIONS AND THE VALSALVA MANOEUVRE: A STUDY IN HEALTHY VOLUNTEERS

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Background: Maintaining adequate blood pressure to ensure proper cerebral blood flow (CBF) during surgery is challenging. Induced mild hypotension, sitting position or unavoidable intra-operative circumstances such as haemorrhage, added to variations in carbon dioxide and oxygen tensions, may influence perfusion. Several of these circumstances may coincide and it is unclear how these may affect CBF. Objective: To describe the variation in transcranial Doppler and regional cerebral oxygen saturation (rSO₂), as a surrogate of CBF, after cardiac preload and gravitational positional changes. Design: Observational study. Setting: Operating room at Hospital Clínic de Barcelona. Volunteers: Ten healthy volunteers, white, both sexes. Interventions: Measurements were performed in the supine, sitting and standing positions during hyperoxia, hypocapnia and hypercapnia protocols and after a Valsalva manoeuvre. Main outcome measures: Cardiac index (CI), haemodynamic and respiratory variables, maximal and mean velocities (V_{max}, V_{mean}) (transcranial Doppler) and rSO₂ were acquired. Results were analysed using a generalised estimating equation technique. Results: CI increases more than 16% after a preload challenge were not accompanied by differences in rSO₂ or V_{max} - V_{mean}. With positional changes, V_{mean} decreased more than 7% (P = 0.042) from the supine to the seated position. Hyperoxia induced a cerebral rSO₂ increase more than 6% (P = 0.0001) with decreases in V_{max}, V_{mean} and CI values more than 3% (P = 0.001, 0.022 and 0.001) in the supine and standing position. During hypocapnia, CI rose more than 20% from supine to seated and standing (P = 0.0001) with a 4.5% decrease in cerebral rSO₂ (P = 0.001) and a decrease of V_{max} - V_{mean} more than 24% in all positions (P = 0.001). Hypercapnia increased cerebral rSO₂ more than 17% (P = 0.001), V_{max} - V_{mean} more than 30% (P = 0.001) with no changes in CI. After a Valsalva manoeuvre, rSO₂ decreased more than 3% in the right hemisphere in the upright position (P = 0.001). V_{max} - V_{mean} decreased

more than 10% ($P = 0.001$) with no changes in CI. Conclusion: CBF changes in response to cerebral vasoconstriction and vasodilatation were detected with rSO₂ and transcranial Doppler in healthy volunteers during cardiac preload and in different body positions. Acute hypercapnia had a greater effect on recorded brain parameters than hypocapnia.

ANESTH ANALG. 2021 JUL 1;133(1):205-214. DOI: 10.1213/ANE.0000000000005262.

ASSOCIATION BETWEEN LOWER PREOPERATIVE COGNITION WITH INTRAOPERATIVE ELECTROENCEPHALOGRAPHIC FEATURES CONSISTENT WITH DEEP STATES OF ANESTHESIA IN OLDER PATIENTS: AN OBSERVATIONAL COHORT STUDY

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Background: Patients with low cognitive performance are thought to have a higher risk of postoperative neurocognitive disorders. Here we analyzed the relationship between preoperative cognition and anesthesia-induced brain dynamics. We hypothesized that patients with low cognitive performance would be more sensitive to anesthetics and would show differences in electroencephalogram (EEG) activity consistent with a brain anesthesia overdose. Methods: This is a retrospective analysis from a previously reported observational study. We evaluated cognitive performance using the Montreal cognitive assessment (MoCA) test. All patients received general anesthesia maintained with sevoflurane or desflurane during elective major abdominal surgery. We analyzed the EEG using spectral, coherence, and phase-amplitude modulation analyses. Results: Patients were separated into a low MoCA group (<26 points, $n = 12$) and a high MoCA group ($n = 23$). There were no differences in baseline EEG, nor end-tidal age-corrected minimum alveolar concentration (MAC_{age}). However, under anesthesia, the low MoCA group had lower α - β power (high MoCA: 2.9 [interquartile range (IQR): 0.6-5.8 dB] versus low MoCA: -1.2 [IQR: -2.1 to 0.6 dB], difference 4.1 [1.0-5.7]) and a lower α peak frequency (high MoCA: 9.0 [IQR: 8.3-9.8 Hz] versus low MoCA: 7.5 [IQR: 6.3-9.0 Hz], difference 1.5 [0-2.3]) compared to the high MoCA group. The low MoCA group also had a lower α band coherence and a stronger peak-max phase-amplitude coupling (PAC). Finally, patients in the low MoCA group had longer emergence times (high MoCA 663 \pm 345 seconds versus low MoCA: 960 \pm 352 seconds, difference 297 [15-578]). Multiple linear regression shows up that both age and MoCA scores are independently associated with intraoperative α - β power. Conclusions: All these EEG features, together with a prolonged emergence time, are consistent with the possibility that older patients with low cognitive performance are receiving a brain anesthesia overdose compare to cognitive normal patients.

DEPARTAMENTO CARDIOVASCULAR

MOLECULES. 2021 SEP 21;26(18):5702. DOI: 10.3390/MOLECULES26185702.

JOINT CARDIOPROTECTIVE EFFECT OF VITAMIN C AND OTHER ANTIOXIDANTS AGAINST REPERFUSION INJURY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Percutaneous coronary intervention (PCI) has long remained the gold standard therapy to restore coronary blood flow after acute myocardial infarction (AMI). However, this procedure leads to the development of increased production of reactive oxygen species (ROS) that can exacerbate the damage caused by AMI, particularly during the reperfusion phase. Numerous attempts based on antioxidant treatments, aimed to reduce the oxidative injury of cardiac tissue, have failed in achieving an effective therapy for these patients. Among these studies, results derived from the use of vitamin C (Vit C) have been inconclusive so far, likely due to suboptimal study designs, misinterpretations, and the erroneous conclusions of clinical trials. Nevertheless, recent clinical trials have shown that the intravenous infusion of Vit C prior to PCI-reduced cardiac injury biomarkers, as well as inflammatory biomarkers and ROS production. In addition, improvements of functional parameters, such as left ventricular ejection fraction (LVEF) and telediastolic left ventricular volume, showed a trend but had an inconclusive association with Vit C. Therefore, it seems reasonable that these beneficial effects could be further enhanced by the association with other antioxidant agents. Indeed, the complexity and the multifactorial nature of the mechanism of injury occurring in AMI demands multitarget agents to reach an enhancement of the expected cardioprotection, a paradigm needing to be demonstrated. The present review provides data supporting the view that an intravenous infusion containing combined safe antioxidants could be a suitable strategy to reduce cardiac injury, thus improving the clinical outcome, life quality, and life expectancy of patients subjected to PCI following AMI.

CICA – CENTRO DE INVESTIGACIÓN CLÍNICA AVANZADA

INT J MOL SCI. 2021 JUN 12;22(12):6311. DOI: 10.3390/IJMS22126311.

ANALYZING OLFACTORY NEURON PRECURSORS NON-INVASIVELY ISOLATED THROUGH NADH FLIM AS A POTENTIAL TOOL TO STUDY OXIDATIVE STRESS IN ALZHEIMER'S DISEASE

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Among all the proposed pathogenic mechanisms to understand the etiology of Alzheimer's disease (AD), increased oxidative stress seems to be a robust and early disease feature where many of those hypotheses converge. However, despite the significant lines of evidence accumulated, an effective diagnosis and treatment of AD are not yet available. This limitation might be partially explained by the use of cellular and animal models that recapitulate partial aspects of the disease and do not account for the particular biology of patients. As such, cultures of patient-

derived cells of peripheral origin may provide a convenient solution for this problem. Peripheral cells of neuronal lineage such as olfactory neuronal precursors (ONPs) can be easily cultured through non-invasive isolation, reproducing AD-related oxidative stress. Interestingly, the autofluorescence of key metabolic cofactors such as reduced nicotinamide adenine dinucleotide (NADH) can be highly correlated with the oxidative state and antioxidant capacity of cells in a non-destructive and label-free manner. In particular, imaging NADH through fluorescence lifetime imaging microscopy (FLIM) has greatly improved the sensitivity in detecting oxidative shifts with minimal intervention to cell physiology. Here, we discuss the translational potential of analyzing patient-derived ONPs non-invasively isolated through NADH FLIM to reveal AD-related oxidative stress. We believe this approach may potentially accelerate the discovery of effective antioxidant therapies and contribute to early diagnosis and personalized monitoring of this devastating disease

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MOBILE ECMO IN COVID-19 PATIENT: CASE REPORT

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At July 25, 2020, WHO had recorded more than 16.1 million confirmed COVID-19 cases, 1% of them developed critical illness. These patients can experience rapid progression to profound hypoxemia and severe acute respiratory distress syndrome (ARDS). Some patients, despite receiving lung-protective ventilation and maximal medical therapy, develop refractory hypoxemia, rendering candidates for extracorporeal membrane oxygenation (ECMO) support. Centers with experience in this technique are available only in a few reference hospitals and some patients are too ill to be transferred with conventional mechanical ventilation so they need mobile ECMO (interhospital transport under ECMO). Here we report the first interhospital extracorporeal membrane oxygenation transport of a COVID-19 patient in Chile, showing that it is feasible and safe to transfer a COVID-19 patient under ECMO support if a mobile ECMO program is correctly implemented and the particularities of protective measures are properly taken.

J ALZHEIMERS DIS. 2021;82(S1):S163-S178. DOI: 10.3233/JAD-201264.

DEF8 AND AUTOPHAGY-ASSOCIATED GENES ARE ALTERED IN MILD COGNITIVE IMPAIRMENT, PROBABLE ALZHEIMER'S DISEASE PATIENTS, AND A TRANSGENIC MODEL OF THE DISEASE

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Background: Disturbances in the autophagy/endolysosomal systems are proposed as early signatures of Alzheimer's disease (AD). However, few studies are available concerning autophagy gene expression in AD patients. Objective: To explore the differential expression of classical genes involved in the autophagy pathway, among them a less characterized one, DEF8 (Differentially expressed in FDCP 8), initially considered a Rubicon family member, in peripheral blood mononuclear cells (PBMCs) from individuals with mild cognitive impairment (MCI) and probable AD (pAD) and correlate the results with the expression of DEF8 in the brain of 5xFAD mice. Method: By real-time PCR and flow cytometry, we evaluated autophagy genes levels in PBMCs from MCI and pAD patients. We evaluated DEF8 levels and its localization in brain samples of the 5xFAD mice by real-time PCR, western blot, and immunofluorescence. Results: Transcriptional levels of DEF8 were significantly reduced in PBMCs of MCI and pAD patients compared with healthy donors, correlating with the MoCA and MoCA-MIS cognitive tests scores. DEF8 protein levels were increased in lymphocytes from MCI but not pAD, compared to controls. In the case of brain samples from 5xFAD mice, we observed a reduced mRNA expression and augmented protein levels in 5xFAD compared to age-matched wild-type mice. DEF8 presented a neuronal localization. Conclusion: DEF8, a protein proposed to act at the final step of the autophagy/endolysosomal pathway, is differentially expressed in PBMCs of MCI and pAD and neurons of 5xFAD mice. These results suggest a potential role for DEF8 in the pathophysiology of AD.

ALZHEIMERS DEMENT. 2021 APR;17(4):653-664. DOI: 10.1002/ALZ.12227.

DOMINANTLY INHERITED ALZHEIMER'S DISEASE IN LATIN AMERICA: GENETIC HETEROGENEITY AND CLINICAL PHENOTYPES

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Introduction: A growing number of dominantly inherited Alzheimer's disease (DIAD) cases have become known in Latin American (LatAm) in recent years. However, questions regarding mutation distribution and frequency by country remain open. Methods: A literature review was completed aimed to provide estimates for DIAD pathogenic variants in the LatAm population. The search strategies were established using a combination of standardized terms for DIAD and LatAm. Results: Twenty-four DIAD pathogenic variants have been reported in LatAm countries. Our combined dataset included 3583 individuals at risk; countries with highest DIAD frequencies were Colombia (n = 1905), Puerto Rico (n = 672), and Mexico (n = 463), usually attributable to founder effects. We found relatively few reports with extensive documentation on biomarker profiles and disease progression. Discussion: Future DIAD studies will be required in LatAm, albeit with a more systematic approach to include fluid biomarker and imaging studies. Regional efforts are under way to extend the DIAD observational studies and clinical trials to Latin America.

DEPARTAMENTO DE CIRUGÍA

NUTRITION. 2021 SEP;89:111283. DOI: 10.1016/J.NUT.2021.111283.

OLIVE OIL-BASED LIPID EMULSION IS NONINFERIOR TO SOYBEAN OIL-BASED LIPID EMULSION IN THE ACUTE CARE SETTING: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

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Objectives. Olive oil (OO)-based intravenous lipid emulsion (IVLE) may have biological advantages for nutrition and inflammation status compared with soybean oil (SO)-based IVLE. We aimed to compare prealbumin levels during infusion of OO- or SO-based IVLE in patients receiving parenteral nutrition in the acute-care setting. Methods. In this prospective, noninferiority, double blind randomized controlled efficacy trial, patients received either OO-based or SO-based IVLE after providing consent. Biochemical and nutrition parameters were collected at baseline and at 7 to 10 d after initiation of parenteral nutrition. Results are expressed as means (standard deviations). Results. A total of 210 patients completed the study: 102 patients in the SO-based IVLE group and 108 patients in the OO-based IVLE group. Both groups had a significant increase in prealbumin levels from baseline (SO: 0.10 [0.06] versus 0.15 [0.08] g/L; $P < 0.0001$; OO: 0.11 [0.06] versus 0.16 [0.08] g/L; $P < 0.0001$), but mean changes between groups were not different ($P = 0.53$). OO-based IVLE was noninferior to SO-based IVLE in maintaining or increasing serum prealbumin levels, with 20% as the noninferiority margin at follow-up (least square geometric mean ratio [95% CI], 1.10 [0.83,1.47]; $P = 0.50$). There was a significant improvement in C-reactive protein levels from baseline within each group (SO: 83.24 [69.72] versus 53.4 [59.78] mg/dL; $P < 0.0001$; OO: 85.13 [68.14] versus 58.75 [60.11] mg/dL; $P = 0.004$), but mean changes between the groups were not different ($P = 0.836$). Mortality, length of stay, and infection rates were not different for both groups. Conclusions. In this study, OO-based IVLE was not inferior to SO-based IVLE in maintaining or increasing the prealbumin level. The improvement of C-reactive protein levels and other clinical outcomes were not different for both groups.

REV MED CHIL. 2021 JUL;149(7):961-970. DOI: 10.4067/S0034-98872021000700961.

EPIDEMIOLOGÍA DE LA PANCREATITIS AGUDA EN CHILE ENTRE LOS AÑOS 2013 Y 2018

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Background: The worldwide incidence of acute pancreatitis (AP) is increasing. Aim: To determine the national incidence of AP between 2013 and 2018. Material and Methods: Analysis of hospital discharge records available at the web page of the Statistical and Information Service of the Chilean Ministry of Health. We recorded the number of patients discharged with a diagnosis of AP, excluding chronic pancreatitis and pancreatic cancer, between 2013 and 2018. We also recorded length of hospital stay, age, etiology, and lethality. Rates of raw and age-adjusted incidence were calculated. Results: During the study period, 46,420 patients with AP were discharged, with an incidence rate ranging between 39 and 43.7/100,000 inhabitants, and a non-significant increase along time of 8.6%. There are important differences between the average adjusted rates of Northern (Arica to Metropolitan) and Southern regions (O'Higgins to Magallanes), with rates of 36.9 and 53.6/100,000 inhabitants respectively ($p < 0.01$). The average hospital stay was 11 days. Two thirds of cases were aged between 20 and 64 years. The case fatality was 4.2%, with no decrease between 2013 and 2018. The mortality rate was 1.6/100,000 inhabitants. Conclusions: The annual incidence of AP is 42.6/100,000 inhabitants, with geographical differences from North to South, which can be associated with the high frequency of biliary tract disease in aboriginal ethnic groups. The age distribution and length hospital stay were stable over time.

CLIN NUTR. 2021 JUN;40(6):4029-4036. DOI: 10.1016/J.CLNU.2021.02.039.

CLINICAL NUTRITION AND HUMAN RIGHTS. AN INTERNATIONAL POSITION PAPER

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The International Working Group for Patients' Right to Nutritional Care presents its position paper regarding nutritional care as a human right intrinsically linked to the right to food and the right to health. All people should have access to food and evidence-based medical nutrition therapy including artificial nutrition and hydration. In this regard, the hospitalized malnourished ill should mandatorily have access to screening, diagnosis, nutritional assessment, with optimal and timely nutritional therapy in order to overcome malnutrition associated morbidity and mortality, while reducing the rates of disease-related malnutrition. This right does not imply there is an obligation to feed all patients at any stage of life and at any cost. On the contrary, this right implies, from an ethical point of view, that the best decision for the patient must be taken and this may include, under certain circumstances, the decision not to feed. Application of the human rights-based approach to the field of clinical nutrition will contribute to the construction of a moral, political and legal focus to the concept of nutritional care. Moreover, it will be the cornerstone to the rationale of political and legal instruments in the field of clinical nutrition.

INT J MOL SCI. 2021 DEC 31;23(1):467. DOI: 10.3390/IJMS23010467.

NOVEL RISK ASSOCIATIONS BETWEEN MICRORNA POLYMORPHISMS AND GASTRIC CANCER IN A CHILEAN POPULATION

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Gastric cancer (GC) is the fifth leading cause of cancer deaths in the world, with variations across geographical regions and ethnicities. Emerging evidence indicates that miRNA expression is dysregulated in GC and its polymorphisms may contribute to these variations, which has yet to be explored in Latin American populations. In a case-control study of 310 GC patients and 311 healthy donors from Chile, we assessed the association of 279 polymorphisms in 242 miRNA genes. Two novel polymorphisms were found to be associated with GC: rs4822739:C>G (miR-548j) and rs701213:T>C (miR-4427). Additionally, rs1553867776:T>TCCCCA (miR-4274) and rs12416605:C>T (miR-938) were associated with intestinal-type GC, and rs4822739:C>G (miR-548j) and rs1439619:T>G (miR-3175) with TNM I-II stage. The polymorphisms rs6149511:T>TGAAGGGCTCCA (miR-6891), rs404337:G>A (miR-8084), and rs1439619:T>G (miR-3175) were identified among *H. pylori*-infected GC patients and rs7500280:T>C (miR-4719) and rs1439619:T>G (miR-3175) were found among *H. pylori* cagPAI+ infected GC cases. Prediction analysis suggests that seven polymorphisms could alter the secondary structure of the miRNA, and the other one is located in the seed region of miR-938. Targets of miRNAs are enriched in GC pathways, suggesting a possible biological effect. In this study, we identified seven novel associations and replicated one previously described in Caucasian population. These findings contribute to the understanding of miRNA genetic polymorphisms in the GC pathogenesis.

PLAST RECONSTR SURG. 2021 DEC 1;148(6):1248-1261. DOI: 10.1097/PRS.0000000000008577.

TULUA LIPOABDOMINOPLASTY: TRANSVERSAL APONEUROTIC PPLICATION, NO UNDERMINING, AND UNRESTRICTED LIPOSUCTION. A MULTICENTER STUDY OF 845 CASES

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Background: TULUA (transverse plication, no undermining, full liposuction, neoumbilicoplasty, and low transverse abdominal scar) is the acronym for a radically different lipoabdominoplasty, intended to add simplicity, improve vascular safety, and attain good results. Modifications are unrestricted liposuction, no flap detachment, massive transverse infraumbilical plication, umbilicus amputation, neoumbilicoplasty, diminished tension wound closure, and low transverse scar settlement. The objectives of this article are to describe the technique and analyze a multicenter experience. Methods: Sixty-eight plastic surgeons from 10 countries provided data for a retrospective review of 845 patients. Aesthetic results were scored by each surgeon using the Salles scale and analyzed in combination with complications to identify associations between patient and surgery characteristics. Results: Of the patients, 95.5 percent were female, 19.7 percent were obese, 35.6 percent had prior scars, 10.4 percent had undergone previous abdominoplasty, 6.5 percent were postbariatric, and 6.6 percent were smokers. One patient had a kidney transplant, and 16.5 percent had comorbidities. Surgery characteristics varied widely, being on average as follows: lipoaspirate, 2967 ml; resection, 1388 g; and surgical time, 3.9 hours; 46.5 percent were not hospitalized. Averaged results were 8.68 of 10 points, besides adequate positioning and proportion of scar and umbilicus, without epigastric compensatory bulging (4.97 of 6 points). Overall complications were 16.2 percent, mostly seroma (8.8 percent); vascular-related complications (i.e., necrosis, wound dehiscence, and infection) constituted 2.7 percent. There were no fatalities. The logistic regression model demonstrated that smoking and obesity duplicate the risk of complications; if age older than 60 years is added, the risk of complication increases seven to nine times. Reported indications were multiple; however, pathologic diastasis was excluded. Conclusion: TULUA lipoabdominoplasty is a new reproducible procedure with good quantified results and an acceptable complication rate.

ANN SURG. 2021 JAN 19. DOI: 10.1097/SLA.0000000000004760.

LONG-TERM (18 YEARS) RESULTS OF PATIENTS WITH LONG-SEGMENT BARRETT'S ESOPHAGUS SUBMITTED TO ACID SUPPRESSION-DUODENAL DIVERSION OPERATION: BETTER THAN NISSEN FUNDOPLICATION?

Attila Csendes, Omar Orellana, Manuel Figueroa, Enrique Lanzarini

Objective: To determine late results of AS-DD procedure in long-segment (LSBE) and extralong-segment BE (ELSBE) using subjective and objective measurements to ascertain the histological impact over intestinal metaplasia (IM) and progression to EAC. Summary of background data: Barrett esophagus (BE) is a known precursor of esophageal adenocarcinoma (EAC), and Nissen fundoplication has proven to be unable to stop mixed reflux among them. Our group proposed a surgical procedure that handles pathophysiological changes responsible for BE. Methods: This prospective study included 127 LSBE and ELSBE subjects submitted to clinical and functional analyses. They were presented to selective vagotomy, fundoplication, partial gastrectomy with Roux-en-Y reconstruction. The changes in IM were determined in both groups. Results: Follow-up was completed at a mean of 18 years in 81% of the cases. Visick I-II scores were seen in 88% of LSBE and 65% in ELSBE ($P < 0.01$). There was significant healing of erosive esophagitis and esophageal peptic ulcers, and strictures were resolved in 71%. There was 38% of IM regression in LSBE. Two cases in each group progressed to EAC at a mean of 15 years. Pathologic acid reflux was abolished in 91% and duodenal in 100%. There was a regression of low-grade dysplasia to IM in 80%. Conclusions: AS-DD permanently eliminates pathologic refluxate to the esophagus. The progression to HGD/EAC is lower compared to medical treatment, with an 8-fold reduction in LSBE and 2.2-fold in ELSBE. AS-DD seems to influence IM behaviors, and it is a tool that could reduce and delay progression to EAC.

OBES SURG. 2021 JAN;31(1):437-438. DOI: 10.1007/S11695-020-04470-Y.

LIES, DAMN LIES, AND BAD STATISTICS?

Italo Braghetto, Manuel Figueroa

A wide spectrum of research such as experimental, randomized trials, cohort or epidemiological studies, technical or control case reports, systematic reviews, and meta-analyses has resulted in a huge amount of publications. These studies and publications may be subject to errors due to poor application of statistical tests, which can lead to misinformation, misinterpretation, and erroneous conclusions, sometimes even considered as lies. In this article, some ideas about this issue are discussed in order to adopt new directions in the future and thus avoid lies and bad statistics.

AM J CLIN NUTR. 2021 JUL 1;114(1):322-329. DOI: 10.1093/AJCN/NQAB039.

ZINC ABSORPTION AND ZINC STATUS ARE REDUCED AFTER EITHER SLEEVE GASTRECTOMY OR ROUX-EN-Y GASTRIC BYPASS IN PREMENOPAUSAL WOMEN WITH SEVERE OBESITY STUDIED PROSPECTIVELY OVER 24 POSTOPERATIVE MONTHS

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Background. Roux-en-Y gastric bypass (RYGBP) is known to reduce zinc absorption; the effects of vertical sleeve gastrectomy (SG) and its long-term implications on zinc absorption have not yet been studied. Objective. The aim was to evaluate the effects of SG and RYGBP on zinc absorption and zinc status in premenopausal women with severe obesity up to 24 mo after surgery. Methods. Twenty-six premenopausal women undergoing SG [BMI (in kg/m²): 37.3 ± 3.2] and 32 undergoing RYGBP (BMI: 42.0 ± 4.2) were studied. A series of anthropometric, dietary, and zinc status parameters (plasma and hair zinc), and the size of the exchangeable zinc pool (EZP), as well as percentage zinc absorption from a standardized dose using a stable isotope methodology were evaluated in the patients before the surgical procedure and at 12 and 24 mo after SG or RYGBP. SG patients received 15 mg and RYGBP received 25 mg of supplemental Zn/d. Results. In premenopausal women, zinc absorption was decreased by 71.9% and 52.0% in SG and RYGBP, respectively, 24 mo postsurgery, compared with initial values. According to 2-factor repeated-measures ANOVA, time effect was significant (P = <0.0001), but not time × group interaction (P = 0.470). Plasma zinc below the cutoff point of 70 µg/dL increased from 0 to 15.4% and 38.1% in SG and RYGBP, respectively. Mean EZP was significantly reduced 24 mo after surgery, although no time × group interactions were observed. Hair zinc did not change across time or between groups. Conclusions. Both SG and RYGBP have profound effects on zinc absorption capacity, which are not compensated for after 24 mo. Although zinc absorption reduction was similar in both types of surgeries, plasma zinc was more affected in RYGBP than SG, despite greater zinc supplementation in RYGBP.

FACIAL PLAST SURG AESTHET MED. JUL-AUG 2021;23(4):278-282. DOI: 10.1089/FPSAM.2020.0274.

INTRAOPERATIVE FLUOROSCOPY REDUCES COMPLICATION AND REOPERATION RATE IN FACIAL FRACTURES

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Purpose: The purpose of this study is to evaluate surgical outcomes of facial fractures after the introduction of intraoperative radiology. Methods: An historic cohort of patients without intraoperative fluoroscopy (IOF) was compared with a prospective cohort of patients with IOF. Main outcomes were postoperative complications and reoperation rate. Results: There were 51 in the non-IOF group and 49 in the IOF group. In the group with IOF 10 patients required intraoperative revisions (20.46%). Overall postoperative complication rate was higher in the non-IOF group (25.49% vs. 6.12%) due to the significantly higher bone-related complication rate (15.69% vs. 2.04%). Reoperation rate was also higher in the non-IOF group (11.76% vs. 0%). Conclusion: This study demonstrates that IOF reduces bone-related complication and reoperation rate by allowing correction of surgical errors immediately during surgery.

UPDATES SURG. 2021 APR;73(2):627-637. DOI: 10.1007/S13304-020-00955-8.

UPPER GI TRAINING OF YOUNG SURGEONS: A REALITY FULL OF HURDLES. AN INTERNATIONAL SURVEY

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Objective: Anecdotal evidence suggests that the training of young surgeons in Upper GI is not homogeneous across the world. This survey aimed to investigate the different training programs and the level of satisfaction of young surgeons with their surgical and scientific education pathway. Design: A multiple-choice and single best answer format questionnaire was sent to 36 Upper GI chairs from international referral centres and then forwarded to young surgeons (attending physician less than 40 years old). The same questionnaire containing 5 main topics (demographics, residency, fellowship, academic research and activities, manual skill improvement) was posted online on a SurveyMonkey website. Setting: San Luigi University Hospital, Orbassano (Turin), Italy; Tertiary University Hospital. Results: Fourteen replies were received from colleagues in 36 referral centres (39% response rate) and 65 voluntary answers from the survey monkey platform. During residency training, only 43% of residents had a specific training in upper GI tract surgery, which was characterized by a small number of interventions performed both with trainer scrubbed and unscrubbed. Fellowship programmes were undertaken by 49% of participants and 64% spent this training period abroad. Operative experience was reported by nearly all respondents with only 27% performing > 10 gastrectomies and only 11% performing > 10 oesophagectomies with the trainer scrubbed. The majority attended less than 10 meetings (58%), and 70% of them

published less than 5 papers. Conclusions: The present survey reveals that the young surgeons of the twenty-first century face many hurdles during their surgical training. Overall, the surgical education settings are limited for both practical and scientific training for upper GI trainees. As a result, it is not possible to train in upper GI surgery to a level of competent independent practice.

CRANIO 2021 OCT 8;1-11. DOI: 10.1080/08869634.2021.1987040.

ASSESSING CERVICAL SPINE AND CRANIOFACIAL MORPHOLOGY IN CLASS II AND CLASS III MALOCCLUSIONS: A GEOMETRIC MORPHOMETRIC APPROACH

Camilo Sandoval, Alejandro Díaz, Germán Manríquez

To compare craniofacial and cervical morphology between skeletal Classes II and III applying Geometric Morphometric Methods (GMM). Twenty-six cervical and craniofacial landmarks of 40 Class II and 39 Class III individuals were digitalized on lateral cephalograms. Procrustes ANOVA, generalized Procrustes, principal component analyses, and thin-plate spline function were applied to assess the pattern of shape variation of craniofacial structure and the cervical spine in relation to skeletal classes. Compared with Class III, Class II individuals presented a maxillary protrusion, mandibular retrusion, shorter mandibular corpus, posterior mandibular ramus rotation, anterior cranial base rotation, and a smaller centroid size. Furthermore, a forward and smaller cervical spine were observed. With GMM, the shape and size differences between skeletal classes can be analyzed visually and numerically.

SERVICIO DE DERMATOLOGÍA

SKIN RES TECHNOL. 2021 AUG 29. DOI: 10.1111/SRT.13099.

ULTRASONOGRAPHY OF CUTANEOUS NODULAR PSEUDOLYMPHOMA AT 18 AND 71 MHZ

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Cutaneous pseudolymphomas are reactive lymphoproliferations. The most frequent type is nodular pseudolymphoma, and to date, their ultrasonographic appearance has not been reported. We reviewed the ultrasound images of histologically confirmed nodular types of pseudolymphomas studied with 18 and 71 MHz linear probes. All lesions were predominantly hypoechoic and presented prominent vascularity. Seventy percent of cases involved dermis and hypodermis, and 30% were only dermal. Seventy percent of cases showed internal hypoechoic globules, and 100% presented a teardrop sign, more clearly detected at 71 MHz. Ultrasound can support the diagnosis, assessment of the extent, and degree of vascularity of cutaneous nodular pseudolymphomas.

AN BRAS DERMATOL. MAR-APR 2021;96(2):234-236. DOI: 10.1016/J.ABD.2020.06.011.

CASE FOR DIAGNOSIS. ATYPICAL GROVER'S DISEASE

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A 55-year-old male presented with an eight-month history of erythematous papules and plaques with demarcated areas of spared skin on his trunk, upper extremities, neck, and face. Grover's disease is a rare, acquired disorder of unknown origin, which is classically characterized by the appearance of erythematous papules on the upper trunk that are usually transient. As in the present case, there are reports of atypical disease, with facial involvement, pityriasis rubra pilaris-like lesions, and a more chronic course.

CENTRO DE IMAGENOLOGÍA

ABDOM RADIOL (NY). 2021 JUL;46(7):3280-3287. DOI: 10.1007/S00261-021-02988-Y.

CT DIFFERENTIATION OF FAT-POOR ANGIOMYOLIPOMAS FROM PAPILLARY RENAL CELL CARCINOMAS: DEVELOPMENT OF A PREDICTIVE MODEL

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Purpose: To identify specific contrast-enhanced CT (CECT) findings and develop a predictive model with logistic regression to differentiate fat-poor angiomyolipomas (fpAML) from papillary renal cell carcinomas (pRCC). Methods: This is a single-institution retrospective study that assess CT features of histologically proven 67 pRCC and 13 fpAML. CECT variables were studied by means of univariate logistic regression. Variables included patients' demographics, tumor attenuation (unenhanced and at arterial, venous and excretory post-contrast phases), type of enhancement, morphological features (axial long and short diameters, long-short axis ratio (LSR) and tumor to kidney angle interface) and presence of visible calcifications or vessels. Those variables with a $p \leq 0.05$ underwent standard stepwise logistic regression to find predictive combinations of clinical variables. Best models were evaluated by AUROC curves and were subjected to Leave-one-out cross validation to assess their robustness. Results: Odds ratio (OR) between pRCC and fpAML was statistically significant for patient's gender, tumor attenuation in arterial, venous and excretory phases, tumor's long diameter, short diameter, LSR, type of enhancement, presence of intratumoral vessels and tumor-kidney angle interface. The best predictive model resulted in an area under the curve (AUC) of 0.971 and included gender, tumor-

kidney angle interface and venous attenuation with the following equation: $\text{Log}(p/1 - p) = -2.834 + 4.052 * \text{gender} + -0.066 * \text{AngleInterface} + 0.074 * \text{VenousphaseHU}$. Conclusions: The combination of patients' gender, tumor to kidney angle interface and venous enhancement helps to distinguish fpAML from pRCC.

FRONT CARDIOVASC MED. 2021 NOV 16;8:751036. DOI: 10.3389/FCVM.2021.751036. ECOLLECTION 2021.

POLYPHENOLS AND NOVEL INSIGHTS INTO POST-KIDNEY TRANSPLANT COMPLICATIONS AND CARDIOVASCULAR DISEASE: A NARRATIVE REVIEW
Nicolas I Bustos, Camilo G Sotomayor, Robert A Pol, Gerjan J Navis, Stephan J L Bakker

Kidney transplantation is the preferred treatment for end-stage kidney disease. It is, however, not devoid of complications. Delayed graft function related to ischemia-reperfusion injury (IRI), calcineurin inhibitor (CNI) nephrotoxicity, diabetes, and a particularly high-rate cardiovascular disease (CVD) risk, represent important complications following kidney transplantation. Oxidative stress and chronic low-grade inflammation are mechanisms of disease incompletely abrogated in stable kidney transplant recipient (KTR), contributing to the occurrence of these complications. Polyphenols, bioactive compounds with recognized antioxidant and anti-inflammatory properties have been strongly associated with prevention of CVD in the general population and have been shown to decrease IRI and antagonize CNI nephrotoxicity in animal experimental models, therefore they may have a role in prevention of complications in KTR. This narrative review aims to summarize and discuss current evidence on different polyphenols for prevention of complications, particularly prevention of CVD in KTR, pointing toward the need of further studies with potential clinical impact.

DIAGNOSTICS (BASEL). 2021 AUG 13;11(8):1470. DOI: 10.3390/DIAGNOSTICS11081470.

CONTENT-BASED MEDICAL IMAGE RETRIEVAL AND INTELLIGENT INTERACTIVE VISUAL BROWSER FOR MEDICAL EDUCATION, RESEARCH AND CARE

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Medical imaging is essential nowadays throughout medical education, research, and care. Accordingly, international efforts have been made to set large-scale image repositories for these purposes. Yet, to date, browsing of large-scale medical image repositories has been troublesome, time-consuming, and generally limited by text search engines. A paradigm shift, by means of a query-by-example search engine, would alleviate these constraints and beneficially impact several practical demands throughout the medical field. The current project aims to address this gap in medical imaging consumption by developing a content-based image retrieval (CBIR) system, which combines two image processing architectures based on deep learning. Furthermore, a first-of-its-kind intelligent visual browser was designed that interactively displays a set of imaging examinations with similar visual content on a similarity map, making it possible to search for and efficiently navigate through a large-scale medical imaging repository, even if it has been set with incomplete and curated metadata. Users may, likewise, provide text keywords, in which case the system performs a content- and metadata-based search. The system was fashioned with an anonymizer service and designed to be fully interoperable according to international standards, to stimulate its integration within electronic healthcare systems and its adoption for medical education, research and care. Professionals of the healthcare sector, by means of a self-administered questionnaire, underscored that this CBIR system and intelligent interactive visual browser would be highly useful for these purposes. Further studies are warranted to complete a comprehensive assessment of the performance of the system through case description and protocolized evaluations by medical imaging specialists.

RADIOLOGY. 2021 OCT;301(1):223-228. DOI: 10.1148/RADIOL.2021203410.

HEPATIC HILAR NERVE BLOCK FOR HEPATIC INTERVENTIONS: ANATOMY, TECHNIQUE, AND INITIAL CLINICAL EXPERIENCE IN THERMAL ABLATION OF LIVER TUMORS

Kevin S He, Rukshan Fernando, Tatiana Cabrera, David Valenti, Abdulaziz Algharras, Nicolás Martínez, David M Liu, Geoffroy Noel, Karl Muchantef, Ali Bessissow, Louis-Martin Boucher

A pilot study of a liver-specific nerve block with 0.25% bupivacaine at the hepatic hilum showed the potential to improve pain control during liver ablative treatment. Background. Image-guided procedures for treatment of liver diseases can be painful and require heavy sedation of the patient. Local-regional nerve blocks improve pain control and reduce oversedation risks, but there are no documented liver-specific nerve blocks. Purpose. To develop a safe and technically simple liver-specific nerve block. Materials and Methods. Between March 2017 and October 2019, three cadavers were dissected to evaluate the hepatic hilar anatomy. The hepatic hilar nerves were targeted with transhepatic placement of a needle adjacent to the main portal vein, under US guidance, and evaluated with use of an injection of methylene blue. A hepatic nerve block, using similar technique and 0.25% bupivacaine, was offered to patients undergoing liver tumoral ablation. In a prospective pilot study, 12 patients who received the nerve block were compared with a control group regarding complications, safety, pain scores, and intraoperative opioid requirement. Student t tests were used to compare the groups' characteristics, and Mann-Whitney U tests were used for the measured outcomes. Results. Cadaver results confirmed that the hepatic nerves coursing in the hepatic hilum can be targeted with US for injection of anesthetic agents, with adequate spread of injected methylene blue around the nerves in the hepatic hilar perivascular space. The 12 participants (mean age \pm standard deviation, 66 years \pm 13; eight men) who received a hepatic hilar block before liver thermal ablations demonstrated reduced pain compared with a control group of 12 participants (mean age, 63 years \pm 15; eight men) who received only intravenous sedation. Participants who received the nerve block had a lower mean visual analog scale score for pain than the control

group (3.9 ± 2.4 vs 7.0 ± 2.8 , respectively; $P = .01$) and decreased need for intraprocedural fentanyl (mean dose, $152 \mu\text{g} \pm 78.0$ vs $235.4 \mu\text{g} \pm 58.2$, respectively; $P = .01$). No major complications occurred in the hepatic hilar nerve block group. Conclusion. A dedicated hepatic hilar nerve block with 0.25% bupivacaine can be safely performed to provide anesthesia during liver tumoral ablation.

J VOICE. 2021 SEP;35(5):807.E1-807.E23. DOI: 10.1016/J.JVOICE.2020.02.005.

THE VOCAL TRACT IN LOUD TWANG-LIKE SINGING WHILE PRODUCING HIGH AND LOW PITCHES

Marcelo Saldías, Anne-Maria Laukkanen, Marco Guzmán, Gonzalo Miranda, Justin Stoney, Paavo Alku, Johan Sundberg

Twang-like vocal qualities have been related to a megaphone-like shape of the vocal tract (epilaryngeal tube and pharyngeal narrowing, and a wider mouth opening), low-frequency spectral changes, and tighter and/or increased vocal fold adduction. Previous studies have focused mainly on loud and high-pitched singing, comfortable low-pitched spoken vowels, or are based on modeling and simulation. There is no data available related to twang-like voices in loud, low-pitched singing. Purpose. This study investigates the possible contribution of the lower and upper vocal tract configurations during loud twang-like singing on high and low pitches in a real subject. Methods. One male contemporary commercial music singer produced a sustained vowel [a:] in his habitual speaking pitch (B2) and loudness. The same vowel was also produced in a loud twang-like singing voice on high (G4) and low pitches (B2). Computerized tomography, acoustic analysis, inverse filtering, and audio-perceptual assessments were performed. Results. Both loud twang-like voices showed a megaphone-like shape of the vocal tract, being more notable on the low pitch. Also, low-frequency spectral changes, a peak of sound energy around 3 kHz and increased vocal fold adduction were found. Results agreed with audio-perceptual evaluation. Conclusions. Loud twang-like phonation seems to be mainly related to low-frequency spectral changes (under 2 kHz) and a more compact formant structure. Twang-like qualities seem to require different degrees of twang-related vocal tract adjustments while phonating in different pitches. A wider mouth opening, pharyngeal constriction, and epilaryngeal tube narrowing may be helpful strategies for maximum power transfer and improved vocal economy in loud contemporary commercial music singing and potentially in loud speech. Further studies should focus on vocal efficiency and vocal economy measurements using modeling and simulation, based on real-singers' data.

J VASC INTERV RADIOL. 2021 AUG;32(8):1221-1226. DOI: 10.1016/J.JVIR.2021.05.001.

TRANSHEPATIC APPROACH FOR RETROGRADE D2 DUODENAL STENT PLACEMENT: NEW TECHNIQUE AND CASE SERIES

Abdulaziz AlGharras, Chris Dey, Nouran Molla, Nicolas Martinez, David Valenti, Tatiana Cabrera, Ali Bessissow, Carlos Torres, Karl Muchantef, Louis-Martin Boucher

Transhepatic duodenal stent placement may be a solution when endoscopy fails or when duodenal and biliary stents are needed simultaneously. This approach is usually not considered as an option when the duodenal stent must be deployed across the ampulla of Vater. The authors present a series of 10 patients who underwent a novel transhepatic technique to place a duodenal stent across the ampulla of Vater by establishing a wire scaffold from the liver toward the jejunum and then curving back on itself retrogradely through the duodenal tumor and out the mouth. Technical success was 90% with no associated mortality.

DEPARTAMENTO DE MEDICINA

ENDOCRINOLOGÍA

REV MED CHIL. 2021 MAR;149(3):399-408. DOI: 10.4067/S0034-98872021000300399.

PUESTA AL DÍA: CARCINOMA PARATIROIDEO

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Parathyroid carcinoma is a rare malignant disease that presents as a sporadic or familial primary hyperparathyroidism (PHP). The latter is associated with some genetic syndromes. It occurs with equal frequency in both sexes, unlike PHP caused by parathyroid adenoma that is more common in women. It should be suspected in cases of severe hypercalcemia, with high parathyroid hormone levels and a palpable cervical mass. Given the difficulty in distinguishing between parathyroid carcinoma and adenoma prior to the surgery, the diagnosis is often made after parathyroidectomy. The only curative treatment is complete surgical resection with oncologic block resection of the primary tumor to ensure free margins. Adjuvant therapies with chemotherapy or radiation therapy do not modify overall or disease-free survival. Recurrences are common and re-operation of resectable recurrent disease is recommended. The palliative treatment of symptomatic hypercalcemia is crucial in persistent or recurrent disease after surgery since morbidity and mortality are more associated with hypercalcemia than with tumor burden.

GASTROENTEROLOGÍA

HEPATOLOGY. 2021 JUN;73(6):2099-2109. DOI: 10.1002/HEP.31797.

OUTCOME OF COVID-19 IN PATIENTS WITH AUTOIMMUNE HEPATITIS: AN INTERNATIONAL MULTICENTER STUDY

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Background and Aims. Data regarding outcome of COVID-19 in patients with autoimmune hepatitis (AIH) are lacking. Approach and Results. We performed a retrospective study on patients with AIH and COVID-19 from 34 centers in Europe and the Americas. We analyzed factors associated with severe COVID-19 outcomes, defined as the need for mechanical ventilation, intensive care admission, and/or death. The outcomes of patients with AIH were compared to a propensity score-matched cohort of patients without AIH but with chronic liver diseases (CLD) and COVID-19. The frequency and clinical significance of new-onset liver injury (alanine aminotransferase $> 2 \times$ the upper limit of normal) during COVID-19 was also evaluated. We included 110 patients with AIH (80% female) with a median age of 49 (range, 18-85) years at COVID-19 diagnosis. New-onset liver injury was observed in 37.1% (33/89) of the patients. Use of antivirals was associated with liver injury ($P = 0.041$; OR, 3.36; 95% CI, 1.05-10.78), while continued immunosuppression during COVID-19 was associated with a lower rate of liver injury ($P = 0.009$; OR, 0.26; 95% CI, 0.09-0.71). The rates of severe COVID-19 (15.5% versus 20.2%, $P = 0.231$) and all-cause mortality (10% versus 11.5%, $P = 0.852$) were not different between AIH and non-AIH CLD. Cirrhosis was an independent predictor of severe COVID-19 in patients with AIH ($P < 0.001$; OR, 17.46; 95% CI, 4.22-72.13). Continuation of immunosuppression or presence of liver injury during COVID-19 was not associated with severe COVID-19. Conclusions. This international, multicenter study reveals that patients with AIH were not at risk for worse outcomes with COVID-19 than other causes of CLD. Cirrhosis was the strongest predictor for severe COVID-19 in patients with AIH. Maintenance of immunosuppression during COVID-19 was not associated with increased risk for severe COVID-19 but did lower the risk for new-onset liver injury during COVID-19.

J HEPATOL. 2021 NOV;75(5):1026-1033. DOI: 10.1016/J.JHEP.2021.06.019.

IDENTIFICATION OF OPTIMAL THERAPEUTIC WINDOW FOR STEROID USE IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS: A WORLDWIDE STUDY

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Background & aims: Corticosteroids are the only effective therapy for severe alcohol-associated hepatitis (AH), defined by a model for end-stage liver disease (MELD) score > 20 . However, there are patients who may be too sick to benefit from therapy. Herein, we aimed to identify the range of MELD scores within which steroids are effective for AH. Methods: We performed a retrospective, international multicenter cohort study across 4 continents, including 3,380 adults with a clinical and/or histological diagnosis of AH. The main outcome was mortality at 30 days. We used a discrete-time survival analysis model, and MELD cut-offs were established using the transform-the-endpoints method. Results: In our cohort, median age was 49 (40-56) years, 76.5% were male, and 79% had underlying cirrhosis. Median MELD at admission was 24 (19-29). Survival was 88% (87-89) at 30 days, 77% (76-78) at 90 days, and 72% (72-74) at 180 days. A total of 1,225 patients received corticosteroids. In an adjusted-survival-model, corticosteroid use decreased 30-day mortality by 41% (hazard ratio [HR] 0.59; 0.47-0.74; $p < 0.001$). Steroids only improved survival in patients with MELD scores between 21 (HR 0.61; 0.39-0.95; $p = 0.027$) and 51 (HR 0.72; 0.52-0.99; $p = 0.041$). The maximum effect of corticosteroid treatment (21-30% survival benefit) was observed with MELD scores between 25 (HR 0.58; 0.42-0.77; $p < 0.001$) and 39 (HR 0.57; 0.41-0.79; $p < 0.001$). No corticosteroid benefit was seen in patients with MELD > 51 . The type of corticosteroids used (prednisone, prednisolone, or methylprednisolone) was not associated with survival benefit ($p = 0.247$). Conclusion: Corticosteroids improve 30-day survival only among patients with severe AH, especially with MELD scores between 25 and 39.

FRONT PHARMACOL. 2021 SEP 24;12:729950. DOI: 10.3389/FPHAR.2021.729950. ECOLLECTION 2021.

PROBIOTICS-BASED TREATMENT AS AN INTEGRAL APPROACH FOR ALCOHOL USE DISORDER IN ALCOHOLIC LIVER DISEASE

Catalina Fuenzalida, María Soledad Dufeu, Jaime Poniachik, Juan Pablo Roblero, Lucía Valenzuela-Pérez, Caroll Jenny Beltrán

Alcoholic liver disease (ALD) is one of the leading causes of morbidity among adults with alcohol use disorder (AUD) worldwide. Its clinical course ranges from steatosis to alcoholic hepatitis, progressing to more severe forms of liver damage, such as cirrhosis and hepatocellular carcinoma. The pathogenesis of ALD is complex and diverse elements are involved in its development, including environmental factors, genetic predisposition, the immune response, and the gut-liver axis interaction. Chronic alcohol consumption induces changes in gut microbiota that are associated with a loss of intestinal barrier function and inflammatory responses which reinforce a liver damage progression triggered by alcohol. Alcohol metabolites such as acetaldehyde, lipid peroxidation-derived aldehyde malondialdehyde (MDA), and protein-adducts act as liver-damaging hepatotoxins and potentiate systemic inflammation. Additionally, ethanol causes direct damage to the central nervous system (CNS) by crossing the blood-brain barrier (BBB), provoking oxidative stress contributing to neuroinflammation. Overall, these processes have been associated with susceptibility to depression, anxiety, and alcohol craving in ALD. Recent evidence has shown that probiotics can reverse alcohol-induced changes of the microbiota and prevent ALD progression by restoring gut microbial composition. However, the impact of probiotics on alcohol consumption behavior has been less explored. Probiotics have been used to treat various conditions by restoring microbiota and decreasing systemic and CNS inflammation. The results of some studies suggest that probiotics might improve mental function

in Alzheimer's, autism spectrum disorder, and attenuated morphine analgesic tolerance. In this sense, it has been observed that gut microbiota composition alterations, as well as its modulation using probiotics, elicit changes in neurotransmitter signals in the brain, especially in the dopamine reward circuit. Consequently, it is not difficult to imagine that a probiotics-based complementary treatment to ALD might reduce disease progression mediated by lower alcohol consumption. This review aims to present an update of the pathophysiologic mechanism underlying the microbiota-gut-liver-brain axis in ALD, as well as to provide evidence supporting probiotic use as a complementary therapy to address alcohol consumption disorder and its consequences on liver damage.

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IRRITABLE BOWEL SYNDROME IN INFLAMMATORY BOWEL DISEASE. SYNERGY IN ALTERATIONS OF THE GUT-BRAIN AXIS?

Edith Pérez de Arce, Rodrigo Quera, Caroll J Beltrán, Ana María Madrid, Pilar Nos

The presence of digestive symptoms associated with irritable bowel syndrome (IBS) in patients with inflammatory bowel disease (IBD) in remission is a topic of growing interest. Although there is heterogeneity in clinical studies regarding the use of IBD remission criteria and the diagnosis of IBS, the available data indicate that the IBD-IBS overlap would affect up to one third of patients in remission, and they agree on the finding of a negative impact on the mental health and quality of life of the individuals who suffer from it. The pathophysiological bases that would explain this potential overlap are not completely elucidated; however, an alteration in the gut-brain axis associated with an increase in intestinal permeability, neuroimmune activation and dysbiosis would be common to both conditions. The hypothesis of a new clinical entity or syndrome of "Irritable Inflammatory Bowel Disease" or "Post-inflammatory IBS" is the subject of intense investigation. The clinical approach is based on certifying the remission of IBD activity and ruling out other non-inflammatory causes of potentially treatable persistent functional digestive symptoms. In the case of symptoms associated with IBS and in the absence of sufficient evidence, comprehensive and personalized management of the clinical picture (dietary, pharmacological and psychotherapeutic measures) should be carried out, similar to a genuine IBS.

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IMPACT OF PUBLIC HEALTH POLICIES ON ALCOHOL-ASSOCIATED LIVER DISEASE IN LATIN AMERICA: AN ECOLOGICAL MULTINATIONAL STUDY

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Background and Aims. Alcohol-associated liver disease (ALD) is the leading cause of liver-related mortality in Latin America, yet the impact of public health policies (PHP) on liver disease is unknown. We aimed to assess the association between alcohol PHP and deaths due to ALD in Latin American countries. Approach and Results. We performed an ecological multinational study including 20 countries in Latin America (628,466,088 inhabitants). We obtained country-level sociodemographic information from the World Bank Open Data source. Alcohol-related PHP data for countries were obtained from the World Health Organization Global Information System of Alcohol and Health. We constructed generalized linear models to assess the association between the number of PHP (in 2010) and health outcomes (in 2016). In Latin America, the prevalence of obesity was 27% and 26.1% among male and female populations, respectively. The estimated alcohol per capita consumption among the population at 15 years old or older was 6.8 L of pure alcohol (5.6 recorded and 1.2 unrecorded). The overall prevalence of alcohol use disorders (AUD) was 4.9%. ALD was the main cause of cirrhosis in 64.7% of male and 40.0% of female populations. A total of 19 (95%) countries have at least one alcohol-related PHP on alcohol. The most frequent PHP were limiting drinking age (95%), tax regulations (90%), drunk-driving policies and countermeasures (90%), and government monitoring systems and community support (90%). A higher number of PHP was associated with a lower ALD mortality (PR, 0.76; 95% CI, 0.61-0.93; P = 0.009), lower AUD prevalence (PR, 0.80; 95% CI, 0.65-0.99; P = 0.045), and lower alcohol-attributable road traffic deaths (PR, 0.81; 95% CI, 0.65-1.00; P = 0.051). Conclusions. Our study indicates that in Latin America, countries with higher number of PHP have lower mortality due to ALD, lower prevalence of AUD, and lower alcohol-attributable road traffic mortality.

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THE DILEMMA OF PERSISTENT IRRITABLE BOWEL SYNDROME SYMPTOMS IN PATIENTS WITH QUIESCENT INFLAMMATORY BOWEL DISEASE

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Irritable bowel syndrome and inflammatory bowel disease differ in their natural evolution, etiopathogenesis, diagnostic criteria, and therapeutic approach. However, recent evidence has suggested some similarities in mechanisms underlying symptom development and progression. There is a relevant role for alterations in the microbiome-brain-gut axis in both diseases. The presence of irritable bowel syndrome symptoms in patients with quiescent inflammatory bowel disease is common in clinical practice. To determine the cause of irritable bowel syndrome symptoms in patients with quiescent inflammatory bowel disease is a clinical challenge. This review aims to illustrate possible causes and solutions for these patients.

DIGEST DIS SCI. 2021 NOV;66(11):3792-3802. DOI: 10.1007/S10620-020-06702-8.

SERTRALINE AND CITALOPRAM ACTIONS ON GUT BARRIER FUNCTION

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Introduction: Disruption of intestinal barrier is a key component to various diseases. Whether barrier dysfunction is the cause or effect in these situations is still unknown, although it is believed that translocation of luminal content may initiate gastrointestinal or systemic inflammatory disorders. Since trauma- or infection-driven epithelial permeability depends on Toll-like receptor (TLR) activity, inhibition of TLR signaling has been proposed as a strategy to protect intestinal barrier integrity after infection or other pathological conditions. Recently, selective serotonin recapture inhibitors including sertraline and citalopram were shown to inhibit TLR-3 activity, but the direct effects of these antidepressant drugs on the gut mucosa barrier remain largely unexplored. Materials and methods: To investigate this, two approaches were used: first, ex vivo studies were performed to evaluate sertraline and citalopram-driven changes in permeability in isolated intestinal tissue. Second, both compounds were tested for their preventive effects in a rat model of disrupted gut barrier, induced by a low protein (LP) diet. Results: Only sertraline was able to increase transepithelial electrical resistance in the rat colon both when used in an ex vivo (0.8 µg/mL, 180 min) or in vivo (30 mg/kg p.o., 20 days) fashion. However, citalopram (20 mg/kg p.o., 20 days), but not sertraline, prevented the increase in phospho-IRF3 protein, a marker of TLR-3 activation, in LP-rat ileum. Neither antidepressant affected locomotion, anxiety-like behaviours or stress-induced defecation. Conclusion: Our data provides evidence to support the investigation of sertraline as therapeutic strategy to protect intestinal barrier function under life-threatening situations or chronic conditions associated with gut epithelial disruption.

J CELL MOL MED. 2021 AUG;25(16):8047-8061. DOI: 10.1111/JCMM.16736.

THE ALTERNATIVE SEROTONIN TRANSPORTER PROMOTER P2 IMPACTS GENE FUNCTION IN FEMALES WITH IRRITABLE BOWEL SYNDROME

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Irritable bowel syndrome (IBS) is a gut-brain disorder in which symptoms are shaped by serotonin acting centrally and peripherally. The serotonin transporter gene SLC6A4 has been implicated in IBS pathophysiology, but the underlying genetic mechanisms remain unclear. We sequenced the alternative P2 promoter driving intestinal SLC6A4 expression and identified single nucleotide polymorphisms (SNPs) that were associated with IBS in a discovery sample. Identified SNPs built different haplotypes, and the tagging SNP rs2020938 seems to associate with constipation-predominant IBS (IBS-C) in females. rs2020938 validation was performed in 1978 additional IBS patients and 6,038 controls from eight countries. Meta-analysis on data from 2,175 IBS patients and 6,128 controls confirmed the association with female IBS-C. Expression analyses revealed that the P2 promoter drives SLC6A4 expression primarily in the small intestine. Gene reporter assays showed a functional impact of SNPs in the P2 region. In silico analysis of the polymorphic promoter indicated differential expression regulation. Further follow-up revealed that the major allele of the tagging SNP rs2020938 correlates with differential SLC6A4 expression in the jejunum and with stool consistency, indicating functional relevance. Our data consolidate rs2020938 as a functional SNP associated with IBS-C risk in females, underlining the relevance of SLC6A4 in IBS pathogenesis.

WORLD J CLIN CASES. 2021 MAY 26;9(15):3716-3725. DOI: 10.12998/WJCC.V9.I15.3716.

SARCOMATOID CARCINOMA OF THE PANCREAS - A RARE TUMOR WITH AN UNCOMMON PRESENTATION AND COURSE: A CASE REPORT AND REVIEW OF LITERATURE

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Background: Sarcomatoid carcinoma of the pancreas (SCP) is a rare type of pancreatic neoplasm, and only a few cases have been described in the literature. Histologically, it is composed mostly of atypical spindle cells with apparent sarcomatous features. Case summary: This is a report of a 61-year-old Chilean woman who underwent medical investigation for acute abdominal pain. Computed tomography identified a solid tumor in the tail of the pancreas with features suspicious of malignancy. En-bloc distal pancreatectomy and splenectomy were performed to excise the tumor. Histopathology and immunohistochemistry were confirmatory of sarcomatoid carcinoma with lymphovascular invasion. After surgery, the patient did not receive chemotherapy. Previous studies indicate a poor prognosis for this type of malignancy. However, our patient has survived for 35 mo with no recurrence to date. Conclusion: The case presented herein is a patient with an SCP with a rare presentation and long-term survival after surgery despite not receiving adjuvant chemotherapy.

ARCH MED RES. 2021 JUL;52(5):529-534. DOI: 10.1016/J.ARCMED.2021.01.011.

PREVALENCE OF HELICOBACTER PYLORI ANTIMICROBIAL RESISTANCE AMONG CHILEAN PATIENTS

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Background: Treatments for Helicobacter pylori (H. pylori) eradication include the use of antibiotics and a proton-pump inhibitor. Antibiotic resistance is a major concern for two drugs: levofloxacin and clarithromycin. The aim was to determine the prevalence of levofloxacin resistance (LevoR) and clarithromycin resistance (ClaR) in an urban population in Santiago, Chile. Methods: Gastric mucosa biopsies were obtained for DNA

isolation from 143 H. pylori-positive individuals aged 18-80 years. Direct sequencing of the quinolone-resistance determining region (QRDR) of the *gyrA* gene was used to determine LevoR. ClaR was determined using restriction-fragment length polymorphism or 5'exonuclease assay. Results: The prevalences of LevoR and ClaR were 29 and 27%, respectively. LevoR was higher in women than in men (39 vs. 13%, $p < 0.001$), while no sex difference was observed for ClaR ($p = 0.123$). The prevalence of LevoR increased with age (p -trend = 0.004) but not for ClaR (p -trend = 0.054). In sex-stratified analyses, both LevoR and ClaR increased with age only among women. Older women (>50 years) had a higher probability to carry LevoR strains as compared to men. The prevalence of dual LevoR and ClaR was 12.6%. Conclusions: The prevalence of ClaR and LevoR is high in Santiago, according to International guidelines that recommend avoiding schemes with antibiotic resistance >15%. Our findings provide evidence to re-evaluate current therapies and guide empirical first- and second-line eradication treatments in Chile.

ANN HEPATOL. MAR-APR 2021;21:100107. DOI: 10.1016/J.AOHEP.2019.06.012.

LIVER TRANSPLANTATION IN ACUTE LIVER FAILURE DUE TO HEPATITIS B. TWO CLINICAL CASES

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Hepatitis B virus (HBV) related acute liver failure (ALF) is uncommon in our region, and there is limited HBV literature regarding the optimal management of these cases. In this article, we report two clinical cases of young men who have sex with men (MSM), both developed severe acute hepatitis caused by HBV, progressed to ALF and afterward required liver transplantation. Antiviral post-transplant treatment included entecavir without Hepatitis B Immunoglobulin (HBIG), and immunosuppression therapy with steroids, tacrolimus, and mycophenolate. Serologic follow-up showed early Hepatitis B surface Antigen (HBsAg) seroconversion, undetectable HBV viral load, and positive Anti-HBs titers. During later follow-up, Anti-HBs titers gradually fell (<10mIU/L after six months), with normal liver function. DISCUSSION: In cases of HBV-related ALF, the liver develops a robust immune response, leading to, an early undetectable viral load and seroconversion, with loss of HBsAg, and the appearance of Anti-HBs as a result of the inflammatory response. The management varies depending on whether this is a de novo acute infection or a reactivation of a previous chronic infection. In both cases, the use of antiviral therapy is recommended, with entecavir or tenofovir, among others, but the use of specific HBIG is supported only in ALF related to chronic HBV infection. The optimal length of the antiviral therapy after liver transplantation is still under discussion. CONCLUSION: These cases of HBV related ALF with an early HBsAg seroconversion demonstrates the relevance of requesting IgM antibody against hepatitis B core antigen (anti-HBc IgM) for the etiological study of ALF with negative HBsAg. Usage of HBIG does not seem essential during the post-transplantation period in these cases.

ANN HEPATOL. NOV-DEC 2021;25:100350. DOI: 10.1016/J.AOHEP.2021.100350.

COMPARISON OF DIFFERENT PROGNOSTIC SCORES FOR PATIENTS WITH CIRRHOSIS HOSPITALIZED WITH SARS-COV-2 INFECTION

Manuel Mendizabal, Ezequiel Ridruejo, Federico Piñero, Margarita Anders, Martín Padilla, Luis G Toro, Aldo Torre, Pedro Montes, Alvaro Urzúa, Esteban Gonzalez Ballerga, María Dolores Silveyra *et al.*

Introduction and objectives: Viral infections have been described to increase the risk of decompensation in patients with cirrhosis. We aimed to determine the effect of SARS-CoV-2 infection on outcome of hospitalized patients with cirrhosis and to compare the performance of different prognostic models for predicting mortality. Patients: We performed a prospective cohort study including 2211 hospitalized patients with confirmed SARS-CoV-2 infection from April 15, 2020 through October 1, 2020 in 38 Hospitals from 11 Latin American countries. We registered clinical and laboratory parameters of patients with and without cirrhosis. All patients were followed until discharge or death. We evaluated the prognostic performance of different scoring systems to predict mortality in patients with cirrhosis using ROC curves. Results: Overall, 4.6% (CI 3.7-5.6) subjects had cirrhosis ($n = 96$). Baseline Child-Turcotte-Pugh (CTP) class was assessed: CTP-A (23%), CTP-B (45%) and CTP-C (32%); median MELD-Na score was 19 (IQR 14-25). Mortality was 47% in patients with cirrhosis and 16% in patients without cirrhosis ($P < .0001$). Cirrhosis was independently associated with death [OR 3.1 (CI 1.9-4.8); $P < .0001$], adjusted by age, gender, and body mass index >30. The areas under the ROC curves for performance evaluation in predicting 28-days mortality for Chronic Liver Failure Consortium (CLIF-C), North American Consortium for the Study of End-Stage Liver Disease (NACSELD), CTP score and MELD-Na were 0.85, 0.75, 0.69, 0.67; respectively ($P < .0001$). Conclusions: SARS-CoV-2 infection is associated with elevated mortality in patients with cirrhosis. CLIF-C had better performance in predicting mortality than NACSELD, CTP and MELD-Na in patients with cirrhosis and SARS-CoV-2 infection. Clinicaltrials.gov:NCT04358380.

ANN HEPATOL. MAR-APR 2021;21:100298. DOI: 10.1016/J.AOHEP.2020.100298.

PROSPECTIVE LATIN AMERICAN COHORT EVALUATING OUTCOMES OF PATIENTS WITH COVID-19 AND ABNORMAL LIVER TESTS ON ADMISSION

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Introduction & objectives: The independent effect of liver biochemistries as a prognostic factor in patients with COVID-19 has not been completely addressed. We aimed to evaluate the prognostic value of abnormal liver tests on admission of hospitalized patients with COVID-19. Materials & methods: We performed a prospective cohort study including 1611 hospitalized patients with confirmed SARS-CoV-2 infection from April 15, 2020 through July 31, 2020 in 38 different Hospitals from 11 Latin American countries. We registered clinical and laboratory parameters, including liver function tests, on admission and during hospitalization. All patients were followed until discharge or death. We fit multivariable logistic regression models, further post-estimation effect through margins and inverse probability weighting. Results: Overall, 57.8% of the patients were male with a

mean age of 52.3 years, 8.5% had chronic liver disease and 3.4% had cirrhosis. Abnormal liver tests on admission were present on 45.2% (CI 42.7-47.7) of the cohort (n = 726). Overall, 15.1% (CI 13.4-16.9) of patients died (n = 244). Patients with abnormal liver tests on admission presented higher mortality 18.7% (CI 15.9-21.7), compared to those with normal liver biochemistries 12.2% (CI 10.1-14.6); P < .0001). After excluding patients with history of chronic liver disease, abnormal liver tests on admission were independently associated with death [OR 1.5 (CI 1.1-2.0); P = 0.01], and severe COVID-19 (2.6 [2.0-3.3], P < .0001), both adjusted by age, gender, diabetes, pneumonia and body mass index >30. Conclusions: The presence of abnormal liver tests on admission is independently associated with mortality and severe COVID-19 in hospitalized patients with COVID-19 infection and may be used as surrogate marker of inflammation. CLINICALTRIALS.GOV: NCT04358380.

NEUROGASTROENTL MOTIL. 2021 OCT 30;27(4):632-638. DOI: 10.5056/JNM20180.

PARADOXICAL STIMULATORY RESPONSE OF REMANENT SPHINCTER OF ODDI TO BUSCAPINA AFTER ENDOSCOPIC SPHINCTEROTOMY
Zoltán Berger, Ana María Madrid S

Background/aims: Endoscopic removal of bile duct stones has become the treatment of choice, which includes endoscopic sphincterotomy (EST) in the majority of cases, destroying at least partially the Oddi sphincter (OS). Loss of sphincter function in variable grade has been described, but changes in innervation are not known. Methods: Endoscopic manometry of OS was performed in 14 patients after EST with specialized perfused catheter. Pressure values were registered before and after 10 mg Buscapina injected intravenously. Results: Choledochoduodenal pressure gradient was absent in all of 14 patients. Basal OS pressure was zero in 7 and conserved in normal range in the remaining 7. Phasic motor activity was registered in 11 patients and was absent in 3 patients. After 10 mg Buscapina intravenous injection, instead of habitual inhibition, increase in basal OS pressure and in frequency of phasic contractions was observed in 9 patients. This response was not related to age of patients, neither with time elapsed between the EST and manometry, nor the estimated size of papillotomy orifice. Duodenal peristalsis was invariably inhibited in all patients. Conclusions: EST destroys not only the smooth muscle of OS, also alters the innervation interrupting the duodeno-sphincteric nerve circuit. This finding questions the use of Buscapina or other anticholinergic agent as spasmolytic in patients after EST.

LIVER INT. 2021 APR;41(4):851-862. DOI: 10.1111/LIV.14736.

RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION: PROGNOSTIC AND PREDICTIVE FACTORS OF SURVIVAL IN A LATIN AMERICAN COHORT

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Background & Aim. Recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) has a poor prognosis, and the adjusted effect of different treatments on post-recurrence survival (PRS) has not been well defined. This study aims to evaluate prognostic and predictive variables associated with PRS. Methods. This Latin American multicenter retrospective cohort study included HCC patients who underwent LT between the years 2005-2018. We evaluated the effect of baseline characteristics at time of HCC recurrence diagnosis and PRS (Cox regression analysis). Early recurrences were those occurring within 12 months of LT. To evaluate the adjusted treatment effect for HCC recurrence, a propensity score matching analysis was performed to assess the probability of having received any specific treatment for recurrence. Results. From a total of 1085 transplanted HCC patients, the cumulative incidence of recurrence was 16.6% (CI 13.5-20.3), with median time to recurrence of 13.0 months (IQR 6.0-26.0). Factors independently associated with PRS were early recurrence (47.6%), treatment with sorafenib and surgery/transarterial chemoembolization (TACE). Patients who underwent any treatment presented "early recurrences" less frequently, and more extrahepatic metastasis. This unbalanced distribution was included in the propensity score matching, with correct calibration and discrimination (receiving operator curve of 0.81 [CI 0.72;0.88]). After matching, the adjusted effect on PRS for any treatment was HR of 0.2 (0.10;0.33); P < .0001, for sorafenib therapy HR of 0.4 (0.27;0.77); P = .003, and for surgery/TACE HR of 0.4 (0.18;0.78); P = .009. Conclusion. Although early recurrence was associated with worse outcome, even in this population, systemic or locoregional treatments were associated with better PRS.

TRANSPL INT. 2021 JAN;34(1):97-109. DOI: 10.1111/TRI.13767.

LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: IMPACT OF EXPANSION CRITERIA IN A MULTICENTER COHORT STUDY FROM A HIGH WAITLIST MORTALITY REGION

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This study aimed to compare liver transplantation (LT) outcomes and evaluate the potential rise in numbers of LT candidates with hepatocellular carcinoma (HCC) of different allocation policies in a high waitlist mortality region. Three policies were applied in two Latin American cohorts (1085 HCC transplanted patients and 917 listed patients for HCC): (i) Milan criteria with expansion according to UCSF downstaging (UCSF-DS), (ii) the AFP score, and (iii) restrictive policy or Double Eligibility Criteria (DEC; within Milan + AFP score ≤2). Increase in HCC patient numbers was evaluated in an Argentinian prospective validation set (INCUCAI; NCT03775863). Expansion criteria in policy A showed that UCSF-DS [28.4% (CI 12.8-56.2)] or "all-comers" [32.9% (CI 11.9-71.3)] had higher 5-year recurrence rates compared to Milan, with 10.9% increase in HCC patients for LT. The policy B showed lower recurrence rates for AFP scores ≤2 points, even expanding beyond Milan criteria, with a 3.3% increase. Patients within DEC had lower 5-year recurrence rates compared with those beyond DEC [13.3% (CI 10.1-17.3) vs 24.2% (CI 17.4-33.1); P = 0.0006], without significant HCC expansion. In conclusion, although the application of a stricter policy may optimize the selection process, this restrictive policy may lead to ethical concerns in organ allocation (NCT03775863).

BIOL RES. 2021 APR 20;54(1):13. DOI: 10.1186/S40659-021-00336-4.

NOD1 RS2075820 (P.E266K) POLYMORPHISM IS ASSOCIATED WITH GASTRIC CANCER AMONG INDIVIDUALS INFECTED WITH CAGPAI-POSITIVE H. PYLORI

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Background. *Helicobacter pylori* is detected by pathogen recognition receptors including toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptors, eliciting an innate immune response against this bacteria. The aim of this study was to assess if polymorphisms of TLR2, TLR4, TLR5, NOD1 and NOD2 genes are associated with gastric cancer, in particular in individuals infected with *H. pylori*. Results. A case-control study of 297 gastric cancer patients and 300 controls was performed to assess the association of 17 polymorphisms. Analyses performed under the allele model did not find association with gastric cancer. However, NOD1 rs2075820 (p.E266K) showed association with intestinal-type gastric cancer among *H. pylori* infected subjects (OR=2.69, 95% CI 1.41–5.13, p=0.0026). The association was not statistically significant in diffuse-type gastric cancer cases (OR = 1.26, 95% CI 0.63–2.52, p=0.51). When the analyses were performed in patients carrying *H. pylori* strains harboring the *cag* pathogenicity island (*cagPAI*), we noticed significant association with NOD1 rs2075820 (OR=4.90, 95% CI 1.80–3.36, p=0.0019), in particular for intestinal-type gastric cancer cases (OR=7.16, 95% CI 2.40–21.33, p=4.1 × 10⁻⁴) but not among diffuse-type gastric cancer cases (OR=3.39, 95% CI 1.13–0.10, p=0.03). Conclusions. NOD1 rs2075820 increases the risk of intestinal-type gastric cancer among individuals infected with *H. pylori*, particularly in those harboring the *cagPAI*.

GENÉTICA

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PREVALENCE OF MICROCEPHALY: THE LATIN AMERICAN NETWORK OF CONGENITAL MALFORMATIONS 2010-2017

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Objective The Latin American Network of Congenital Malformations: ReLAMC was established in 2017 to provide accurate congenital anomaly surveillance. This study used data from ReLAMC registries to quantify the prevalence of microcephaly from 2010 to 2017 (before, during and after the Zika virus epidemic). Design Nine ReLAMC congenital anomaly registries provided case-level data or aggregate data for any live births, still births or terminations of pregnancy with microcephaly. Births to pregnant women infected with Zika virus first occurred in Brazil in 2015, and in the remaining registry areas in 2016 with the exception of Chile that did not experience Zika virus. Therefore the prevalence of microcephaly for 2010–2014 and individual years 2015, 2016 and 2017 was estimated using multilevel random effect Poisson models. Clinical classification and characteristics of the cases were compared pre and post Zika for all centres providing individual case-level data. Results The prevalence of microcephaly for all registries excluding Brazil was 2.3 per 10 000 (95% CI 2.0 to 2.6) for 2010–2014 rising to 5.4 (95% CI 4.8 to 6.0) in 2016 and 5.9 (95% CI 5.3 to 6.6) in 2017. Brazil had a prevalence of 0.6 per 10 000 (95% CI 0.5 to 0.6) in 2010–2014, rising to 5.8 (95% CI 5.6 to 6.1) in 2015, 8.0 (95% CI 7.6 to 8.3) in 2016 and then falling in 2017. Only 29 out of 687 cases of microcephaly were reported as congenital Zika syndrome in countries excluding Brazil. Conclusions The prevalence of microcephaly was influenced both by Zika causing congenital Zika syndrome and by increased reporting awareness.

PEDIATR RES. 2021 MAR;89(4):1020-1025. DOI: 10.1038/S41390-020-0994-3.

GENETIC VARIANTS IN S-ADENOSYL-METHIONINE SYNTHESIS PATHWAY AND NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN CHILE

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Background. The S-adenosyl-methionine (SAM) availability is crucial for DNA methylation, an epigenetic mechanism involved in nonsyndromic cleft lip with or without cleft palate (NSCL/P) expression. The aim of this study was to assess the association between single-nucleotide polymorphisms (SNPs) of genes involved in SAM synthesis and NSCL/P in a Chilean population. Methods. In 234 cases and 309 controls, 18 SNPs in AHCY, MTR, MTRR, and MAT2A were genotyped, and the association between them and the phenotype was evaluated based on additive (allele), dominant, recessive and haplotype models, by odds ratio (OR) computing. Results. Three deep intronic SNPs of MTR showed a protective effect on NSCL/P expression: rs10925239 (OR 0.68; p=0.0032; q=0.0192), rs10925254 (OR 0.66; p=0.0018; q=0.0162), and rs3768142 (OR 0.66; p=0.0015; q=0.0162). Annotations in expression database demonstrate that the protective allele of the three SNPs is associated with a reduction of MTR expression summed to the prediction by bioinformatic tools of its potentiality to modify splicing sites. Conclusions. The protective effect against NSCL/P of these intronic MTR SNPs seems to be related to a decrease in MTR enzyme expression, modulating the SAM availability for proper substrate methylation. However, functional analyses are necessary to confirm our findings.

EUR J ORAL SCI. 2021 OCT;129(5):E12813. DOI: 10.1111/EOS.12813.

MATERNAL GENOTYPES OF FOLATE/ONE-CARBON METABOLISM GENE VARIANTS AND NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE RISK IN CHILE

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The aim of this study was to evaluate, in a case-control design, the association between maternal genotypes for variants in 23 genes involved in folate/one-carbon metabolism and nonsyndromic cleft lip with or without cleft palate (NSCL/P) in a Chilean population. After applying several filters to an Illumina array, we extracted 175 single nucleotide polymorphisms (SNPs) from 150 mothers of NSCL/P cases and 150 control women. Association was evaluated using computed odds ratio (OR) with a 95% confidence interval (95% CI) in additive, recessive, and dominant models. After multiple comparison correction, only SNP rs4451422 (A>C), located 237 bp downstream of the gene encoding the human folypolyglutamate synthetase (FPGS), maintained a significant association with NSCL/P in the offspring (OR 3.03; 95% CI 1.69–5.26). The variant rs4451422 is associated with a decrease in FPGS expression according to database annotation. Our results lead to a new hypothesis that a lower activity of FPGS enzyme reduces intracellular folate levels and increases the risk of an offspring having NSCL/P.

GERIATRÍA

J AM MED DIR ASSOC. 2021 APR;22(4):853-858. DOI: 10.1016/J.JAMDA.2020.07.032.

OSTEOSARCOPENIA PREDICTS FALLS, FRACTURES, AND MORTALITY IN CHILEAN COMMUNITY-DWELLING OLDER ADULTS

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Objectives: The objective of this study was to describe the prevalence of osteosarcopenia and its association with falls, fractures, and mortality in community-dwelling older adults. **Design:** Follow-up of ALEXANDROS cohorts designed to study disability associated with obesity in older adults. **Setting and participants:** Community-dwelling people aged 60 years and older living in Chile. **Measures:** At baseline, 1119 of 2372 participants had a dual-energy X-ray absorptiometry scan and the measurements for the diagnosis of sarcopenia. World Health Organization standards for bone mineral density were used to classify them as normal, osteopenia, and osteoporosis. Sarcopenia was identified using the algorithm from the European Working Group on Sarcopenia in Older People 1, validated for the Chilean population. Osteosarcopenia was defined as having sarcopenia plus osteoporosis or osteopenia. **Results:** The sample of 1119 participants (68.5% female) had a mean age of 72 years. At baseline, osteoporosis was identified in 23.2%, osteopenia in 49.8%, sarcopenia in 19.5%, and osteosarcopenia in 16.4% of the sample. The prevalence of osteosarcopenia increases with age, reaching 33.7% for those older than 80 years. Sarcopenia was found in 34.4% of osteoporotic people and osteoporosis in 40.8% of those with sarcopenia. After 5640 person-years of follow-up, 86 people died. The mortality was significantly higher for the group with osteosarcopenia (15.9%) compared with those without the condition (6.1%). After an adjusted Cox Regression analysis, the hazard ratio for death in people with osteosarcopenia was 2.48. Falls, fractures, and functional impairment were significantly more frequent in osteosarcopenic patients. **Conclusions and implications:** Osteosarcopenia is a common condition among older adults and is associated with an increased risk of falls, fractures, functional impairment, and mortality. Considering the high proportion of sarcopenia among osteoporotic patients and vice versa, screening for the second condition when the first is suspected should be advised.

ARCH CLIN NEUROPSYCH. 2021 OCT 20;ACAB080. DOI: 10.1093/ARCLIN/ACAB080.

WORKING GROUP RECOMMENDATIONS FOR THE PRACTICE OF TELENEUROPSYCHOLOGY IN LATIN AMERICA

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Objective: Teleneuropsychology (teleNP) could potentially expand access to services for patients who are confined, have limited personal access to healthcare, or live in remote areas. The emergence of the COVID-19 pandemic has significantly increased the use of teleNP for cognitive assessments. The main objective of these recommendations is to identify which procedures can be potentially best adapted to the practice of teleNP in Latin America, and thereby facilitate professional decision-making in the region. **Method:** Steps taken to develop these recommendations included (1) formation of an international working group with representatives from 12 Latin American countries; (2) assessment of rationale, scope, and objectives; (3) formulation of clinical questions; (4) evidence search and selection; (5) evaluation of existing evidence and summary; and (6) formulation of recommendations. Levels of evidence were graded following the Oxford Centre for Evidence-Based Medicine system. Databases examined included PubMed, WHO-IRIS, WHO and PAHO-IRIS, Índice Bibliográfico Español en Ciencias de la Salud (IBCS), and LILACS. **Results:** Working group members reviewed 18,400 titles and 422 abstracts and identified 19 articles meeting the criteria for level of evidence, categorization, and elaboration of recommendations. The vast majority of the literature included teleNP tests in the English language. The working group proposed a series of recommendations that can be potentially best adapted to the practice of teleNP in Latin America. **Conclusions:** There is currently sufficient evidence to support the use of videoconferencing technology for remote neuropsychological assessments. These recommendations will likely contribute to the advancement of teleNP research and practice in the region.

WORLD ALLERGY ORGAN. 2021 MAY 18;14(5):100543. DOI: 10.1016/J.WAOJOU.2021.100543. ECOLLECTION 2021 MAY. CURRENT SITUATION OF ALLERGY EDUCATION IN MEXICO AND OTHER PARTS OF LATIN AMERICA

Sandra Nora Gonzalez-Diaz, Bryan Martin, Cindy Elizabeth de Lira-Quezada, Rosalaura Virginia Villarreal-Gonzalez, Rosa Ivett Guzman-Avilan, Alejandra Macías-Weinmann, José Antonio Ortega-Martell, Carlos Macouzet-Sanchez, Mario Sánchez-Borges, Nelson Augusto Rosario Filho, Anahí Yañez, María Antonieta Guzman-Melendez, Ricardo Cardona, Olga Patricia Monge-Ortega, Ivan Cherez-Ojeda y otros

Allergic diseases are one of the most frequent chronic diseases in the world. It has been established that there is a worldwide epidemic of allergic diseases; therefore, the treatment of allergies should be acknowledged as a worldwide priority and the specialty of allergy should be considered an important field in medicine. Due to the fact that allergic diseases involve many organs, and Allergy and Clinical Immunology is one of the specialties in which physicians may be trained to treat patients of all ages, the subject in medical schools is not always taught as an individual specialty but often as part of another subject such as internal medicine or pediatrics. Certified allergists are an important contribution to health systems, providing the necessary care for patients who have allergic diseases. Undergraduate programs in many universities do not include allergy as a subject, contributing to a lack of knowledge regarding the correct management of allergic diseases. World Health Organization (WHO) recommends 1 allergist per 50,000 people; however, there is an uneven distribution of allergy and clinical immunology specialists. Most practitioners are localized mainly in larger cities and state capitals, while in other regions, specialists are still greatly needed. Support and training systems are required for allergy and clinical immunology specialists to promote continuing education and keep their clinical competence up to date, which will lead to better care for their patients. Increased exposure to the concepts of allergy and clinical immunology diagnosis and treatment in undergraduate education may also potentially lead to an increase in interest in the field of allergy and clinical immunology among physicians in training. This review will approach allergy education in Mexico and other parts of Latin America.

ALZHEIMERS DEMENT. 2021 FEB;17(2):295-313. DOI: 10.1002/ALZ.12202.

DEMENTIA IN LATIN AMERICA: PAVING THE WAY TOWARD A REGIONAL ACTION PLAN

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Across Latin American and Caribbean countries (LACs), the fight against dementia faces pressing challenges, such as heterogeneity, diversity, political instability, and socioeconomic disparities. These can be addressed more effectively in a collaborative setting that fosters open exchange of knowledge. In this work, the Latin American and Caribbean Consortium on Dementia (LAC-CD) proposes an agenda for integration to deliver a Knowledge to Action Framework (KtAF). First, we summarize evidence-based strategies (epidemiology, genetics, biomarkers, clinical trials, nonpharmacological interventions, networking, and translational research) and align them to current global strategies to translate regional knowledge into transformative actions. Then we characterize key sources of complexity (genetic isolates, admixture in populations, environmental factors, and barriers to effective interventions), map them to the above challenges, and provide the basic mosaics of knowledge toward a KtAF. Finally, we describe strategies supporting the knowledge creation stage that underpins the translational impact of KtAF.

MEDICINA INTERNA

REV CHILENA INFECTOL. 2021 JUN;38(3):344-348. DOI: 10.4067/S0716-10182021000300344.

COMPARACIÓN ENTRE XPRT® Y COBAS®-TAQMAN® PARA LA MEDICIÓN DE CARGA VIRAL DE VIRUS HEPATITIS B Y C.

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Background: The measurement of viral load (VL) of hepatitis B (HBV) and C (HCV) viruses is essential in the follow-up of patients with antiviral therapy. The most widely used methodology for this determination is COBAS®-TaqMan®. Recently, the Xpert® technology was developed and needs to be evaluated. Aim: To compare the measurement of the VL of HBV and HCV by Xpert® methodology with COBAS®-TaqMan® as a reference method. Material and methods: 39 serum samples from patients with HBV and 39 with HCV, previously quantified by COBAS®-TaqMan®, were analyzed using Xpert® and the results were compared using Deming regression and Bland-Altman plot. Results: There was a high correlation between Xpert® and COBAS®-TaqMan®. For HBV, the Deming equation was $Xpert_{HBV} = 0.44 + 0.99 \times COBAS_{TaqMan_{HBV}}$, with a correlation coefficient of 0.94 and a difference between means of -0.401 log (95% CI: -1.985 to 1.183). For HCV, the Deming equation was $Xpert_{HCV} = 0.36 + 0.87 \times COBAS_{TaqMan_{HCV}}$, with a correlation coefficient of 0.98 and a difference between means of 0.328 log₁₀ (95% CI: -0.449 to 1.105). Conclusion: The new Xpert® system shows a good correlation with COBAS®-TaqMan® for the measurement of the VL of HBV and HCV, being a good alternative for the follow-up of patients under treatment.

INT J CLIN PRACT. 2021 DEC;75(12):E14919. DOI: 10.1111/IJCP.14919.

CLINICAL CHARACTERISTICS AND IN-HOSPITAL MORTALITY OF PATIENTS WITH COVID-19 IN CHILE: A PROSPECTIVE COHORT STUDY

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Aims of this study. To describe the Latin American population affected by COVID-19, and to determine relevant risk factors for in-hospital mortality. Methods. We prospectively registered relevant clinical, laboratory, and radiological data of adult patients with COVID-19, admitted within the first 100 days of the pandemic from a single teaching hospital in Santiago, Chile. The primary outcome was in-hospital mortality. Secondary outcomes included the need for respiratory support and pharmacological treatment, among others. We combined the chronic

disease burden and the severity of illness at admission with predefined clinically relevant risk factors. Cox regression models were used to identify risk factors for in-hospital mortality. Results. We enrolled 395 adult patients, their median age was 61 years; 62.8% of patients were male and 40.1% had a Modified Charlson Comorbidity Index (MCCI) ≥ 5 . Their median Sequential Organ Failure Assessment (SOFA) score was 3; 34.9% used a high-flow nasal cannula and 17.5% required invasive mechanical ventilation. The in-hospital mortality rate was 14.7%. In the multivariate analysis, were significant risk factors for in-hospital mortality: MCCI ≥ 5 (HR 4.39, $P < .001$), PaO₂/FiO₂ ratio ≤ 200 (HR 1.92, $P = .037$), and advanced chronic respiratory disease (HR 3.24, $P = .001$); pre-specified combinations of these risk factors in four categories was associated with the outcome in a graded manner. Conclusions and clinical implications. The relationship between multiple prognostic factors has been scarcely reported in Latin American patients with COVID-19. By combining different clinically relevant risk factors, we can identify COVID-19 patients with high-, medium- and low-risk of in-hospital mortality.

HEALTH SOC CARE COMM. 2021 AUG 25. DOI: 10.1111/HSC.13527.

DETERMINANTS OF THE INTENTION TO SPEAK UP ABOUT MEDICAL ERROR IN PRIMARY HEALTHCARE SETTINGS IN CHILE

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Medical error frequently occurs in ambulatory care, and healthcare professionals may encounter situations in which they need to speak up to ensure better practice. This study aims to investigate the factors that influenced the intention to speak up about medical errors among healthcare professionals in primary care settings. Data were generated through a national cross-sectional survey of primary healthcare centres in the Republic of Chile. A research instrument was designed using the constructs of the theory of planned behaviour and was analysed using the structural equation model technique. In total, 203 healthcare professionals were recruited between March and May 2020. The model showed that the intention to speak up was directly and positively influenced by attitudes towards speaking up and perceived control (standard deviation [SD] = 0.284 and 0.576, respectively). Subjective norms indirectly and negatively influenced the intention to speak up through attitudes towards speaking up and perceived control (total effect SD = -0.303). The exploratory construct of willingness to change self-behaviour positively influenced the attitude towards behaviour. The intention to speak up strongly influenced the speaking up behaviour (total effect SD = 0.631). The proposed model explained 40% of the variance in behaviour. Based on this model, it was concluded that the intention to speak up strongly influenced the speaking up behaviour and predicted it by 40%. Factors that modify the intention to speak up are expected to influence the occurrence of this behaviour. This knowledge will inform strategies to enhance communication among healthcare professionals, improve speaking up behaviour and improve patient care.

REV MED CHIL. 2021 JUN;149(6):864-872. DOI: 10.4067/S0034-98872021000600864.

PRÁCTICAS NACIONALES DE ANALGESIA, SEDACIÓN Y DELIRIUM EN LAS UNIDADES DE CUIDADOS INTENSIVOS DE ADULTOS EN CHILE

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Background: The appropriate use of analgesia, sedation, neuromuscular blockade and the diagnosis and prevention of delirium (ASBD) are associated with better outcomes in critically ill patients at Intensive Care Unit (ICUs). Aim: To know the practices about analgesia, sedation, delirium, and neuromuscular blockade use among healthcare professionals working in adult ICUs in Chile. Material and Methods: An electronic survey was sent to 812 professionals working in ICUs using a previously published instrument, which was adapted and authorized by the author. Results: We received 278 surveys. Fifty two percent of respondents were physicians, 34% nurses and 11% physical therapists. Their age ranged between 30 and 39 years in 43% and was over 50 years in 9%. Eighty four percent evaluated pain routinely, but only 26% use a validated scale. Sedation was routinely evaluated with a validated scale and 73% referred to have a protocol. Neuromuscular block is seldom used, and little monitoring occurs (43%). Delirium is routinely evaluated by 48% of respondents, usually using the CAM-ICU scale. Conclusions: There is a heterogeneous adherence to the ASBD recommended practices. The main gaps are in the assessment of pain, monitoring of neuromuscular blockade and diagnosis of delirium through validated instruments.

PEDIATR DIABETES. 2021 NOV;22(7):1092-1098. DOI: 10.1111/PEDI.13245.

RISKY SEXUAL BEHAVIORS IN ADOLESCENTS AND YOUNG ADULT WOMEN WITH TYPE 1 DIABETES: AN OVERLOOKED PROBLEM

Franco Giraudó, Ignacio Lalanne, Ismael Valdés, Abraham Gajardo, Denise Charron-Prochownik5, Ethel Codner

The presence of unprotected sex activity in women living with type 1 diabetes (T1D) who have insufficient glycemic control should be considered as a specific risky behavior. To evaluate risky behaviors, including unprotected sexual activity, sources of information and knowledge related to reproductive health in adolescents and young adult women with T1D (PwT1D) compared to a group of adolescents and young adult women without diabetes (Comparison group). PwT1D and the Comparison group completed a questionnaire with validated measures that assessed reproductive health. PwT1D ($n = 115$, age = 17.7 ± 3.2 years) and Comparison group ($n = 386$, age = 18.3 ± 2.9) were recruited. The proportion of women reporting having sex without any contraceptive was similar in both groups (57.1% and 50%, in PwT1D and Comparison group, respectively). The use of non-effective contraceptive was reported in 63.2% and 63.6% of the PwT1D and Comparison group, respectively. Among PwT1D, parents, formal sex education, and friends were the primary source of information on reproductive health. Low levels of knowledge about diabetes and pregnancy were observed in PwT1D. HbA_{1c} level was associated with having at least one sexual activity without any contraception (OR = 1.63, $p = 0.039$). PwT1D have similar rates of risky behaviors compared to a Comparison group. Sexual risky behaviors should be especially considered in PwT1D with glycemic control above the optimal level. Parents are an important source of reproductive health information for PwT1D. Use of effective contraception should be reinforced in sexually active PwT1D.

MEDICINA NUCLEAR

J NUCL CARDIOL. 2021 AUG;28(4):1413-1421. DOI: 10.1007/S12350-019-01845-2.

DIASTOLIC DYSSYNCHRONY ASSESSMENT BY GATED MYOCARDIAL PERFUSION-SPECT IN SUBJECTS WHO UNDERWENT CARDIAC RESYNCHRONIZATION THERAPY

Erick Alexanderson-Rosas, Nilda Espinola-Zavaleta, Ernest V Garcia, Amalia Peix, Teresa Massardo, Luz M Pabon y otros

Background. Left ventricular diastolic dyssynchrony (LVDD) can be assessed by gated myocardial perfusion single-photon emission computed tomography (GMP-SPECT). LVDD is an area of interest in subjects who underwent cardiac resynchronization therapy (CRT). The aim of this post hoc analysis was to assess the role of LVDD in subjects with CRT who were followed up at 6-month period. Material & Methods. Left ventricular diastolic dyssynchrony was assessed by GMP-SPECT at baseline and after CRT procedure in 160 subjects from 10 different cardiological centers. CRT procedure was performed as per current guidelines. Outcomes were defined as improvement in ≥ 1 New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF) by 5%, and reduction in end-systolic volume (ESV) by 15% and 5% points in Minnesota Living with Heart Failure Questionnaire. LVDD was defined as diastolic phase standard deviation $\geq 40 \pm 14^\circ$. Results. Improvement in NYHA functional class occurred in 105 (65.6%), LVEF in 74 (46.3%), decrease in ESV in 86 (53.8%), and Minnesota score in 85 (53.1%) cases. Baseline LV diastolic standard deviation was $53.53^\circ \pm 20.85$ and at follow-up $40.44^\circ \pm 26.1283$; ($P < 0.001$). LVDD was not associated with improvement in clinical outcomes at follow-up. Conclusion. CRT improves both systolic and diastolic dyssynchrony values at 6-month follow-up. LVDD at baseline is correlated with cardiac functionality at follow-up, but not with overall favorable clinical outcomes.

J NUCL CARDIOL. 2021 FEB;28(1):55-64. DOI: 10.1007/S12350-018-01589-5.

VALUE OF INTRAVENTRICULAR DYSSYNCHRONY ASSESSMENT BY GATED-SPECT MYOCARDIAL PERFUSION IMAGING IN THE MANAGEMENT OF HEART FAILURE PATIENTS UNDERGOING CARDIAC RESYNCHRONIZATION THERAPY (VISION-CRT)

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Background. Placing the left ventricular (LV) lead in a viable segment with the latest mechanical activation (vSOLA) may be associated with optimal cardiac resynchronization therapy (CRT) response. We assessed the role of gated SPECT myocardial perfusion imaging (gSPECT MPI) in predicting clinical outcomes at 6 months in patients submitted to CRT. Methods. Ten centers from 8 countries enrolled 195 consecutive patients. All underwent gSPECT MPI before and 6 months after CRT. The procedure was performed as per current guidelines, the operators being unaware of gSPECT MPI results. Regional LV dyssynchrony (Phase SD) and vSOLA were automatically determined using a 17 segment model. The lead was considered on-target if placed in vSOLA. The primary outcome was improvement in ≥ 1 of the following: ≥ 1 NYHA class, left ventricular ejection fraction (LVEF) by $\geq 5\%$, reduction in end-systolic volume by $\geq 15\%$, and ≥ 5 points in Minnesota Living With Heart Failure Questionnaire (MLHFQ). Results. Sixteen patients died before the follow-up gSPECT MPI. The primary outcome occurred in 152 out of 179 (84.9%) cases. Mean change in LV phase standard deviation (PSD) at 6 months was 10.5° . Baseline dyssynchrony was not associated with the primary outcome. However, change in LV PSD from baseline was associated with the primary outcome (OR 1.04, 95% CI 1.01-1.07, $P = .007$). Change in LV PSD had an AUC of 0.78 (0.66-0.90) for the primary outcome. Improvement in LV PSD of 4° resulted in the highest positive likelihood ratio of 7.4 for a favorable outcome. In 23% of the patients, the CRT lead was placed in the vSOLA, and in 42% in either this segment or in a segment within 10° of it. On-target lead placement was not significantly associated with the primary outcome (OR 1.53, 95% CI 0.71-3.28). Conclusion. LV dyssynchrony improvement by gSPECT MPI, but not on-target lead placement, predicts clinical outcomes in patients undergoing CRT.

NEUROPSYCHOBIOLOGY. 2022 JAN 28;1-15. DOI: 10.1159/000521104.

EFFECT OF LOW-DOSE STATINS IN ADDITION TO STANDARD THERAPY ON BRAIN PERFUSION AND NEUROCOGNITIVE PERFORMANCE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Teresa Massardo, Juan C Quintana, Luis Risco, Sebastian Corral, Jane Spuler, Daniel Vicentini, Gabriel Castro-Muñoz, Byron Riedel, Carolina Villa, Jaime I Pereira

Introduction: Major depressive disorder (MDD) is a prevalent condition which has a well-known association with ischemic cardiomyopathy, probably explained by an inflammatory mediator mechanism. Statins, besides reducing cholesterol production, have pleiotropic effects including anti-inflammatory activity. The goal was to evaluate the effect of statins as an addition to standard therapy on mood status, brain perfusion, and neurocognitive performance in MDD. Methods: We studied 20 MDD patients with brain single-photon emission tomography and Cambridge Neuropsychological Test Automated Battery (CANTAB), half randomized to 10 mg of Rosuvastatin or placebo, in addition to selective serotonin reuptake inhibitors (SSRIs) therapy and being reevaluated 3 months later. The images were compared using Statistical Parametric Mapping; clinical scores (Hamilton Depression Score with 17 items and Beck's Depression Inventory) as well as neurocognitive parameters were applied as covariates (CoV) to estimate regional cerebral blood flow (rCBF) changes with both therapies. Results: Clinical scores decreased in both groups ($p = 0.0001$); Beck's presented a larger decrease with statins. We observed significantly rCBF changes expressed as significant larger clusters of voxels ($p < 0.05$) in the pre/subgenual anterior cingulate plus orbitofrontal cortex and a small area in the posterior cingulate gyrus in the statins group, whereas it was not observed with placebo, when using clinical scores as CoV. A similar pattern of rCBF changes was present with emotions recognition, attentional, paired associates learning, spatial planning, and working

memory tasks. Conclusion: Short-term use of low-dose statins in MDD patients under SSRIs results in important rCBF changes in key mood associated areas to improvement in neurocognitive performance. These findings, even though demonstrated in a small sample, could open a new therapeutic tool in the comprehensive management of this disorder.

NEUROPSYCHOBIOLOGY. 2021;80(3):214-224. DOI: 10.1159/000508110.

REGIONAL BRAIN PERFUSION IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION MARKERS IN MAJOR DEPRESSIVE DISORDER

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Background: Major depressive disorder (MDD) is an important independent risk factor for cardiovascular disease. Cumulative data suggest that depressive patients exhibit derangement in regional cerebral blood flow (rCBF), although underlying mechanisms remain mostly unknown. Endothelial dysfunction (ED), defined as different forms of abnormal endothelial activity, plays a key role in the pathogenesis of vascular disease. ED is associated with several clinical conditions characterized by high cardiovascular risk. Diverse ED markers have been found in mood disorders. Purpose: To evaluate the association between rCBF and peripheral ED markers in MDD patients, at baseline and after selective serotonin receptor inhibitors (SSRIs) therapy. Patients and methods: Twenty-seven untreated unipolar MDD patients in their first episode were evaluated with the Hamilton Depression Rating Scale (HAM-D) and brain perfusion SPECT at baseline and after 2 months of SSRIs. Statistical Parametric Mapping (SPM) was employed to evaluate rCBF; circulating endothelial cells (CECs), plasma soluble intercellular adhesion molecule (sICAM), and high-sensitivity C-reactive protein (hsCRP) were used as independent covariates. Results: Baseline CECs and sICAM were increased in MDD patients compared with matching controls ($p = 0.0001$) and hsCRP ($p = 0.03$). HAM-D scores (21 items) and CECs diminished after SSRI therapy in MDD patients ($p < 0.0001$). There was a significant rCBF decrease, mainly in deep central structures. HAM-D change was associated with rCBF decrease at the left amygdala, right striatum levels, and Brodmann area 25. CEC change was associated with rCBF at deep brain level and sICAM with large rCBF areas at the left caudate and tectum; hsCRP was associated, to a lesser extent, with the left dorsal striatum and mesencephalic tectum. Conclusion: ED markers in patients with MDD are associated with significant changes in rCBF which are features of depression. These findings suggest that systemic damage/activation of the endothelium may contribute to the abnormal rCBF observed in MDD patients.

NEFROLOGÍA

PEDIATR TRANSPLANT. 2021 DEC;25(8):E14096. DOI: 10.1111/PETR.14096.

LONG-TERM OUTCOME OF EARLY STEROID WITHDRAWAL IN PEDIATRIC RENAL TRANSPLANTATION

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Background: Steroid use in renal transplant is related to multiple adverse effects. Long-term effects of early withdrawal steroids in pediatric renal transplant were assessed. Methods: Renal transplant children with low immunological risk treated on basiliximab, tacrolimus, and mycophenolate with steroid withdrawal or steroid control were evaluated between 2003 and 2019. Clinical variables, treatment adherence, acute rejection, graft loss, and death were analyzed through hazard ratios, and Kaplan-Meier and multivariate analyses. Results: The study included 152 patients, 71.1% steroid withdrawal, mean follow-up 8.5 years, 64.5% structural abnormalities, and 81.6% deceased donor. At 12 years of transplant, event-free survival analysis for graft loss or death showed no significant difference between steroid withdrawal and control steroid treatment (85.9% vs. 80.4%, $p = .36$) nor in acute rejection at 10 years (18.5% vs. 20.5%, $p = .78$) or in donor-specific antibody appearance (19.6% vs. 21.4%, $p = .98$). Delta height Z-score was increased in the steroid withdrawal group ($p < .01$). The main predictor of graft loss or death was non-adherence to treatment ($p = .001$; OR: 17.5 [3.3-90.9]). Conclusions: Steroid withdrawal therapy was effective and safe for low-risk pediatric renal transplant in long-term evaluation. Non-adherence was the main predictor of graft loss or death.

SOUTH MED J. 2021 FEB;114(2):63-69. DOI: 10.14423/SMJ.0000000000001206.

ATTENDED AUTOMATED OFFICE BLOOD PRESSURE MEASUREMENT VERSUS AMBULATORY BLOOD PRESSURE MONITORING IN A PRIMARY HEALTHCARE SETTING IN CHILE

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Objectives: As part of the HEARTS in the Americas initiative, Chilean primary healthcare centers have implemented novel hypertension management strategies, including new diagnostic approaches. This study evaluated the concordance between attended automated office blood pressure (AOBP) measurements with an oscillometric device and ambulatory blood pressure monitoring (ABPM). Methods: This was an observational cohort study to evaluate and compare attended AOBP and ABPM for the diagnosis of hypertension in adults in a primary healthcare setting. Results: The study evaluated 309 participants (54.2 ± 15.7 years; 50.5% male) from four primary healthcare centers in Santiago, Chile. Attended AOBP measurements were obtained at the clinic on two separate days, followed by ABPM. AOBP values indicated that 69.6% of patients had a systolic blood pressure (SBP) of ≥ 140 mm Hg and 34.6% had a diastolic blood pressure (DBP) of ≥ 90 mm Hg. A total of 83.5% had hypertension, 45.3% had high SBP, and 56.0% had high DBP. ABPM values indicated that 65.0% of patients had hypertension. The combined AOBP and ABPM analysis showed that 57.0% of patients had sustained hypertension, 26.5% had white coat hypertension, 8.1%

had masked hypertension, and 8.4% were normotensive. The concordance between AOBP and ABPM (κ coefficient) was low ($\kappa = 0.133$; 95% confidence interval 0.028-0.237). The comparison of AOBP and ABPM measurements (Bland-Altman plots and bias calculations) showed an important bias in BP as measured using the AOBP method, especially for SBP (13.7 ± 11.6 , 95% confidence interval -9.1 to 36.5). Conclusions: Attended AOBP alone may not be sufficient for adequate classification, diagnosis, and management of hypertension in Chile or other countries with similar demographics.

SEMIN DIALYSIS 2021 MAY;34(3):257-262. DOI: 10.1111/SDI.12980.

EXTRACORPOREAL CO₂ REMOVAL AND RENAL REPLACEMENT THERAPY IN ACUTE SEVERE RESPIRATORY FAILURE IN COVID-19 PNEUMONIA: CASE REPORT

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The COVID-19 pandemic significates an enormous number of patients with pneumonia that get complicated with severe acute respiratory distress syndrome (ARDS), some of them with refractory hypercapnia and hypoxemia that need mechanical ventilation (MV). Those patients who are not candidate to extracorporeal membrane oxygenation (ECMO), the extracorporeal removal of CO₂ (ECCO₂R) can allow ultra protective MV to limit the transpulmonary pressures and avoid ventilatory induced lung injury (VILI). We report a first case of prolonged ECCO₂R support in 38 year male with severe COVID-19 pneumonia refractory to conventional support. He was admitted tachypneic and oxygen saturation 71% without supplementary oxygen. The patient's clinical condition worsens with severe respiratory failure, increasing the oxygen requirement and initiating MV in the prone position. After 21 days of protective MV, PaCO₂ rise to 96.8 mmHg, making it necessary to connect to an ECCO₂R system coupled continuous veno-venous hemodialysis (CVVHD). However, due to the lack of availability of equipment in the context of the pandemic, a pediatric gas exchange membrane adapted to CVVHD allowed to maintain the removal of CO₂ until completing 27 days, being finally disconnected from the system without complications and with a satisfactory evolution.

NEUMOLOGÍA

J MED VIROL. 2021 AUG;93(8):4786-4793. DOI: 10.1002/JMV.27080.

CYCLOVIRUS DETECTION IN CHILEAN ADULTS WITH AND WITHOUT COMMUNITY-ACQUIRED PNEUMONIA

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Cycloviruses (CyV) (genus Cyclovirus, family Circoviridae) are nonenveloped DNA viruses. The first report in humans was in 2010 and research has focused only on disease-associated human sample detection. The only HuACyV (CyCV-ChileNPA1, HuACyV10) reported in the Chilean population was in children (3.3%) with an acute respiratory infection. Its detection in respiratory samples from adults, with/without respiratory disease remains unknown. The aim of this study was to detect HuACyV10 in adults with and without respiratory disease. HuACyV10 was studied in nasopharyngeal swabs from 105 hospitalized adults with community-acquired pneumonia (CAP) and 104 adults without respiratory symptoms. Total nucleic acids were extracted, and viral rep and cp gene fragments were amplified by real-time polymerase chain reaction. HuACyV10 was detected in 19.05% adults with CAP and in 0.96% asymptomatic adults, being significantly higher in adult CAP than asymptomatic ($n=1$) ones ($p=0.0001$). Ct values were between 26.7 and 39.6, and the median was 34.1 for rep and 33.8 for the CAP in adults CAP ($p=0.68$), and 35.7 and 36.0, respectively, in the asymptomatic case. HuACyV10 detection in CAP adults concentrated in the Autumn–Winter season of the Southern hemisphere. The only asymptomatic adult with HuACyV10 was detected in the Spring–Summer period. In this first report of HuACyV10 in respiratory samples from adults, detection was significantly higher in CAP than in asymptomatic adults. As the sensitivity of both rep and cp genes was similar, both can be applied for detecting HuACyV10. It would be advisable to investigate the pathogenic role of HuACyV10 in adult respiratory infections.

COPD. 2021 AUG;18(4):393-400. DOI: 10.1080/15412555.2021.1937090.

PHYSICAL ACTIVITY LEVELS AND ASSOCIATED FACTORS IN A LATIN AMERICAN COPD POPULATION OF PATIENTS. THE LASSYC STUDY

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Reduced physical activity (PA) is an independent risk factor for lung function decline, hospitalization and mortality in chronic obstructive pulmonary disease (COPD) and affects a large proportion of patients from Europe and the United States. However, little is known of the level of PA of COPD patients in Latin America. The aim of this study was to provide information of the level of PA and its determinants in COPD patients in Latin America. This is an observational, cross-sectional study on patients with COPD in seven Latin American countries. PA level was evaluated with the short version of the International Physical Activity Questionnaire (IPAQ) and the association between PA and other variables was investigated. Complete information of PA level was obtained in 734 COPD patients consecutively recruited from specialized outpatient clinics; 448 (61%) were men, with a mean age of 69.6 years (standard deviation [SD] = 8.7) and a mean FEV₁ (% predicted) = 49.1% (17.5%). In 37.9% the level of PA was low, and the average sitting time was 36.1 h per week. Patients with low levels of PA were older, with higher levels of dyspnea and higher CAT scores. Additionally, we found that patients with low level of PA presented more symptoms during the day. Low levels of PA have been observed in a large proportion of COPD patients of Latin America, which is higher in women and older patients and it is related with worse functional and clinical characteristics.

ONCOLOGÍA

HEPATOLOGY. 2021 MAY;73(5):1783-1796. DOI: 10.1002/HEP.31537.

GALLSTONES, BODY MASS INDEX, C-REACTIVE PROTEIN, AND GALLBLADDER CANCER: MENDELIAN RANDOMIZATION ANALYSIS OF CHILEAN AND EUROPEAN GENOTYPE DATA

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Background and aims: Gallbladder cancer (GBC) is a neglected disease with substantial geographical variability: Chile shows the highest incidence worldwide, while GBC is relatively rare in Europe. Here, we investigate the causal effects of risk factors considered in current GBC prevention programs as well as C-reactive protein (CRP) level as a marker of chronic inflammation. Approach and results: We applied two-sample Mendelian randomization (MR) using publicly available data and our own data from a retrospective Chilean and a prospective European study. Causality was assessed by inverse variance weighted (IVW), MR-Egger regression, and weighted median estimates complemented with sensitivity analyses on potential heterogeneity and pleiotropy, two-step MR, and mediation analysis. We found evidence for a causal effect of gallstone disease on GBC risk in Chileans ($P = 9 \times 10^{-5}$) and Europeans ($P = 9 \times 10^{-5}$). A genetically elevated body mass index (BMI) increased GBC risk in Chileans ($P = 0.03$), while higher CRP concentrations increased GBC risk in Europeans ($P = 4.1 \times 10^{-6}$). European results suggest causal effects of BMI on gallstone disease ($P = 0.008$); public Chilean data were not, however, available to enable assessment of the mediation effects among causal GBC risk factors. Conclusions: Two risk factors considered in the current Chilean program for GBC prevention are causally linked to GBC risk: gallstones and BMI. For Europeans, BMI showed a causal effect on gallstone risk, which was itself causally linked to GBC risk.

FRONT PHARMACOL. 2021 APR 12;12:630658. DOI: 10.3389/FPHAR.2021.630658. ECOLLECTION 2021.

A NEW INSIGHT FOR THE IDENTIFICATION OF ONCOGENIC VARIANTS IN BREAST AND PROSTATE CANCERS IN DIVERSE HUMAN POPULATIONS, WITH A FOCUS ON LATINOS

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Background: Breast cancer (BRCA) and prostate cancer (PRCA) are the most commonly diagnosed cancer types in Latin American women and men, respectively. Although in recent years large-scale efforts from international consortia have focused on improving precision oncology, a better understanding of genomic features of BRCA and PRCA in developing regions and racial/ethnic minority populations is still required. Methods: To fill in this gap, we performed integrated in silico analyses to elucidate oncogenic variants from BRCA and PRCA driver genes; to calculate their deleteriousness scores and allele frequencies from seven human populations worldwide, including Latinos; and to propose the most effective therapeutic strategies based on precision oncology. Results: We analyzed 339,100 variants belonging to 99 BRCA and 82 PRCA driver genes and identified 18,512 and 15,648 known/predicted oncogenic variants, respectively. Regarding known oncogenic variants, we prioritized the most frequent and deleterious variants of BRCA ($n = 230$) and PRCA ($n = 167$) from Latino, African, Ashkenazi Jewish, East Asian, South Asian, European Finnish, and European non-Finnish populations, to incorporate them into pharmacogenomics testing. Lastly, we identified which oncogenic variants may shape the response to anti-cancer therapies, detailing the current status of pharmacogenomics guidelines and clinical trials involved in BRCA and PRCA cancer driver proteins. Conclusion: It is imperative to unify efforts where developing countries might invest in obtaining databases of genomic profiles of their populations, and developed countries might incorporate racial/ethnic minority populations in future clinical trials and cancer researches with the overall objective of fomenting pharmacogenomics in clinical practice and public health policies.

REUMATOLOGÍA

J INFLAMM RES. 2021 JAN 26;14:191-198. DOI: 10.2147/JIR.S292513. ECOLLECTION 2021.

IN VITRO PHENOTYPE INDUCTION OF CIRCULATING MONOCYTES: CD16 AND CD163 ANALYSIS

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Introduction: CD14 (monocyte differentiation antigen, LPS binding protein - endotoxin receptor) and CD16 (Fc γ RIII, Low-affinity receptor for IgG) define three subpopulations of circulating monocytes with different inflammatory and phagocytic capabilities. Contradictory reports exist regarding both in vivo monocyte phenotype-disease association and response of these circulating monocytes to in vitro stimulation. We analyzed phenotypic changes in circulating monocytes when stimulated with LPS (pro-inflammatory stimulus) and IL-4 (alternative inflammatory stimulus). Methods: Mononuclear cells from nine healthy donors were extracted and studied for surface and intracellular markers using flow cytometry. PBMC were extracted using Ficoll technic and immediately analyzed using flow cytometry. Pro-inflammatory interleukin IL-1 β and IL-6 were measured by intracellular cytometry. Mononuclear cells were stimulated using LPS and IL-4 as previously described. Changes against non-stimulated populations were statistically analyzed. Results: Compared to non-stimulated and IL-4 stimulated monocytes, LPS-stimulated cells display a singular pattern of markers, with higher levels of intracellular IL-1 β and IL-6 directly correlating with CD14+CD163- cell frequency and diminishing membrane CD163 fluorescence. CD14+CD16- classical monocytes show greater percentage of CD163- cells upon LPS stimulation. CD86 levels on monocytes' surface did not change with LPS or IL-4 stimulation. Conclusions and discussion: We showed

that CD14+CD16- classical monocytes display higher sensitivity to LPS stimulation, with more IL-1 β and IL-6 levels than intermediate and non-classical monocytes. This subset also diminishes its CD163 levels on the membrane after LPS stimulation with a contemporary raise in CD163-cells, suggesting that classical monocytes preferentially acquire CD163- defined M1 characteristics upon in vitro LPS stimulation. Intermediate and non-classical monocytes respond with lower levels of interleukins and display surface proteins in an M2-type profile (CD163+).

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AN UNUSUAL EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA PRESENTING AS CHRONIC LARYNGITIS: A CASE REPORT
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Rationale: Nasal-type, extranodal natural killer (NK)/T-cell lymphoma is a rare lymphoma. The tumor usually shows ulcerative and necrotic lesions in the nasal cavities and sinuses. Tissue involvement outside the nasal cavity is uncommon.

Patient concern: We describe a 30-year-old man with a 2-month history of hoarseness, weight loss, and dyspnea. Diagnosis: Magnetic resonance image (MRI) showed edema of the larynx with obliteration of the airway. Laryngoscopic examination described necrotic tissue in the glottis and larynx. The biopsy showed chronic, necrotizing laryngitis, with no granulomas, vasculitis, or atypical cells. The immunologic and microbiologic study was negative. Later, after immunosuppressive therapy, the patient presented erythema and diffuse enlargement of the right arm. MRI showed myositis of the biceps and brachial muscles. Infection was rule out, and direct microscopy showed an extensive muscle infiltration by mononuclear cells and abundant mitosis. Immunohistochemistry was positive for CD3, CD8, Ki 67 (90%), and CD56 compatible with extranodal NK/T cell lymphoma. Interventions: The patient initially received immunosuppression treatments (corticoids, cyclofosamide, and Rituximab) with relapsing episodes. When lymphoma was diagnosed, chemotherapy was started. Outcomes: The patient died during chemotherapy. Lessons: Nasal-type, extranodal NK/T-cell lymphoma should be suspected even when there are no classical findings of neoplasms on histology. Immunohistochemistry is mandatory to rule it out.

UNIDAD DE PACIENTES CRÍTICOS

AM J RESPIR CRIT CARE MED. 2021 JUL 1;204(1):34-43. DOI: 10.1164/RCCM.202011-41660C.

EXTRACORPOREAL MEMBRANE OXYGENATION FOR COVID-19-ASSOCIATED SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME IN CHILE: A NATIONWIDE INCIDENCE AND COHORT STUDY

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Rationale: The role of and needs for extracorporeal membrane oxygenation (ECMO) at a population level during the coronavirus disease (COVID-19) pandemic have not been completely established. Objectives: To identify the cumulative incidence of ECMO use in the first pandemic wave and to describe the Nationwide Chilean cohort of ECMO-supported patients with COVID-19. Methods: We conducted a population-based study from March 3 to August 31, 2020, using linked data from national agencies. The cumulative incidence of ECMO use and mortality risk of ECMO-supported patients were calculated and age standardized. In addition, a retrospective cohort analysis was performed. Outcomes were 90-day mortality after ECMO initiation, ECMO-associated complications, and hospital length of stay. Cox regression models were used to explore risk factors for mortality in a time-to-event analysis. Measurements and Main Results: Ninety-four patients with COVID-19 were supported with ECMO (0.42 per population of 100,000, 14.89 per 100,000 positive cases, and 1.2% of intubated patients with COVID-19); 85 were included in the cohort analysis, and the median age was 48 (interquartile range [IQR], 41-55) years, 83.5% were men, and 42.4% had obesity. The median number of pre-ECMO intubation days was 4 (IQR, 2-7), the median PaO₂/FiO₂ ratio was 86.8 (IQR, 64-99) mm Hg, 91.8% of patients were prone positioned, and 14 patients had refractory respiratory acidosis. Main complications were infections (70.6%), bleeding (38.8%), and thromboembolism (22.4%); 52 patients were discharged home, and 33 died. The hospital length of stay was a median of 50 (IQR, 24-69) days. Lower respiratory system compliance and higher driving pressure before ECMO initiation were associated with increased mortality. A duration of pre-ECMO intubation \geq 10 days was not associated with mortality. Conclusions: Documenting nationwide ECMO needs may help in planning ECMO provision for future COVID-19 pandemic waves. The 90-day mortality of the Chilean cohort of ECMO-supported patients with COVID-19 (38.8%) is comparable to that of previous reports.

VIRUSES. 2021 DEC 13;13(12):2493. DOI: 10.3390/V13122493.

CARDIOMYOPATHY ASSOCIATED WITH ANTI-SARS-COV-2 VACCINATION: WHAT DO WE KNOW?

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The SARS-CoV-2 pandemic has mobilized many efforts worldwide to curb its impact on morbidity and mortality. Vaccination of the general population has resulted in the administration of more than 6,700,000,000 doses by the end of October 2021, which is the most effective method to prevent hospitalization and death. Among the adverse effects described, myocarditis and pericarditis are low-frequency events (less than 10 per 100,000 people), mainly observed with messenger RNA vaccines. The mechanisms responsible for these effects have not been specified, considering an exacerbated and uncontrolled immune response and an autoimmune response against specific cardiomyocyte proteins. This greater immunogenicity and reactogenicity is clinically manifested in a differential manner in pediatric patients, adults, and the elderly, determining specific characteristics of its presentation for each age group. It generally develops as a condition of mild to moderate severity, whose symptoms and imaging findings are self-limited, resolving favorably in days to weeks and, exceptionally, reporting deaths

associated with this complication. The short- and medium-term prognosis is favorable, highlighting the lack of data on long-term evolution, which should be determined in longer follow-ups.

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DYSREGULATED IMMUNE RESPONSES IN COVID-19 PATIENTS CORRELATING WITH DISEASE SEVERITY AND INVASIVE OXYGEN REQUIREMENTS

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The prognosis of severe COVID-19 patients has motivated research communities to uncover mechanisms of SARS-CoV-2 pathogenesis also on a regional level. In this work, we aimed to understand the immunological dynamics of severe COVID-19 patients with different degrees of illness, and upon long-term recovery. We analyzed immune cellular subsets and SARS-CoV-2-specific antibody isotypes of 66 COVID-19 patients admitted to the Hospital Clínico Universidad de Chile, which were categorized according to the WHO ten-point clinical progression score. These included 29 moderate patients (score 4-5) and 37 severe patients under either high flow oxygen nasal cannula (18 patients, score 6), or invasive mechanical ventilation (19 patients, score 7-9), plus 28 convalescent patients and 28 healthy controls. Furthermore, six severe patients that recovered from the disease were longitudinally followed over 300 days. Our data indicate that severe COVID-19 patients display increased frequencies of plasmablasts, activated T cells and SARS-CoV-2-specific antibodies compared to moderate and convalescent patients. Remarkably, within the severe COVID-19 group, patients rapidly progressing into invasive mechanical ventilation show higher frequencies of plasmablasts, monocytes, eosinophils, Th1 cells and SARS-CoV-2-specific IgG than patients under high flow oxygen nasal cannula. These findings demonstrate that severe COVID-19 patients progressing into invasive mechanical ventilation show a distinctive type of immunity. In addition, patients that recover from severe COVID-19 begin to regain normal proportions of immune cells 100 days after hospital discharge and maintain high levels of SARS-CoV-2-specific IgG throughout the study, which is an indicative sign of immunological memory. Thus, this work can provide useful information to better understand the diverse outcomes of severe COVID-19 pathogenesis.

ACTA ANAESTH SCAND. 2021 FEB;65(2):228-235. DOI: 10.1111/AAS.13723.

ESTIMATION OF CHANGES IN CYCLIC LUNG STRAIN BY ELECTRICAL IMPEDANCE TOMOGRAPHY: PROOF-OF-CONCEPT STUDY

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Rationale. Cyclic strain may be a determinant of ventilator-induced lung injury. The standard for strain assessment is the computed tomography (CT), which does not allow continuous monitoring and exposes to radiation. Electrical impedance tomography (EIT) is able to monitor changes in regional lung ventilation. In addition, there is a correlation between mechanical deformation of materials and detectable changes in its electrical impedance, making EIT a potential surrogate for cyclic lung strain measured by CT (StrainCT). Objectives. To compare the global StrainCT with the change in electrical impedance (ΔZ). Methods. Acute respiratory distress syndrome patients under mechanical ventilation (VT 6 mL/kg ideal body weight with positive end-expiratory pressure 5 [PEEP 5] and best PEEP according to EIT) underwent whole-lung CT at end-inspiration and end-expiration. Biomechanical analysis was used to construct 3D maps and determine StrainCT at different levels of PEEP. CT and EIT acquisitions were performed simultaneously. Multilevel analysis was employed to determine the causal association between StrainCT and ΔZ . Linear regression models were used to predict the change in lung StrainCT between different PEEP levels based on the change in ΔZ . Main results. StrainCT was positively and independently associated with ΔZ at global level ($P < .01$). Furthermore, the change in StrainCT (between PEEP 5 and Best PEEP) was accurately predicted by the change in ΔZ (R^2 0.855, $P < .001$ at global level) with a high agreement between predicted and measured StrainCT. Conclusions. The change in electrical impedance may provide a noninvasive assessment of global cyclic strain, without radiation at bedside.

BRAZ J ANESTH. JAN-FEB 2021;71(1):58-64. DOI: 10.1016/J.BJANE.2020.09.011.

EFFECTS OF INTRAOPERATIVE ADRENERGIC ADMINISTRATION ON POSTOPERATIVE HYPERLACTATEMIA IN OPEN COLON SURGERY: AN OBSERVATIONAL STUDY

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Background: Postoperative Hyperlactatemia (PO-HL) is a frequent condition associated with poor prognosis. In recent years, there has been growing evidence that adrenergic stimulation may contribute to increased lactate levels. The use of adrenergic agonists for the control of intraoperative hypotension is frequent, and its impact on the development of PO-HL is unknown. Objective: To evaluate whether the use of intraoperative adrenergic agents is associated with the occurrence of PO-HL. Methods: This was a prospective observational study. The inclusion criteria were undergoing elective open colon surgery, being ≥ 60 years old and signing informed consent. The exclusion criteria were cognitive impairment, unplanned surgery, and anticipated need for postoperative mechanical ventilation. Baseline and intraoperative variables were collected, and arterial lactate data were collected at baseline and every 6 hours postoperatively for 24 hours. Hyperlactatemia was defined as lactate >2.1 mEq.L⁻¹. Results: We studied 28 patients, 61% of whom developed hyperlactatemia. The variables associated with PO-

HL in the univariate analysis were anesthetic time, the total dose of intraoperative ephedrine, and lower intraoperative central venous oxygen saturation (ScvO₂). Multivariate analysis confirmed the association between the use of ephedrine ($p = 0.004$), intraoperative hypotension ($p = 0.026$), and use of phenylephrine ($p = 0.001$) with PO-HL. Conclusions: The use of intraoperative ephedrine, phenylephrine and intraoperative hypotension were independently associated with the development of PO-HL. This finding should lead to new studies in this field, as well as a judicious interpretation of the finding of a postoperative increase in lactate levels.

BR J ANAESTH. 2021 NOV;127(5):807-814. DOI: 10.1016/J.BJA.2021.07.031.

EFFECT OF POSITIVE END-EXPIRATORY PRESSURE ON LUNG INJURY AND HAEMODYNAMICS DURING EXPERIMENTAL ACUTE RESPIRATORY DISTRESS SYNDROME TREATED WITH EXTRACORPOREAL MEMBRANE OXYGENATION AND NEAR-APNOEIC VENTILATION

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Background: Lung rest has been recommended during extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS). Whether positive end-expiratory pressure (PEEP) confers lung protection during ECMO for severe ARDS is unclear. We compared the effects of three different PEEP levels whilst applying near-apnoeic ventilation in a model of severe ARDS treated with ECMO. **Methods:** Acute respiratory distress syndrome was induced in anaesthetised adult male pigs by repeated saline lavage and injurious ventilation for 1.5 h. After ECMO was commenced, the pigs received standardised near-apnoeic ventilation for 24 h to maintain similar driving pressures and were randomly assigned to PEEP of 0, 10, or 20 cm H₂O ($n=7$ per group). Respiratory and haemodynamic data were collected throughout the study. Histological injury was assessed by a pathologist masked to PEEP allocation. Lung oedema was estimated by wet-to-dry-weight ratio. **Results:** All pigs developed severe ARDS. Oxygenation on ECMO improved with PEEP of 10 or 20 cm H₂O, but did not in pigs allocated to PEEP of 0 cm H₂O. Haemodynamic collapse refractory to norepinephrine ($n=4$) and early death ($n=3$) occurred after PEEP 20 cm H₂O. The severity of lung injury was lowest after PEEP of 10 cm H₂O in both dependent and non-dependent lung regions, compared with PEEP of 0 or 20 cm H₂O. A higher wet-to-dry-weight ratio, indicating worse lung injury, was observed with PEEP of 0 cm H₂O. Histological assessment suggested that lung injury was minimised with PEEP of 10 cm H₂O. **Conclusions:** During near-apnoeic ventilation and ECMO in experimental severe ARDS, 10 cm H₂O PEEP minimised lung injury and improved gas exchange without compromising haemodynamic stability.

ANN INTENSIVE CARE. 2022 FEB 4;12(1):9. DOI: 10.1186/S13613-022-00985-Y.

PRACTICES IN SEDATION, ANALGESIA, MOBILIZATION, DELIRIUM, AND SLEEP DEPRIVATION IN ADULT INTENSIVE CARE UNITS (SAMDS-ICU): AN INTERNATIONAL SURVEY BEFORE AND DURING THE COVID-19 PANDEMIC

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Background. Since the publication of the 2018 Clinical Guidelines about sedation, analgesia, delirium, mobilization, and sleep deprivation in critically ill patients, no evaluation and adequacy assessment of these recommendations were studied in an international context. This survey aimed to investigate these current practices and if the COVID-19 pandemic has changed them. **Methods.** This study was an open multinational electronic survey directed to physicians working in adult intensive care units (ICUs), which was performed in two steps: before and during the COVID-19 pandemic. **Results.** We analyzed 1768 questionnaires and 1539 (87%) were complete. Before the COVID-19 pandemic, we received 1476 questionnaires and 292 were submitted later. The following practices were observed before the pandemic: the Visual Analog Scale (VAS) (61.5%), the Behavioral Pain Scale (BPS) (48.2%), the Richmond Agitation Sedation Scale (RASS) (76.6%), and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (66.6%) were the most frequently tools used to assess pain, sedation level, and delirium, respectively; midazolam and fentanyl were the most frequently used drugs for inducing sedation and analgesia (84.8% and 78.3%, respectively), whereas haloperidol (68.8%) and atypical antipsychotics (69.4%) were the most prescribed drugs for delirium treatment; some physicians regularly prescribed drugs to induce sleep (19.1%) or ordered mechanical restraints as part of their routine (6.2%) for patients on mechanical ventilation; non-pharmacological strategies were frequently applied for pain, delirium, and sleep deprivation management. During the COVID-19 pandemic, the intensive care specialty was independently associated with best practices. Moreover, the mechanical ventilation rate was higher, patients received sedation more often (94% versus 86.1%, $p < 0.001$) and sedation goals were discussed more frequently in daily rounds. Morphine was the main drug used for analgesia (77.2%), and some sedative drugs, such as midazolam, propofol, ketamine and quetiapine, were used more frequently. **Conclusions.** Most sedation, analgesia and delirium practices were comparable before and during the COVID-19 pandemic. During the pandemic, the intensive care specialty was a variable that was independently associated with the best practices. Although many findings are in accordance with evidence-based recommendations, some practices still need improvement.

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ACUTE LIVER FAILURE DUE TO HERPES SIMPLEX VIRUS: DIAGNOSTIC CLUES AND POTENTIAL ROLE OF PLASMAPHERESIS: A CASE REPORT

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Introduction: Acute liver failure (ALF) is a life-threatening condition that remains challenging for physicians despite several advances in supportive care. Etiologies vary worldwide, with herpes simplex virus (HSV) hepatitis representing less than 1% of cases. Despite its low incidence, ALF is a lethal cause of acute necrotizing hepatitis and has a high mortality. Early antiviral treatment is beneficial for survival and

decreased liver transplantation necessity. However, plasmapheresis, despite its theoretical potential benefit, is scarcely reported. Patient concerns: A 25-year-old woman with no known disease presented with painful pharynx ulcers, increased transaminases and impaired liver function. Diagnosis: ALF due to a disseminated HSV-2 primary infection was diagnosed with a positive polymerase chain reaction for HSV-2 in the biopsied liver tissue and blood. Interventions: Empiric antiviral treatment was initiated. After clinical deterioration, plasmapheresis was also initiated. Outcomes: After 6 cycles of plasmapheresis and supportive care, the patient's condition improved without undergoing liver transplantation. Conclusions: ALF is a life-threatening condition, and HSV as an etiology must be suspected based on background, clinical manifestation, and laboratory information. The potential role of plasmapheresis in HSV hepatitis should be considered.

MED INTENSIVA (ENGL ED). 2021 APR;45(3):138-146. DOI: 10.1016/J.MEDIN.2019.09.004.

IDENTIFYING AND MANAGING PATIENT-VENTILATOR ASYNCHRONY: AN INTERNATIONAL SURVEY

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Objective: To describe the main factors associated with proper recognition and management of patient-ventilator asynchrony (PVA). Design: An analytical cross-sectional study was carried out. Setting: An international study conducted in 20 countries through an online survey. Participants: Physicians, respiratory therapists, nurses and physiotherapists currently working in the Intensive Care Unit (ICU). Main variables of interest: Univariate and multivariate logistic regression models were used to establish associations between all variables (profession, training in mechanical ventilation, type of training program, years of experience and ICU characteristics) and the ability of HCPs to correctly identify and manage 6 PVA. Results: A total of 431 healthcare professionals answered a validated survey. The main factors associated to proper recognition of PVA were: specific training program in mechanical ventilation (MV) (OR 2.27; 95%CI 1.14-4.52; p=0.019), courses with more than 100h completed (OR 2.28; 95%CI 1.29-4.03; p=0.005), and the number of ICU beds (OR 1.037; 95%CI 1.01-1.06; p=0.005). The main factor influencing the management of PVA was the correct recognition of 6 PVAs (OR 118.98; 95%CI 35.25-401.58; p<0.001). Conclusion: Identifying and managing PVA using ventilator waveform analysis is influenced by many factors, including specific training programs in MV, the number of ICU beds, and the number of recognized PVAs.

UNIDAD DEL DOLOR

AM J CRIT CARE. 2022 JAN 1;31(1):24-32. DOI: 10.4037/AJCC2022585.

AN INTENSIVE CARE UNIT TEAM REFLECTS ON END-OF-LIFE EXPERIENCES WITH PATIENTS AND FAMILIES IN CHILE

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Background: Deaths in the intensive care unit (ICU) represent an experience of suffering for patients, their families, and professionals. End-of-life (EOL) care has been added to the responsibilities of the ICU team, but the evidence supporting EOL care is scarce, and there are many barriers to implementing the clinical recommendations that do exist. Objectives: To explore the experiences and perspectives of the various members of an ICU care team in Chile regarding the EOL care of their patients. Methods: A qualitative study was performed in the ICU of a high-complexity academic urban hospital. The study used purposive sampling with focus groups as a data collection method. A narrative analysis based on grounded theory was done. Results: Four discipline-specific focus groups were conducted; participants included 8 nurses, 6 nursing assistants, 8 junior physicians, and 6 senior physicians. The main themes that emerged in the analysis were emotional impact and barriers to carrying out EOL care. The main barriers identified were cultural difficulties related to decision-making, lack of interprofessional clinical practice, and lack of effective communication. Communication difficulties within the team were described along with lack of self-efficacy for family-centered communication. Conclusion: These qualitative findings expose gaps in care that must be filled to achieve high-quality EOL care in the ICU. Significant emotional impact, barriers related to EOL decision-making, limited interprofessional clinical practice, and communication difficulties were the main findings cross-referenced.

SERVICIO DE MEDICINA FÍSICA Y REHABILITACIÓN

INT J GERIATR PSYCHIATRY. 2021 FEB;36(2):302-313. DOI: 10.1002/GPS.5425.

CONSOLIDATED FRAMEWORK FOR ADVANCING IMPLEMENTATION SCIENCE FOR THE IMPLEMENTATION PROCESS AND ADHERENCE ASSESSMENT OF A NON-PHARMACOLOGICAL DELIRIUM PREVENTION PROGRAM

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Objective: To evaluate the contribution of applying the theoretical framework of implementation science for adherence to non-pharmacological interventions to prevent delirium. Methods: A quasi-experimental prospective design was conducted from March 2017 to October 2018 in a teaching hospital. Participants included 149 healthcare staff and 72 elderly inpatients. A non-pharmacological delirium prevention program was designed, applied and evaluated in accordance with the consolidated framework for advancing implementation research (CFIR). The primary outcome was the global adherence rate to 12 predefined indicators, comparing measurements at baseline (O1), after training (O2) and at a 6-month follow-up (O3) assessed by an external reviewer. Staff knowledge and beliefs about delirium were assessed using a validated tool, and delirium incidence was evaluated using the confusion assessment method. Results: Overall adherence increased from 58.2% (O1) to 77.9% (O2) and 75.6% (O3) (O2 vs. O1: p < 0.001 and O3 vs. O1: p < 0.001). Staff perceptions regarding implementation of non-pharmacological

interventions increased from 74.8% to 81.9% ($p = 0.004$). Delirium incidence was non-significantly reduced from 20% (O1) to 16% (O3) ($p = 0.99$). Conclusions: Implementation of a delirium prevention program using a CFIR model was useful in improving adherence to activities included in this program, as well as improving the knowledge and beliefs regarding delirium by healthcare workers. The impact of this implementation strategy on the incidence of delirium should be evaluated in a larger scale multicenter trial.

SERVICIO DE NEUROLOGÍA Y NEUROCIRUGÍA

EUR J NEUROL. 2021 SEP;28(9):3201-3210. DOI: 10.1111/ENE.14904.

RHEUMATOID MENINGITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and purpose. Rheumatoid meningitis (RM) is a neurological complication of rheumatoid arthritis (RA). Current evidence is based on case reports and partial reviews. **Methods.** This is a systematic review and meta-analysis following the PRISMA statement. The aim is to describe the characteristics of the disease, including clinical, imaging and laboratory findings, treatment, outcomes and prognosis reported in the literature. **Results.** In all, 103 studies with 130 cases were included. RM affected adults with an average age of 62 years, with or without a previous RA diagnosis. RA activity and time with the disease were associated with a worse prognosis. Most common clinical manifestations were transient focal neurological signs (64.6%), systemic symptoms (51.3%), episodic headache (50.4%) and neuropsychiatric alterations (47.7%). Joint manifestations were present in only 27.4% of cases. Brain magnetic resonance imaging showed unilateral or bilateral involvement, predominantly frontoparietal. Both pachymeninges and leptomeninges were affected, the latter more frequently (82.88%). The laboratory findings included increased levels of rheumatoid factor (89.71%), anti-cyclic citrullinated peptide (89.47%), C-reactive protein (82.54%) and erythrocyte sedimentation rate (81.81%). Cerebrospinal fluid analysis showed an increase in the protein level (76.14%), with pleocytosis (85.19%) of mononuclear predominance (89.19%). Biopsy was performed in 72.52% of the patients. Corticosteroid pulse therapy was the main induction therapy. Disease relapse occurred in 31.17% of patients, whilst 54.54% had a full recovery. **Conclusions.** Rheumatoid meningitis must be considered in adult patients with or without RA diagnosis, high-dose corticosteroid induction therapy should be installed and maintenance therapy plays a key role. It is not recommended to use anti-TNF as an induction therapy. Nowadays, RM has a significantly better outcome. These findings may aid clinicians in timely RM diagnosis and treatment, thus improving its outcomes.

J AUTOIMMUN. 2021 SEP;123:102702. DOI: 10.1016/J.JAUT.2021.102702.

CELLULAR AND MOLECULAR REGULATION OF THE PROGRAMMED DEATH-1/PROGRAMMED DEATH LIGAND SYSTEM AND ITS ROLE IN MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE DISEASES

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Programmed Cell Death 1 (PD-1) receptor and its ligands (PD-Ls) are essential to maintain peripheral immune tolerance and to avoid tissue damage. Conversely, altered gene or protein expression of this system of co-inhibitory molecules has been involved in the development of cancer and autoimmunity. Substantial progress has been achieved in the study of the PD-1/PD-Ls system in terms of regulatory mechanisms and therapy. However, the role of the PD-1/PD-Ls pathway in neuroinflammation has been less explored despite being a potential target of treatment for neurodegenerative diseases. Multiple Sclerosis (MS) is the most prevalent, chronic, inflammatory, and autoimmune disease of the central nervous system that leads to demyelination and axonal damage in young adults. Recent studies have highlighted the key role of the PD-1/PD-Ls pathway in inducing a neuroprotective response and restraining T cell activation and neurodegeneration in MS. In this review, we outline the molecular and cellular mechanisms regulating gene expression, protein synthesis and traffic of PD-1/PD-Ls as well as relevant processes that control PD-1/PD-Ls engagement in the immunological synapse between antigen-presenting cells and T cells. Also, we highlight the most recent findings regarding the role of the PD-1/PD-Ls pathway in MS and its murine model, experimental autoimmune encephalomyelitis (EAE), including the contribution of PD-1 expressing follicular helper T (TFH) cells in the pathogenesis of these diseases. In addition, we compare and contrast results found in MS and EAE with evidence reported in other autoimmune diseases and their experimental models, and review PD-1/PD-Ls-targeting therapeutic approaches.

REV MED CHIL. 2021 FEB;149(2):295-303. DOI: 10.4067/S0034-98872021000200295.

RHEUMATOID MENINGITIS: REPORT OF TWO CASES

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Rheumatoid meningitis (RM) is a rare complication of rheumatoid arthritis (RA). RM mimics many other conditions such as subdural empyema, unsteady gait, focal brain dysfunction, stroke, relapsing-remitting motor signs, headache, neuropsychiatric disorders, seizures, parkinsonism, and meningeal tumors. RM is considered a disease with poor prognosis. However, cases reported in the last decade show a good outcome. We report two cases with a favorable outcome. A 48-year-old man with a three-year history of RA admitted for headache, sensory disturbances, and speech difficulties. Brain magnetic resonance imaging (MRI) showed a left parietal subdural laminar lesion with restricted diffusion and a small left superior frontal acute infarction. A subdural empyema was originally suspected, and antimicrobials were prescribed. A follow-up MRI did not show progression of the subdural lesion and the patient was discharged 14 days after admission without focal deficits. A 44-year-old

female patient with two years of seronegative RA was admitted for severe headache, confusion, nausea and vomiting. Brain MRI showed subtle supra and infratentorial leptomeningeal involvement and a left cerebellar acute infarct. A meningoencephalitis due to etanercept was initially thought and treated with dexamethasone. The patient was discharged but had to be admitted again and a new MRI showed a progression of the leptomeningeal involvement. She worsened and required endotracheal intubation. Cyclophosphamide was started and the patient became asymptomatic three months later. We propose that treatment should not be delayed waiting a biopsy when a diagnosis of RM is made and after a cerebrospinal fluid infection has been ruled out.

FRONT NEUROL. 2021 MAR 11;12:631722. DOI: 10.3389/FNEUR.2021.631722. ECOLLECTION 2021.

THE MULTI-PARTNER CONSORTIUM TO EXPAND DEMENTIA RESEARCH IN LATIN AMERICA (REDLAT): DRIVING MULTICENTRIC RESEARCH AND IMPLEMENTATION SCIENCE

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Dementia is becoming increasingly prevalent in Latin America, contrasting with stable or declining rates in North America and Europe. This scenario places unprecedented clinical, social, and economic burden upon patients, families, and health systems. The challenges prove particularly pressing for conditions with highly specific diagnostic and management demands, such as frontotemporal dementia. Here we introduce a research and networking initiative designed to tackle these ensuing hurdles, the Multi-partner consortium to expand dementia research in Latin America (ReDLat). First, we present ReDLat's regional research framework, aimed at identifying the unique genetic, social, and economic factors driving the presentation of frontotemporal dementia and Alzheimer's disease in Latin America relative to the US. We describe ongoing ReDLat studies in various fields and ongoing research extensions. Then, we introduce actions coordinated by ReDLat and the Latin America and Caribbean Consortium on Dementia (LAC-CD) to develop culturally appropriate diagnostic tools, regional visibility and capacity building, diplomatic coordination in local priority areas, and a knowledge-to-action framework toward a regional action plan. Together, these research and networking initiatives will help to establish strong cross-national bonds, support the implementation of regional dementia plans, enhance health systems' infrastructure, and increase translational research collaborations across the continent.

AM J NEURORADIOL. 2021 JUL;42(7):1276-1281. DOI: 10.3174/AJNR.A7115.

ENDOVASCULAR TREATMENT OF SMALL AND VERY SMALL INTRACRANIAL ANEURYSMS WITH THE WOVEN ENDOBRIDGE DEVICE

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Background and purpose: The Woven EndoBridge has proved to be a safe and effective treatment, especially for wide-neck intracranial aneurysms. The recent fifth-generation Woven EndoBridge came with smaller devices. The purpose of this study was to assess the safety and efficiency of Woven EndoBridge treatment of small and very small aneurysms. Materials and methods: Between September 2017 and March 2020, all consecutive patients treated with a 3- or 3.5 mm-width Woven EndoBridge device were included in this retrospective intention-to-treat study. Clinical and radiologic findings were evaluated at immediate and last-available follow-up. Angiographic outcome was assessed by an external expert reader. Results: One hundred twenty-eight aneurysms were treated with a fifth-generation Woven EndoBridge device including 29 with a width of ≤ 3.5 mm. Ten aneurysms were ruptured (34%). In 3 cases (10%), Woven EndoBridge treatment could not be performed because the aneurysm was still too small for the smallest available Woven EndoBridge device and another endovascular strategy was chosen. The median follow-up time was 11.2 months. Complete and adequate occlusion was obtained in 71% and 90% of the treated aneurysms, respectively. Retreatment was needed in 2 cases (10%). Symptomatic ischemic complications leading to transient neurologic deficits occurred in 2 cases (7%) (1 procedure-related and 1 device-related) but with full spontaneous recovery at discharge. Conclusions: The fifth-generation Woven EndoBridge device seems to be a safe and technically feasible treatment for both ruptured and unruptured small and very small intracranial aneurysms, with satisfactory occlusion rates on midterm follow-up. However, further study is needed to evaluate longer-term efficiency.

FRONT GENET. 2021 JUL 28;12:649764. DOI: 10.3389/FGENE.2021.649764. ECOLLECTION 2021.

FILTERING OF DATA-DRIVEN GENE REGULATORY NETWORKS USING DROSOPHILA MELANOGASTER AS A CASE STUDY

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Gene Regulatory Networks (GRNs) allow the study of regulation of gene expression of whole genomes. Among the most relevant advantages of using networks to depict this key process, there is the visual representation of large amounts of information and the application of graph theory to generate new knowledge. Nonetheless, despite the many uses of GRNs, it is still difficult and expensive to assign Transcription Factors (TFs) to the regulation of specific genes. ChIP-Seq allows the determination of TF Binding Sites (TFBSs) over whole genomes, but it is still an expensive technique that can only be applied one TF at a time and requires replicates to reduce its noise. Once TFBSs are determined, the assignment of each TF and its binding sites to the regulation of specific genes is not trivial, and it is often performed by carrying out site-specific experiments that are unfeasible to perform in all possible binding sites. Here, we addressed these relevant issues with a two-step methodology using *Drosophila melanogaster* as a case study. First, our protocol starts by gathering all transcription factor binding sites (TFBSs) determined with ChIP-Seq experiments available at ENCODE and FlyBase. Then each TFBS is used to assign TFs to the regulation of likely target genes based on the TFBS proximity to the transcription start site of all genes. In the final step, to try to select the most likely

regulatory TF from those previously assigned to each gene, we employ GENIE3, a random forest-based method, and more than 9,000 RNA-seq experiments from *D. melanogaster*. Following, we employed known TF protein-protein interactions to estimate the feasibility of regulatory events in our filtered networks. Finally, we show how known interactions between co-regulatory TFs of each gene increase after the second step of our approach, and thus, the consistency of the TF-gene assignment. Also, we employed our methodology to create a network centered on the *Drosophila melanogaster* gene Hr96 to demonstrate the role of this transcription factor on mitochondrial gene regulation.

FRONT AGING NEUROSCI. 2021 DEC 24;13:769462. DOI: 10.3389/FNAGI.2021.769462. ECOLLECTION 2021.

DUAL-TASK GAIT AS A PREDICTIVE TOOL FOR COGNITIVE IMPAIRMENT IN OLDER ADULTS: A SYSTEMATIC REVIEW

Felipe Ramírez, Myriam Gutiérrez

The use of the dual-task model as a cognitive-motor interface has been extensively investigated in cross-sectional studies as a training task in cognitive impairment. However, few existing longitudinal studies prove the usefulness of this tool as a clinical marker of cognitive impairment in older people. What is the evidence in prospective studies about dual-task gait as a predictor of cognitive impairment in older adults? This study aims to review and discuss the current state of knowledge in prospective studies on the use of dual-task gait as a predictive tool for cognitive impairment in older adults. The methodology used was a systematic review, according to the PRISMA criteria for the search, summarize and report. A search in 3 databases (Pubmed, Web of Science, and Scopus) was carried out until April 2021. The search terms used were: "(gait OR walking) AND (cognitive decline) AND (dual-task) AND (follow-up OR longitudinal OR long-term OR prospective OR cohort OR predict)." We included prospective research articles with older people with cognitive evaluation at the beginning and the end of the follow-up and dual-task gait paradigm as initial evaluation associated with the presentation of cognitive impairment prediction using any dual-task gait parameters. After exclusion criteria, 12 studies were reviewed. The results indicate that eight studies consider dual-task gait parameters a useful cognitive-motor tool, finding that some of the evaluated parameters of dual-task gait significantly correlate with cognitive impairment over time. The most promising DT parameters associated with cognitive impairment prediction seem to be gait speed, speed cost, DT time, numbers of words during DT, among others. In sum, this study reviews the variety of dual-task gait parameters and their relevance as a simple tool for early cognitive impairment screening, opening a diagnostic window for the screening of cognitive impairment in older people.

J ALZHEIMERS DIS. 2021;82(S1):S283-S297. DOI: 10.3233/JAD-201031.

ASSOCIATION OF VITAMIN D RECEPTOR POLYMORPHISMS WITH AMYLOID- β TRANSPORTERS EXPRESSION AND RISK OF MILD COGNITIVE IMPAIRMENT IN A CHILEAN COHORT

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Background: Amyloid- β peptide (A β) deposition in Alzheimer's disease (AD) is due to an imbalance in its production/clearance rate. A β is transported across the blood-brain barrier by LRP1 and P-gp as efflux transporters and RAGE as influx transporter. Vitamin D deficit and polymorphisms of the vitamin D receptor (VDR) gene are associated with high prevalence of mild cognitive impairment (MCI) and AD. Further, vitamin D promotes the expression of LRP1 and P-gp in AD-animal model brains. Objective: To associate VDR polymorphisms Apa I (rs7975232), Taq I (rs731236), and Fok I (rs2228570) with the risk of developing MCI in a Chilean population, and to evaluate the relationship of these polymorphisms to the expression of VDR and A β -transporters in peripheral blood mononuclear cells (PBMCs). Methods: VDR polymorphisms Apa I, Taq I, and Fok I were determined in 128 healthy controls (HC) and 66 MCI patients. mRNA levels of VDR and A β -transporters were evaluated in subgroups by qPCR. Results: Alleles A of Apa I and C of Taq I were associated with a lower risk of MCI. HC with the Apa I AA genotype had higher mRNA levels of P-gp and LRP1, while the expression of VDR and RAGE were higher in MCI patients and HC. For Fok I, the TC genotype was associated with lower expression levels of A β -transporters in both groups. Conclusion: We propose that the response to vitamin D treatment will depend on VDR polymorphisms, being more efficient in carriers of protective alleles of Apa I polymorphism.

BR J NEUROSURG. 2021 DEC;35(6):703-713. DOI: 10.1080/02688697.2021.1950623.

SURGICAL RESECTION VERSUS STEREOTACTIC RADIOSURGERY ON LOCAL RECURRENCE AND SURVIVAL FOR PATIENTS WITH A SINGLE BRAIN METASTASIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background. Brain metastases (BM) are the most frequent intracranial tumours in adults. In patients with solitary BM, surgical resection (SR) or stereotactic radiosurgery (SRS) is performed. There is limited evidence comparing one treatment over the other. Objective. To compare SR versus SRS on patients with solitary BMs, regarding local recurrence (LR) and overall survival (OS) conducting a systematic review and meta-analysis. Methods. Systematic review of literature following PRISMA guidelines, using the databases of Medline, Clinicaltrials.gov, Embase, Web of Science, Sciondirect, CINAHL, Wiley Online Library, Springerlink and LILACS. Following study selection based on inclusion and exclusion criteria, data extraction and a critical analysis of the literature was performed according to the GRADE scale. For quantitative analysis, a random effects model was used. Data were synthesized and evaluated on a forest plot and funnel plot. Results. Two randomized clinical trials, four cohort studies and one case-control studies met our inclusion criteria for the qualitative analysis. None was excluded subsequently.

Overall, 614 patients with single metastasis were included. Studies had high heterogeneity. Multiple significant variables affecting the outcome were signalized. Meta-analysis showed no significant differences for survival (HR, 1.10; 95% CI, 0.75–1.45) or LR (HR, 0.81; 95% CI, 0.42–1.20). Conclusions. According to current evidence, in patients with a single small metastasis there is no statistically significant difference in OS or LR among the chosen techniques (SR or SRS). Multiple significant co-variables may affect both outcomes. Different outcomes better than OS should be evaluated in further randomized studies.

ARCH CLIN NEUROPSYCHOL. 2021 MAY 21;36(4):455-464. DOI: 10.1093/ARCLIN/ACAA072.

ACALCULIA IN APHASIA

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Background: Patients with aphasia can present a type of acalculia referred to as aphasic acalculia. Aims: To investigate the correlation and to test regression models for one- and two-digit calculation skills using verbal and nonverbal predictors. Methods and procedures: We selected an aphasia sample of 119 men and 81 women with a mean age of 57.37 years (SD = 15.56) and an average level of education of 13.52 years (SD = 4.08). Spanish versions of the Western Aphasia Battery and Boston Diagnostic Aphasia Examination, plus a Written Calculation test, were individually administered. The calculation section of the Western Aphasia Battery and the Written Calculation tests were used to pinpoint calculation difficulties. Outcomes and results: Calculation difficulties were more severe in Global and Mixed non-fluent aphasia; they were very similar in Broca, Conduction, and Amnesic Aphasia. All correlations between the two calculation subtests and the other subtests of the Western Aphasia Battery were statistically significant. Calculation subtests correlated negatively with age and positively with schooling. Sex and time post-onset did not show any correlation with the calculation scores. Education, Reading, Block Design, and Raven's Colored Progressive Matrices were significant predictors of Western Aphasia Battery Calculation. Writing was the only significant predictor of the Written Calculation scores. Conclusions: Nonverbal abilities were predictors of calculation tests, whereas agraphia defects were predictors of the Written Calculation test. Therefore, calculation abilities can be regarded both as written language-dependent and verbal language-independent.

INT J GERIATR PSYCH. 2021 AUG;36(8):1171-1178. DOI: 10.1002/GPS.5501.

NEURAL LINKS BETWEEN FACIAL EMOTION RECOGNITION AND COGNITIVE IMPAIRMENT IN PRESBYCUSIS

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Objectives: Facial emotion recognition (FER) is impaired in people with dementia and with severe to profound hearing loss, probably reflecting common neural changes. Here, we aim to study the association between brain structures and FER impairment in mild to moderate age-related hearing loss participants. Methods: We evaluated FER in a cross-sectional cohort of 111 Chilean nondemented elderly participants. They were assessed for FER in seven different categories using 35 facial stimuli. We collected pure-tone average (PTA) audiometric thresholds, cognitive and neuropsychiatric assessments, and morphometric brain imaging using a 3-Tesla MRI. Results: According to PTA threshold levels, participants were classified as controls (≤ 25 dB, $n = 56$) or presbycusis (> 25 dB, $n = 55$), with an average PTA of 17.08 ± 4.8 dB HL and 36.27 ± 9.5 dB HL respectively. Poorer total FER score was correlated with worse hearing thresholds ($r = -0.23$, $p < 0.05$) in participants with presbycusis. Multiple regression models explained 57 % of the variability of FER in presbycusis and 10% in controls. In both groups, the main determinant of FER was cognitive performance. In the brain structure of presbycusis participants, FER was correlated with the atrophy of the right insula, right hippocampus, bilateral cingulate cortex and multiple areas of the temporal cortex. In controls, FER was only associated with bilateral middle temporal cortex volume. Conclusions: FER impairment in presbycusis is distinctively associated with atrophy of neural structures engaged in the perceptual and conceptual level of face emotion processing.

OAIC – OFICINA DE APOYO A LA INVESTIGACIÓN CLÍNICA

J ULTRAS MED. 2021 JUN;40(6):1125-1130. DOI: 10.1002/JUM.15489.

SUBCLINICAL ULTRASOUND CHARACTERISTICS OF INFANTILE HEMANGIOMAS THAT MAY POTENTIALLY AFFECT INVOLUTION

María McNab, Carolina García, Denise Tabak, Ligia Aranibar, Ariel Castro, Ximena Wortsman

Objectives. Infantile hemangiomas (IHs) are the most common benign tumors in children. Color Doppler ultrasound is a noninvasive imaging modality that can show subclinical anatomic parameters in a wide range of dermatologic conditions. The purpose of this study was to describe the ultrasound characteristics of IHs and look for subclinical features with the potential to influence the involution and therapeutic response. Methods. A review of the ultrasound database of children with clinical and ultrasound IH diagnoses was conducted. The clinically reported duration and the ultrasound assessment of the proliferative phase were compared. Descriptive and statistical analyses of qualitative and quantitative parameters of the series were performed. Significance was set at $P < .05$. Results. A total of 204 IHs were included. Twenty percent had arteriovenous shunts; 15% had afferent branches from main regional arteries; and almost 30% showed involvement of deep structures. Sixty-one percent of IHs were in the head and neck. Deep hemangiomas showed significantly thicker lesional vessels. A prolonged

proliferative stage was significantly associated with a higher presence of arteriovenous shunts and a higher peak systolic velocity of the arterial vessels (≥ 15 cm/s) within the lesions. Conclusions. Color Doppler ultrasound can support the detection of subclinical anatomic features that may potentially influence the involution and response to treatment of IHs. Some of these characteristics may serve as potential markers to predict and manage IHs in prolonged proliferative stages.

DEPARTAMENTO DE OBSTETRICIA Y GINECOLOGÍA

J OBSTET GYNAECOL 2021 OCT;41(7):1102-1106. DOI: 10.1080/01443615.2020.1835843.

5,926 HYSTERECTOMIES: COMPLICATIONS DESCRIBED BY CLAVIEN-DINDO CLASSIFICATION

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Hysterectomy is the most common major gynaecological surgery. Due to its high volume, the analysis of its results is relevant. The objective of this study was to describe intraoperative complications and reoperations, for both benign and malignant causes, using the Clavien-Dindo classification (approved by local ethics committee, number 100220). Between 2000 and 2019, 5926 elective hysterectomies were performed, of which 90.2% were for benign aetiology and 9.8% for malignant causes. The abdominal route was 52.7%, vaginal 40.1% and laparoscopic 7.2%. Intraoperative complications and reoperations (grade III Clavien-Dindo) were 4% and 2.1%, respectively. Oncological surgery had significantly more intraoperative complications (10% vs. 3.4%) and reoperations (3.6% vs. 1.9%) than benign procedures. Noteworthy, intraoperative complications required a new operation in only 3.4% for malignant and 2.8% for benign surgery. Our data showed the relevance of detecting and rectifying intraoperative complications during surgery, which consequently leads to a lower reoperation rate, minimising postoperative morbidity and mortality for patients. Impact Statement What is already known on this subject? The surgical complications of hysterectomy, both intraoperative and postoperative, are extensively described. However, this information is not well systematised, in which elective and emergency surgery are mixed. In addition to the above, there are few documents comparing the results of hysterectomies due to benign versus malignant causes. What the results of this study add? Using the Clavien-Dindo classification, this study adds an organised description of intraoperative complications and reoperations of hysterectomy in the context of elective surgery. In addition, it provides information on the comparison between surgery for benign versus malignant causes, as well as information on intraoperative complications requiring a new operation. What the implications are of these findings for clinical practice and/or further research? These findings provide clear and orderly data about the risks of elective hysterectomy and showed the relevance of detecting and rectifying intraoperative complications during the procedure. This is useful for specialists to preoperatively identify the risks for each hysterectomy group and provide their patients with more detailed information during informed consent.

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PRESCRIPTIVE STANDARDS OF ECHOCARDIOGRAPHIC MORPHOMETRIC AND FUNCTIONAL PARAMETERS IN UNCOMPLICATED MONOCHORIONIC DIAMNIOTIC FETUSES

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Objective. To create prescriptive standards of cardiac morphometric and functional parameters in a cohort of uncomplicated monochorionic diamniotic (MCDA) twins. Method. Fetal echocardiography was performed in a cohort of uncomplicated monochorionic twin fetuses scanned longitudinally, including comprehensive morphometric and functional parameters, using 2-D imaging, M-mode and conventional Doppler. A multilevel polynomial hierarchical model adjusted by gestational age and estimated fetal weight was used to fit each cardiac parameter. Results. The global heart dimensions including the atrial and ventricular areas, the ventricles dimensions and myocardial wall thicknesses and most of the functional parameters, such as the longitudinal myocardial motion and the biventricular cardiac output showed a positive quadratic increment throughout pregnancy. On the other hand, the left ejection fraction, shortening fraction and right fractional area change decreased with gestational age. Scatterplots for the main structural and functional parameters and ratios by gestational age, with mean, 5th, 10th, 90th, and 95th percentiles are provided. Regression equations by estimated fetal weight are also created. Conclusion. We provide specific comprehensive echocardiographic prescriptive standards for uncomplicated MCDA twin fetuses following current standardized methodology. The implementation of these charts will potentially help to better identify abnormal cardiovascular parameters associated to monochorionic complications.

EUR RADIOL. 2021 OCT;31(10):7242-7250. DOI: 10.1007/S00330-021-07857-2.

ASSESSMENT OF MYOCARDIAL DEFORMATION WITH CMR: A COMPARISON WITH ULTRASOUND SPECKLE TRACKING

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Objectives: Myocardial deformation integrated with cardiac dimensions provides a comprehensive assessment of cardiac function, which has proven useful to differentiate cardiac pathology from physiological adaptation to situations such as chronic intensive training. Feature tracking (FT) can measure myocardial deformation from cardiac magnetic resonance (CMR) cine sequences; however, its accuracy is not yet fully validated. Our aim was to compare the accuracy and reproducibility of FT with speckle tracking echocardiography (STE) in highly trained

endurance athletes. Methods: Ninety-three endurance athletes (> 12-h training/week during the last 5 years, 52% male, 35 ± 5.1 years old) and 72 age-matched controls underwent resting CMR and transthoracic echocardiography to assess biventricular exercise-induced remodeling and biventricular global longitudinal strain (GLS) by CMR-FT and STE. Results: Strain values were significantly lower when assessed by CMR-FT compared to STE ($p < 0.001$), with good reproducibility for the left ventricle (bias = 3.94%, limit of agreement [LOA] = ± 4.27 %) but wider variability for right ventricle strain. Strain values by both techniques proportionally decreased with increasing ventricular volumes, potentially depicting the functional biventricular reserve that characterizes athletes' hearts. Conclusions: Biventricular longitudinal strain values were lower when assessed by FT as compared to STE. Both methods were statistically comparable when measuring LV strain but not RV strain. These differences might be justified by the lower in-plane spatial and temporal resolution of FT, which is particularly relevant for the complex anatomy of the RV.

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INCIDENCE OF OCCULT UTERINE SARCOMA AND OTHER UNEXPECTED PATHOLOGIES IN PATIENTS HAVING SURGERY FOR PRESUMED MYOMAS: A RETROSPECTIVE OBSERVATIONAL STUDY

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Objective: To determine the incidence of occult uterine sarcomas and other unexpected pathologies in patients undergoing hysterectomies or myomectomies with a pre-operative diagnosis of uterine leiomyomas. Study design: Retrospective study. Setting: Tertiary hospital in Santiago, Chile. Population: 921 women who underwent surgery for presumed myomas. Database analysis of surgical and pathological notes, from January 2007 to December 2017 with a preoperative diagnosis of uterine leiomyoma. Main outcome measures: number of patients with uterine sarcoma confirmed on histology. Results: During this period, a total of 921 gynecological surgeries were performed for benign uterine fibroids of which 787 were hysterectomies and 134 were myomectomies. We found four cases of malignant neoplasms (0.43 %). Two were uterine leiomyosarcoma (LMS), one mixed epithelial and mesenchymal tumor, and one case of incidental cervical cancer. This gives an LMS incidence of 1 in 460 and 1 in 921 of mixed epithelial and mesenchymal tumor. There were seven cases of unexpected benign pathology. This included six atypical myomas and one leiomyoblastoma epithelioid myoma. If we combine the malignant and benign cases, we would have an incidence of 1.2 % of unexpected pathology. Conclusion: In our series of patients undergoing myomectomies or hysterectomies for presumed myomas the incidence of LMS was 1 in 460. The incidence of any unexpected pathology including benign ones in presumed myomas was 1 in 83 (six atypical myomas, one leiomyoblastoma epithelioid myoma, two LMS, one mixed epithelial and mesenchymal tumor, one incidental cervical cancer).

CLIN PHYSIOL FUNCTI. 2021 MAY;41(3):262-270. DOI: 10.1111/CPF.12693.

ATRIOVENTRICULAR PLANE DISPLACEMENT VERSUS MITRAL AND TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION: A COMPARISON BETWEEN CARDIAC MAGNETIC RESONANCE AND M-MODE ECHOCARDIOGRAPHY

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Introduction: Both echocardiography and CMR imaging are used to quantify longitudinal function. Inter-method variability for mitral (MAPSE) and tricuspid (TAPSE) annular plane systolic excursion, and variability between directly measured MAPSE and TAPSE and as based on atrioventricular plane displacement (AVPD) analysis by CMR, are, however, not known. This study, therefore, assessed inter-method variability and variability between annular plane systolic excursion and AVPD-based values in a healthy adult population. Methods: Echocardiography and CMR were performed in 111 adults (35 [32-38] years). Method comparisons were assessed with Deming regression, Bland-Altman analysis and coefficient of variation. Observer reproducibility was assessed by the concordance correlation coefficient. Results: Echocardiography and semi-automatic CMR agreed on MAPSE (17 ± 2 mm vs. 17 ± 2 mm, $p = 0.1$) and TAPSE (25 ± 3 mm vs. 25 ± 3 mm, $p = 0.5$), correlated highly between methods (fitted-slope 1.22 [95% CI 1.07-1.38] and 1.12 [95% CI 0.95-1.29]) and showed low bias (0.42 [95% CI - 2.05 to 2.88] and - 0.18 [95% CI - 4.78 to 4.43]). Intra-/inter-observer reproducibility was high for both methods for both MAPSE (echocardiography 0.96/0.86; CMR 0.87/0.85) and TAPSE (echocardiography 0.96/0.95; CMR 0.97/0.96). MAPSE (16 ± 2 mm vs. 17 ± 2 mm; $p < 0.001$) and TAPSE (24 ± 3 vs. 25 ± 3 mm; $p < 0.001$) based on AVPD were similar but statistically different compared with semi-automatic CMR. Conclusions: Echocardiography and semi-automatic CMR have low variability and provide similar values for MAPSE and TAPSE and are thus interchangeable for follow-up studies. Lateral values based on tracked data from AVPD analysis are not clinically significantly different and could be used as a representation of annular displacement.

J PEDIATR GASTROENTEROL NUTR. 2021 OCT 5. DOI: 10.1097/MPG.0000000000003321.

GROWTH OF VERY LOW BIRTH WEIGHT INFANTS WHO RECEIVED A LIQUID HUMAN MILK FORTIFIER: A RANDOMIZED, CONTROLLED MULTICENTER TRIAL: A RANDOMIZED, CONTROLLED MULTICENTER TRIAL

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Objectives: To evaluate growth (weight, length, head circumference, and knee-heel length [KHL]) in very low birth weight (VLBW) infants (500-1500 g) who received human milk with a liquid fortifier (LHMF) with high protein and fatty acid content versus a traditional powder fortifier (PHMF) for 45 days or until discharge. Methods: This was a multicenter, randomized, controlled trial. An intention-to-treat analysis was performed to determine adverse events and withdrawal causes. We also performed an efficacy analysis involving the infants who completed

at least 2 weeks of study. Results: Of the 158 infants enrolled in the study, 146 completed at least 2 weeks, and 125 completed the entire study. The biodemographic characteristics were similar between groups, with no differences in increments of weight (22.9 vs 22.7 g kg⁻¹ day⁻¹), length (1.03 vs 1.09 cm/week), head circumference (0.91 vs 0.90 cm/week), or KHL (3.6 vs 3.3 mm/week). The KHL increment was greater in infants weighing >1 kg receiving LHM (3.7 vs 3.2 mm/week, *P* = 0.027). Although there were no significant differences in serious adverse events, the incidence difference of the composite outcome death/necrotizing enterocolitis between groups warrants attention (1.3% with LHM and 8.1% with PHM). Conclusion: There were no differences in the overall growth between VLBW infants receiving either fortifier.

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EXERCISE CAPACITY IN YOUNG ADULTS BORN SMALL FOR GESTATIONAL AGE

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Importance Being born small for gestational age (SGA), approximately 10% of all births, is associated with increased risk of cardiovascular mortality in adulthood, but mechanistic pathways are unclear. Cardiac remodeling and dysfunction occur in fetuses SGA and children born SGA, but it is uncertain whether and how these changes persist into adulthood. **Objective** To evaluate baseline cardiac function and structure and exercise capacity in young adults born SGA. **Design, Setting, and Participants** This cohort study conducted from January 2015 to January 2018 assessed a perinatal cohort born at a tertiary university hospital in Spain between 1975 and 1995. Participants included 158 randomly selected young adults aged 20 to 40 years born SGA (birth weight below the 10th centile) or with intrauterine growth within standard reference ranges (controls). Participants provided their medical history, filled out questionnaires regarding smoking and physical activity habits, and underwent incremental cardiopulmonary exercise stress testing, cardiac magnetic resonance imaging, and a physical examination, with blood pressure, glucose level, and lipid profile data collected. **Exposure** Being born SGA. **Main Outcomes and Measures** Cardiac structure and function assessed by cardiac magnetic resonance imaging, including biventricular end-diastolic shape analysis. Exercise capacity assessed by incremental exercise stress testing. **Results** This cohort study included 81 adults born SGA (median age at study, 34.4 years [IQR, 30.8-36.7 years]; 43 women [53%]) and 77 control participants (median age at study, 33.7 years [interquartile range (IQR), 31.0-37.1 years]; 33 women [43%]). All participants were of White race/ethnicity and underwent imaging, whereas 127 participants (80% of the cohort; 66 control participants and 61 adults born SGA) completed the exercise test. Cardiac shape analysis showed minor changes at rest in right ventricular geometry (DeLong test *z*, 2.2098; *P* = .02) with preserved cardiac function in individuals born SGA. However, compared with controls, adults born SGA had lower exercise capacity, with decreased maximal workload (mean [SD], 180 [62] W vs 214 [60] W; *P* = .006) and oxygen consumption (median, 26.0 mL/min/kg [IQR, 21.5-33.5 mL/min/kg vs 29.5 mL/min/kg [IQR, 24.0-36.0 mL/min/kg]; *P* = .02). Exercise capacity was significantly correlated with left ventricular mass ($\rho = 0.7934$; *P* < .001). **Conclusions and Relevance** This cohort of young adults born SGA had markedly reduced exercise capacity. These results support further research to clarify the causes of impaired exercise capacity and the potential association with increased cardiovascular mortality among adults born SGA.

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FETAL CARDIAC FILLING AND EJECTION TIME FRACTIONS BY PULSED-WAVE DOPPLER: REFERENCE RANGES AND POTENTIAL CLINICAL APPLICATION

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Objectives. Fetal cardiac function can be evaluated using a variety of parameters. Among these, cardiac cycle time-related parameters, such as filling time fraction (FTF) and ejection time fraction (ETF), are promising but rarely studied. We aimed to report the feasibility and reproducibility of fetal FTF and ETF measurements using pulsed-wave Doppler, to provide reference ranges for fetal FTF and ETF, after evaluating their relationship with heart rate (HR), gestational age (GA) and estimated fetal weight (EFW), and to evaluate their potential clinical utility in selected fetal conditions. **Methods.** This study included a low-risk prospective cohort of singleton pregnancies and a high-risk population of fetuses with severe twin-twin transfusion syndrome (TTTS), aortic stenosis (AoS) or aortic coarctation (CoA), from 18 to 41 weeks' gestation. Left ventricular (LV) and right ventricular inflow and outflow pulsed-wave Doppler signals were analyzed, using valve clicks as landmarks. FTF was calculated as: (filling time/cycle time) × 100. ETF was calculated as: (ejection time/cycle time) × 100. Intraclass correlation coefficients (ICC) were used to evaluate the intra- and interobserver reproducibility of FTF and ETF measurements in low-risk fetuses. The relationships of FTF and ETF with HR, GA and EFW were evaluated using multivariate regression analysis. Reference ranges for FTF and ETF were then constructed using the low-risk population. Z-scores of FTF and ETF in the high-risk fetuses were calculated and analyzed. **Results.** In total, 602 low-risk singleton pregnancies and 54 high-risk fetuses (nine pairs of monozygotic twins with severe TTTS, 16 fetuses with AoS and 20 fetuses with CoA) were included. Adequate Doppler traces for FTF and ETF could be obtained in 95% of low-risk cases. Intraobserver reproducibility was good to excellent (ICC, 0.831–0.905) and interobserver reproducibility was good (ICC, 0.801–0.837) for measurements of all timing parameters analyzed. Multivariate analysis of FTF and ETF in relation to HR, GA and EFW in low-risk fetuses identified HR as the only variable predictive of FTF, while ETF was dependent on both HR and GA. FTF increased with decreasing HR in low-risk fetuses, while ETF showed the opposite behavior, decreasing with decreasing HR. Most recipient twins with severe TTTS showed reduced FTF and preserved ETF. AoS was associated with decreased FTF and increased ETF in the LV, with seemingly different patterns associated with univentricular vs biventricular

postnatal outcome. The majority of fetuses with CoA had FTF and ETF within the normal range in both ventricles. Conclusions. Measurement of FTF and ETF using pulsed-wave Doppler is feasible and reproducible in the fetus. The presented reference ranges account for associations of FTF with HR and of ETF with HR and GA. These time fractions are potentially useful for clinical monitoring of cardiac function in severe TTTS, AoS and other fetal conditions overloading the heart. © 2020 International Society of Ultrasound in Obstetrics and Gynecology

ULTRASOUND OBSTET GYNECOL. 2021 SEP;58(3):388-397. DOI: 10.1002/UOG.23127.

REFERENCE RANGES FOR FETAL CARDIAC, VENTRICULAR AND ATRIAL RELATIVE SIZE, SPHERICITY, VENTRICULAR DOMINANCE, WALL ASYMMETRY AND RELATIVE WALL THICKNESS FROM 18 TO 41 GESTATIONAL WEEKS

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Objective: To construct nomograms for fetal cardiac, ventricular and atrial relative size and geometry parameters from 18 to 41 weeks' gestation using a low-risk population of singleton pregnancies. Methods: This was a prospective cohort study of 602 low-risk singleton pregnancies undergoing comprehensive fetal echocardiography, from 18 to 41 weeks of gestation, to assess fetal cardiac, atrial and ventricular relative size and sphericity, ventricular dominance, wall asymmetry and relative wall thickness. Intra- and interobserver measurement reproducibility was evaluated using intraclass correlation coefficients (ICC). In order to construct reference ranges across pregnancy, parametric regressions were tested to model each measurement against gestational age and estimated fetal weight. The measurements evaluated were: cardiothoracic ratio; atrial-to-heart area ratios; ventricular-to-heart area ratios; cardiac, ventricular and atrial sphericity indices; right-to-left basal and midventricular ratios; septal-to-free wall thickness ratios; and relative wall thickness. Results: Fetal cardiac, ventricular and atrial morphometry for assessing relative size and geometry could be successfully performed in > 95% of the population, with moderate-to-excellent interobserver reproducibility (ICC, 0.623-0.907) and good-to-excellent intraobserver reproducibility (ICC, 0.787-0.938). Cardiothoracic ratio and ventricular right-to-left ratio showed a modest increase throughout gestation. Atrial-to-heart and ventricular-to-heart area ratios, atrial sphericity indices and septal-to-free wall thickness ratios were constant with gestational age. Left and right ventricular basal sphericity indices showed a tendency to decrease at the end of gestation, while left and right midventricular sphericity indices tended to decrease in the second trimester. The cardiac sphericity index and left and right relative wall thickness showed a modest decrease with gestational age. Nomograms across gestation were constructed for all echocardiographic parameters described. Conclusions: The assessment of cardiac, ventricular and atrial relative size and geometry is feasible and reproducible in the fetus. We provide standardized reference ranges for these parameters throughout gestation, enabling the accurate assessment of cardiac remodeling patterns during fetal life.

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EXPERIENCES AND WELL-BEING OF HEALTHCARE PROFESSIONALS WORKING IN THE FIELD OF ULTRASOUND IN OBSTETRICS AND GYNAECOLOGY AS THE SARS-COV-2 PANDEMIC WERE EVOLVING: A CROSS-SECTIONAL SURVEY STUDY

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Objective Assess experience of healthcare professionals (HCPs) working with ultrasound in obstetrics and gynaecology during the evolving SARS-CoV-2 pandemic, given the new and unprecedented challenges involving viral exposure, personal protective equipment (PPE) and well-being. Design Prospective cross-sectional survey study. Setting Online international survey. Single-best, open box and Hospital Anxiety and Depression Scale (HADS) questions. Participants The survey was sent to 35 509 HCPs in 124 countries and was open from 7 to 21 May 2020. 2237/3237 (69.1%) HCPs from 115 countries who consented to participate completed the survey. 1058 (47.3%) completed the HADS. Primary outcome measures Overall prevalence of SARS-CoV-2, depression and anxiety among HCPs in relation to country and PPE availability. Analyses Univariate analyses were used to investigate associations without generating erroneous causal conclusions. Results Confirmed/suspected SARS-CoV-2 prevalence was 13.0%. PPE provision concerns were raised by 74.1% of participants; highest among trainees/resident physicians (83.9%) and among HCPs in Spain (89.7%). Most participants worked in self-perceived high-risk areas with SARS-CoV-2 (67.5%–87.0%), with proportionately more trainees interacting with suspected/confirmed infected patients (57.1% vs 24.2%–40.6%) and sonographers seeing more patients who did not wear a mask (33.3% vs 13.9%–7.9%). The most frequent PPE combination used was gloves and a surgical mask (22.3%). UK and US respondents reported spending less time self-isolating (8.8 days) and lower satisfaction with their national pandemic response (37.0%–43.0%). 19.8% and 8.8% of respondents met the criteria for moderate to severe anxiety and depression, respectively. Conclusions Reported prevalence of SARS-CoV-2 in HCPs is consistent with literature findings. Most respondents used gloves and a surgical mask, with a greater SARS-CoV-2 prevalence compared with those using 'full' PPE. HCPs with the least agency (trainees and sonographers) were not only more likely to see high-risk patients but also less likely to be protected. A fifth of respondents reported moderate to severe anxiety.

FETAL DIAGN THER. 2021 FEB 8;1-7. DOI: 10.1159/000510648.

THE NOVEL ULTRASONOGRAPHIC MARKER OF UTEROCERVICAL ANGLE FOR PREDICTION OF SPONTANEOUS PRETERM BIRTH IN SINGLETON AND TWIN PREGNANCIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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The alteration of the uterocervical angle (UCA) has been proposed to play an important role in spontaneous preterm birth (sPTB). The aim of this systematic review and meta-analysis was to evaluate the evidence on the UCA predictive role in sPTB. In this study, PubMed, Web of Science, Scopus, and Google scholar were systematically searched from inception up to June 2020. Inter-study heterogeneity was also assessed using

Cochrane's Q test and the I2 statistic. Afterward, the random-effects model was used to pool the weighted mean differences (WMDs) and the corresponding 95% confidence intervals (CIs). Eleven articles that reported second-trimester UCA of 5,061 pregnancies were included in this study. Our meta-analysis results indicate that a wider UCA significantly increases the risk of sPTB in following cases: all pregnancies (WMD = 15.25, 95% CI: 11.78–18.72, $p < 0.001$; I2 = 75.9%, $p < 0.001$), singleton (WMD = 14.43, 95% CI: 8.79–20.06, $p < 0.001$; I2 = 82.4%, $p < 0.001$), and twin pregnancies (WMD = 15.14, 95% CI: 13.42–16.87, $p < 0.001$; I2 = 0.0%, $p = 0.464$). A wider ultrasound-measured UCA in the second trimester seems to be associated with the increased risk of sPTB in both singleton and twin pregnancies, which reinforces the clinical evidence that UCA has the potential to be used as a predictive marker of sPTB.

FETAL DIAGN THER. 2021;48(8):596-602. DOI: 10.1159/000518093.

EFFECT OF MATERNAL AND FETAL CHARACTERISTICS IN FETO-PLACENTAL DOPPLER AND IMPACT OF USING ADJUSTED STANDARDS IN THE DEFINITION OF FETAL GROWTH RESTRICTION AT TERM

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Introduction: This study aimed to determine the effect and clinical impact of physiological characteristics on the 95th/5th centile of the umbilical artery (UA) Doppler and the cerebroplacental ratio (CPR), at 36+ weeks. **Methods:** From the multicenter randomized trial "Ratio37," we selected 4,505 low-risk pregnant women between June 2016 and January 2020. We registered physiological characteristics and the pulsatility indexes (PI) of the UA and middle cerebral artery (36-39 weeks). The 95th/5th centile of the UA PI and CPR was modeled by quantile regression. To evaluate the clinical impact of adjusting Doppler, we retrospectively applied gestational age (GA) and fully adjusted standards to 682 small for gestational age (SGA)-suspected fetuses (37 weeks) from a cohort of consecutive patients obtained between January 2010 and January 2020. **Results:** Several physiological characteristics significantly influenced the 95th/5th centile of the UA and CPR PI. The fully adjusted 95th centile of the UA was higher, and the 5th centile of the CPR was lower than GA-only-adjusted standards. Of the 682 SGA fetuses, 150 (22%) were classified as late fetal growth restricted only by GA and 112 (16.4%) when we adjusted Doppler. These 38 fetuses had similar perinatal outcome than the SGA group. **Discussion:** The 95th/5th centile of the UA and CPR PI is significantly influenced by physiological characteristics. Adjusting Doppler standards could differentiate better between FGR and SGA.

LABORATORIO DE ENDOCRINOLOGÍA Y BIOLOGÍA DE LA REPRODUCCIÓN

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CURRENT TREATMENTS AND NEW POSSIBLE COMPLEMENTARY THERAPIES FOR EPITHELIAL OVARIAN CANCER

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Epithelial ovarian cancer (EOC) is one of the deadliest gynaecological malignancies. The late diagnosis is frequent due to the absence of specific symptomatology and the molecular complexity of the disease, which includes a high angiogenesis potential. The first-line treatment is based on optimal debulking surgery following chemotherapy with platinum/gemcitabine and taxane compounds. During the last years, anti-angiogenic therapy and poly adenosine diphosphate-ribose polymerases (PARP)-inhibitors were introduced in therapeutic schemes. Several studies have shown that these drugs increase the progression-free survival and overall survival of patients with ovarian cancer, but the identification of patients who have the greatest benefits is still under investigation. In the present review, we discuss about the molecular characteristics of the disease, the recent evidence of approved treatments and the new possible complementary approaches, focusing on drug repurposing, non-coding RNAs, and nanomedicine as a new method for drug delivery

LIFE (BASEL). 2021 DEC 21;12(1):8. DOI: 10.3390/LIFE12010008.

ROLE OF MITOCHONDRIA IN INTERPLAY BETWEEN NGF/TRKA, MIR-145 AND POSSIBLE THERAPEUTIC STRATEGIES FOR EPITHELIAL OVARIAN CANCER

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Ovarian cancer is the most lethal gynecological neoplasm, and epithelial ovarian cancer (EOC) accounts for 90% of ovarian malignancies. The 5-year survival is less than 45%, and, unlike other types of cancer, the proportion of women who die from this disease has not improved in recent decades. Nerve growth factor (NGF) and tropomyosin kinase A (TRKA), its high-affinity receptor, play a crucial role in pathogenesis through cell proliferation, angiogenesis, invasion, and migration. NGF/TRKA increase their expression during the progression of EOC by upregulation of oncogenic proteins as vascular endothelial growth factor (VEGF) and c-Myc. Otherwise, the expression of most oncoproteins is regulated by microRNAs (miRs). Our laboratory group reported that the tumoral effect of NGF/TRKA depends on the regulation of miR-145 levels in EOC. Currently, mitochondria have been proposed as new therapeutic targets to activate the apoptotic pathway in the cancer cell. The mitochondria are involved in a myriad of functions as energy production, redox control, homeostasis of Ca²⁺, and cell death. We demonstrated that NGF stimulation produces an augment in the Bcl-2/BAX ratio, which supports the anti-apoptotic effects of NGF in EOC cells. The review aimed to discuss the role of mitochondria in the interplay between NGF/TRKA and miR-145 and possible therapeutic strategies that may decrease mortality due to EOC

ONCOL REP. 2021 MAY;45(5):58. DOI: 10.3892/OR.2021.8009.

KNOCKDOWN OF ZEB1 REVERSES CANCER STEM CELL PROPERTIES IN PROSTATE CANCER CELLS

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Prostate cancer (PCa) is the second most diagnosed type of cancer in men worldwide. Advanced PCa is resistant to conventional therapies and high recurrence has been associated with high rates of metastasis. Cancer stem cells (CSCs) have been proposed to be responsible for this, due to their ability of self-renewal and differentiation into other cell types. Zinc finger E-box-binding homeobox 1 (ZEB1), a transcription factor involved in the regulation of epithelial-mesenchymal transition (EMT), has been associated with the activation of several mechanisms that lead to resistance to treatment. As recent evidence has shown that CSCs may originate from non-CSCs during EMT, it was hypothesized that knocking down ZEB1 expression in PCa cell lines could revert some properties associated with CSCs. Using lentiviral transduction, ZEB1 expression was silenced in the PCa DU145 and LNCaP cell lines. The mRNA and protein expression levels of key canonical CSC markers (Krüppel-like factor 4, SOX2, CD44 and CD133) were determined using reverse transcription-quantitative PCR and western blot analysis, respectively. In addition, the colony forming ability of the ZEB1-knockdown cells was evaluated, and the type of colonies formed (holoclones, paraclones and meroclones) was also characterized. Finally, the ability to form prostatospheres was evaluated in vitro. It was found that in ZEB1-knockdown DU145 cells, the expression levels of CSC phenotype markers (CD44, CD133 and SOX2) were decreased compared with those in the control group. Furthermore, ZEB1-knockdown cells exhibited a lower ability to form prostatospheres and to generate colonies. In conclusion, stable silencing of ZEB1 reversed CSC properties in PCa cell lines. Since ZEB1 is associated with malignancy, therapy resistance and a CSC phenotype in PCa cell lines, targeting ZEB1 may be a key factor to eradicate CSCs and improve the prognosis of patients with advanced PCa.

ONCOL REP. 2021 AUG;46(2):171. DOI: 10.3892/OR.2021.8122.

ENDOTHELIN-1 INDUCES CHANGES IN THE EXPRESSION LEVELS OF STEROIDOGENIC ENZYMES AND INCREASES ANDROGEN RECEPTOR AND TESTOSTERONE PRODUCTION IN THE PC3 PROSTATE CANCER CELL LINE

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Endothelin-1 (ET-1) is involved in the regulation of steroidogenesis. Additionally, patients with castration-resistant prostate cancer (PCa) have a higher ET-1 plasma concentration than those with localized PCa and healthy individuals. The aim of the present study was to evaluate the effect of ET-1 on steroidogenesis enzymes, androgen receptor (AR) and testosterone (T) production in PCa cells. The expression levels of endothelin receptors in prostate tissue from patients with localized PCa by immunohistochemistry, and those in LNCaP and PC3 cells were determined reverse transcription-quantitative PCR (RT-qPCR) and western blotting. Furthermore, the expression levels of ET-1 were determined in LNCaP and PC3 cells by RT-qPCR and western blotting. The ET-1 receptor activation was evaluated by intracellular calcium measurement, the expression levels of AR and enzymes participating in steroidogenesis [cytochrome P450 family 11 subfamily A member 1 (CYP11A1), cytochrome P450 family 17 subfamily A member 1, aldo-keto reductase family member C2 and 3 β -hydroxysteroid dehydrogenase/isomerase 2 (3 β HSD2)] were determined by western blotting and T concentration was determined by ELISA using PC3 cells. The present results revealed higher expression levels of endothelin A receptor (ETAR) in tissues obtained from samples of patients with PCa with a low Gleason Score. No changes were identified for endothelin B receptor (ETBR). PC3 cells expressed higher levels of ET-1 and ETAR, while LNCaP cells exhibited higher expression levels of ETBR. Blocking of ETAR and endothelin B receptor decreased the expression levels of CYP11A1 and 3 β HSD2 enzymes and AR in PC3 cells, as well as T secretion. These findings suggested that ET-1 has a potential role in modulating the intratumoral steroidogenesis pathway and might have relevance as a possible therapeutic target.

SERVICIO DE OFTALMOLOGÍA

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MIRNA LANDSCAPE IN PATHOGENESIS AND TREATMENT OF VOGT-KOYANAGI-HARADA DISEASE

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miRNAs, one of the members of the noncoding RNA family, are regulators of gene expression in inflammatory and autoimmune diseases. Changes in miRNA pool expression have been associated with differentiation of CD4⁺ T cells toward an inflammatory phenotype and with loss of self-tolerance in autoimmune diseases. Vogt-Koyanagi-Harada (VKH) disease is a chronic multisystemic pathology, affecting the uvea, inner ear, central nervous system, and skin. Several lines of evidence support an autoimmune etiology for VKH, with loss of tolerance against retinal pigmented epithelium-related self-antigens. This deleterious reaction is characterized by exacerbated inflammation, due to an aberrant TH1 and TH17 polarization and secretion of their proinflammatory hallmark cytokines interleukin 6 (IL-6), IL-17, interferon γ , and tumor necrosis factor α , and an impaired CD4⁺ CD25^{high} FoxP3⁺ regulatory T cell function. To restrain inflammation, VKH is pharmacologically treated with corticosteroids and immunosuppressive drugs as first and second line of therapy, respectively. Changes in the expression of miRNAs related to immunoregulatory pathways have been associated with VKH development, whereas some genetic variants of miRNAs have been found to be risk modifiers of VKH. Furthermore, the drugs commonly used in VKH treatment have great influence on miRNA expression, including those miRNAs associated to VKH disease. This relationship between response to therapy and

miRNA regulation suggests that these small noncoding molecules might be therapeutic targets for the development of more effective and specific pharmacological therapy for VKH. In this review, we discuss the latest evidence regarding regulation and alteration of miRNA associated with VKH disease and its treatment.

GRAEFES ARCH CLIN EXP OPHTHALMOL. 2021 OCT;259(10):2905-2911. DOI: 10.1007/S00417-021-05166-4.

ASSOCIATION OF RETINAL DETACHMENT WITH AGE 50 YEARS OR YOUNGER AT ONSET IN PATIENTS WITH ACUTE RETINAL NECROSIS
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Background: Due to the guarded prognosis of acute retinal necrosis (ARN), it is relevant to develop a strategy to early categorize those patients in a higher risk of worse outcomes. The purpose of this study is to describe clinical features and predictive factors for retinal detachment (RD) in patients with ARN. Methods: Retrospective observational case series of 34 adult patients (38 eyes) with ARN examined between January 2005 and July 2015 in the National Eye Institute (Bethesda, USA), the Department of Ophthalmology, University of Chile (Santiago, Chile), and APEC (CDMX, Mexico). Results: A total of 16 males and 18 females with a mean age at presentation of 44.5 ± 16.8 years were included. Twenty-seven patients (79.4%) received intravenous acyclovir as first-line treatment, and 7 patients received either oral antiviral (4 patients) or oral plus intravitreal antiviral (3 patients). All subjects were treated with prednisone, with a mean initial dose of 57.7 ± 16.3 mg per day. Seventeen patients (50.0%) developed retinal detachment. An association of retinal detachment with age at onset was observed ($p = 0.04$), with patients younger than 50 years presenting a higher risk ($OR = 14.86$, $p = 0.0009$). Additionally, patients in this higher risk group had more inflammation in both anterior chamber and vitreous ($p = 0.04$ and 0.03 , respectively). No other predictive factor for retinal detachment was found in the present study. Conclusions: RD represents an important complication in patients with ARN. Younger patients may be at higher risk of this complication, possibly secondary to the presence of a higher level of inflammation.

SERVICIO DE OTORRINOLARINGOLOGÍA

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PREVALENCE, RISK FACTORS AND CAUSES OF HEARING LOSS AMONG ADULTS 50 YEARS AND OLDER IN SANTIAGO, CHILE: RESULTS FROM A RAPID ASSESSMENT OF HEARING LOSS SURVEY

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Objective. Among a representative sample of adults aged 50 years and older to (i) determine the prevalence of hearing loss, (ii) evaluate probable causes and risk factors of hearing loss, and (iii) assess the association between hearing loss measured by audiometry and self-report. Design. A population-based survey of adults aged 50 and older in Santiago, Chile using the Rapid Assessment of Hearing Loss (RAHL) survey. Study sample. 538 participants completed a questionnaire, which included questions on socio-demographic and health characteristics and self-reported hearing loss. Hearing and possible cause of hearing loss was assessed using pure tone audiometry (0.5–4.0 kHz), tympanometry, and otoscopy. Results. The prevalence of any level of hearing loss in adults aged 50 years and older was 41% (95% CI 33.2, 49.2). In terms of aetiologies, 89.3% of ears with mild or worse hearing loss were classified as sensorineural. Otoscopy was abnormal in 10.7% of subjects with impacted earwax being the most common finding (4.4%) followed by chronic otitis media (3.5%). Hearing aid usage was 16.6%. Older age, lower socioeconomic position, lack of education, and solvent exposure were significantly associated with hearing loss. Conclusion. Hearing loss among individuals aged over 50 years was common in Santiago, Chile.

FRONT NEUROSCI. 2021 DEC 9;15:759219. DOI: 10.3389/FNINS.2021.759219. ECOLLECTION 2021.

THE STRENGTH OF THE MEDIAL OLIVOCOCHLEAR REFLEX IN CHINCHILLAS IS ASSOCIATED WITH DELAYED RESPONSE PERFORMANCE IN A VISUAL DISCRIMINATION TASK WITH VOCALIZATIONS AS DISTRACTORS

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The ability to perceive the world is not merely a passive process but depends on sensorimotor loops and interactions that guide and actively bias our sensory systems. Understanding which and how cognitive processes participate in this active sensing is still an open question. In this context, the auditory system presents itself as an attractive model for this purpose as it features an efferent control network that projects from the cortex to subcortical nuclei and even to the sensory epithelium itself. This efferent system can regulate the cochlear amplifier sensitivity through medial olivocochlear (MOC) neurons located in the brainstem. The ability to suppress irrelevant sounds during selective attention to visual stimuli is one of the functions that have been attributed to this system. MOC neurons are also directly activated by sounds through a brainstem reflex circuit, a response linked to the ability to suppress auditory stimuli during visual attention. Human studies have suggested that MOC neurons are also recruited by other cognitive functions, such as working memory and predictability. The aim of this research was to explore whether cognitive processes related to delayed responses in a visual discrimination task were associated with MOC function. In this behavioral condition, chinchillas held their responses for more than 2.5 s after visual stimulus offset, with and without auditory distractors, and the accuracy of these responses was correlated with the magnitude of the MOC reflex. We found that the animals' performance decreased in presence of auditory distractors and that the results observed in MOC reflex could predict this performance. The individual MOC strength

correlated with behavioral performance during delayed responses with auditory distractors, but not without them. These results in chinchillas, suggest that MOC neurons are also recruited by other cognitive functions, such as working memory.

J NEUROPHYSIOL. 2021 JUN 1;125(6):2309-2321. DOI: 10.1152/JN.00032.2020.

THE MEDIAL OLIVOCOCHLEAR REFLEX STRENGTH IS MODULATED DURING A VISUAL WORKING MEMORY TASK

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Top-down modulation of sensory responses to distracting stimuli by selective attention has been proposed as an important mechanism by which our brain can maintain relevant information during working memory tasks. Previous works in visual working memory (VWM) have reported modulation of neural responses to distracting sounds at different levels of the central auditory pathways. Whether these modulations occur also at the level of the auditory receptor is unknown. Here, we hypothesize that cochlear responses to irrelevant auditory stimuli can be modulated by the medial olivocochlear system during VWM. Twenty-one subjects (13 males, mean age 25.3 yr) with normal hearing performed a visual change detection task with different VWM load conditions (high load = 4 visual objects; low load = 2 visual objects). Auditory stimuli were presented as distractors and allowed the measurement of distortion product otoacoustic emissions (DPOAEs) and scalp auditory evoked potentials. In addition, the medial olivocochlear reflex strength was evaluated by adding contralateral acoustic stimulation. We found larger contralateral acoustic suppression of DPOAEs during the visual working memory period (n = 21) compared with control experiments (n = 10), in which individuals were passively exposed to the same experimental conditions. These results show that during the visual working memory period there is a modulation of the medial olivocochlear reflex strength, suggesting a possible common mechanism for top-down filtering of auditory responses during cognitive processes. **NEW & NOTEWORTHY** The auditory efferent system has been proposed to function as a biological filter of cochlear responses during selective attention. Here, we recorded electroencephalographic activity and otoacoustic emissions in response to auditory distractors during a visual working memory task in humans. We found that the olivocochlear efferent activity is modulated during the visual working memory period suggesting a common mechanism for suppressing cochlear responses during selective attention and working memory.

EUR ANN OTORHINOLARYNGOL HEAD NECK DIS. 2021 SEP 21;S1879-7296(21)00217-9. DOI: 10.1016/J.ANORL.2021.07.010.

CENTRAL NYSTAGMUS AND ALTERATIONS IN VESTIBULAR TESTS DUE TO AN INADVERTENT GENTAMICIN ADMINISTRATION INTO SPINAL SPACE: A CARE CASE REPORT

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Introduction: Gentamicin has a well-known potential for damaging the peripheral vestibular organs. However, it is considered to be innocuous to the CNS as it crosses the blood-brain barrier poorly. Here, we describe central neuro-otological abnormalities developed by a patient after deployment of gentamicin into his spinal space. Case summary: A 61-year-old male unintentionally received gentamicin during spinal locoregional anesthesia for a urological procedure. During the first 48 hours the patient presented upper extremity dysmetria, dysarthria, and bilateral abducens nerve paralysis from which he recovered completely. He remained asymptomatic from day 3 to 10 after the incident. On day 11 he presented an acute vestibular syndrome. Severe bilateral vestibulopathy was confirmed by means of video head impulse testing. From day 14 onwards, he presented a persistent horizontal left-beating nystagmus, showing no variation or signs of compensation after 14 months, not responding to intensive vestibular rehabilitation or vestibular suppressant drugs. During follow-up, intercurrent gaze-evoked/direction-changing nystagmus has been recorded in various opportunities. Discussion: We interpreted these findings as signs of both severe peripheral bilateral vestibulopathy and cerebellar and/or midbrain late-onset neurotoxicity, which can be explained by the intrinsic neurotoxic capability of high doses of gentamicin in the CNS.

DEPARTAMENTO DE PSIQUIATRÍA Y SALUD MENTAL

PLOS ONE. 2021 FEB 19;16(2):E0246998. DOI: 10.1371/JOURNAL.PONE.0246998. ECOLLECTION 2021.

PERCEIVED DISCRIMINATION AND CONTEXTUAL PROBLEMS AMONG CHILDREN AND ADOLESCENTS IN NORTHERN CHILE

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Discriminatory behaviors among inter-ethnic relations in schools have long been noted and studied, but there are several correlations between discriminatory behaviors and other constructs that need further investigation. As an example, the relation between perceived discrimination and contextual problems-which include family, school and peer problems-among children and adolescents in Latin America has received little attention from previous studies. Further, the mediating role of ethnic identification and collective self-esteem in this relation also needs to be considered as they could be proven as protective factors for discriminatory behavior and its outcomes. Therefore, this study aimed to, first, establish the relationship between perceived discrimination and contextual problems in inter-ethnic students aged 8-19 years living in Arica, Chile; and second, to identify the role that ethnic identification and collective self-esteem play within this relation. In order to investigate this matter, a cross-sectional study was carried out with 3700 students in 29 schools between the fourth year of primary education and the last year of secondary education, aged between 9-18 years, with 48.4% men and 51.6% women. The sample was divided into primary and secondary school groups. The scales utilized were the Everyday Discrimination Scale, Multi-Group Ethnic Identity Measure-Revised Scale, Collective Self-Esteem Scale and

the dimensions of contextual family, school and peer problems, as well as the general index of contextual problems of the Child and Adolescent Assessment System. For data analysis, we tested a path analytic model at both the within and between levels to account for the relations between variables. In each group the models obtained an optimal fit. We found that perceived discrimination and ethnic identification were directly related to contextual problems (.23-.39), and collective self-esteem had only a mediating role. This study showed that strategized interventions focusing on ethnic identification and perceived discrimination should be utilized by schools to create a better developing environment.

J CLIN PSYCHIATRY. 2021 JAN 12;82(1):19M13136. DOI: 10.4088/JCP.19M13136.

CITALOPRAM FOR ACUTE AND PREVENTIVE EFFICACY IN BIPOLAR DEPRESSION (CAPE-BD): A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Objective: To assess the efficacy and safety of citalopram in the acute and maintenance phases of bipolar depression in a randomized, double-blind, placebo-controlled trial. Methods: Between 2007 and 2014, 119 subjects with acute major depressive episodes diagnosed with DSM-IV bipolar disorder, type I or type II, were randomized blindly to citalopram or placebo, added to standard mood stabilizers. They were followed for 6 weeks for acute efficacy (primary outcome) and up to 1 year for maintenance efficacy (secondary outcome) using scores on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Mania Rating Scale of the Schedule for Affective Disorders and Schizophrenia (MRS-SADS). The study was powered for a clinically meaningful effect size. Results: Mean \pm SD MADRS scores changed from a baseline value of 27.4 ± 9.1 to 13.1 ± 8.4 at the end of the acute phase for citalopram versus a change from 27.4 ± 7.3 to 15.2 ± 9.9 for placebo, a clinically and statistically nonsignificant difference. Maintenance efficacy also was not better with citalopram than with placebo. Acute manic/hypomanic episodes were similar in both groups, and subjects with type II illness did not have better outcomes than subjects with type I illness. In maintenance treatment, MRS-SADS scores were greater overall, especially in subjects with a rapid-cycling illness course, with citalopram versus placebo. Conclusions: Citalopram, added to standard mood stabilizers, did not have clinically meaningful benefit versus placebo for either acute or maintenance treatment of bipolar depression. Acute mania did not worsen with citalopram, but maintenance treatment led to worsened manic symptoms, especially in subjects with a rapid-cycling course.

FRONT PSYCHIATRY. 2021 APR 26;12:650706. DOI: 10.3389/FPSYT.2021.650706. ECOLLECTION 2021.

EARLY ADVERSE STRESS AND DEPRESSIVE AND BIPOLAR DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF TREATMENT INTERVENTIONS

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Introduction: A significant proportion of adults with depressive or bipolar disorders exposed to early adverse stressors do not adequately respond to standard treatments. This review aimed at synthesizing the evidence on the effectiveness of treatment interventions for depressive or bipolar disorders in adult individuals (aged 18 years or more) exposed to adverse stress early in life. Methods: Systematic review and meta-analysis including experimental and quasi-experimental published studies indexed in CINAHL, EMBASE, PubMed, and Web of Science databases and/or in reference lists. Data management and critical appraisal (with the Study Quality Assessment Tools) was conducted independently by multiple researchers. A quality-effects model for meta-analysis was used for data synthesis and publication bias was assessed using the Doi plot and LFK index. The main outcome was short-term reductions in depressive symptoms. Results: Eight randomized controlled trials, three controlled before-and-after (pre-post) studies, and three uncontrolled before-and-after studies were included. Studies lacked bipolar disorder patients. Unclear randomization procedures and reporting of blinded outcome assessor, and limited use of intention-to-treat analysis, were relevant potential sources of bias. Meta-analyses indicated that psychological, pharmacological, and combined interventions were effective in reducing depressive symptoms in the short- (Cohen's $d = -0.55$, 95% CI -0.75 to -0.36 , $I^2 = 0\%$) and mid-term (Cohen's $d = -0.66$, 95% CI -1.07 to -0.25 , $I^2 = 65.0\%$). However, a high risk of publication bias was detected for these outcomes. A small number of studies, with mixed results, reported interventions with long-term improvements in depressive symptomatology, and short- and mid-term response to treatment and remission. Conclusion: Despite the well-documented long-lasting, negative, and costly impact of early adverse stressors on adult psychopathology, evidence on treatment alternatives remains scant. Trauma-focused treatment interventions—whether psychological interventions alone or in combination with pharmacotherapy—may have the potential to reduce the severity of depressive symptom in adults who were exposed to early adverse stress. Findings must be interpreted with considerable caution, as important study and outcome-level limitations were observed and gray literature was not considered in this systematic review and meta-analysis.

INT J ENVIRON RES PUBLIC HEALTH. 2021 SEP 13;18(18):9628. DOI: 10.3390/IJERPH18189628.

FEASIBILITY AND ACCEPTABILITY OF “CUIDA TU ÁNIMO” (TAKE CARE OF YOUR MOOD): AN INTERNET-BASED PROGRAM FOR PREVENTION AND EARLY INTERVENTION OF ADOLESCENT DEPRESSION IN CHILE AND COLOMBIA

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The rapid internet penetration in Latin American countries has made it possible to implement digital mental health interventions. “Cuida tu Ánimo” (Take Care of Your Mood) is an internet-based program for the prevention and early intervention of depression in adolescents. A pilot study was conducted in Chile and Colombia to study the feasibility and acceptability of the program and estimate its effects. There were 199 participants (53.3% women; mean age = 14.8 years, SD = 1.0) recruited from two schools in Chile and two schools in Colombia. Qualitative

and quantitative methods were applied for data collection and analyses. Although the levels of acceptance were moderate to high across all variables, adherence was lower than expected. The participants deemed important for an intervention of this type offered a higher level of interaction with team members through internet-based and face-to-face activities. Post-intervention outcomes show a reduction in depressive and anxious symptoms in adolescents in Chile, while there were no significant changes in the level of symptomatology in adolescents in Colombia. The women used the program more than the men. Results show the need to improve the intervention by increasing its levels of customization and developing strategies to achieve better adherence. The contradictory results of the program in Chile and Colombia suggest the importance of other variables beyond the content of the intervention, such as the setting or context of the intervention.

MOL PSYCHIATRY. 2021 AUG;26(8):4496-4510. DOI: 10.1038/S41380-020-0654-3.

GENETIC CONTRIBUTORS TO RISK OF SCHIZOPHRENIA IN THE PRESENCE OF A 22Q11.2 DELETION

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Schizophrenia occurs in about one in four individuals with 22q11.2 deletion syndrome (22q11.2DS). The aim of this International Brain and Behavior 22q11.2DS Consortium (IBBC) study was to identify genetic factors that contribute to schizophrenia, in addition to the ~20-fold increased risk conveyed by the 22q11.2 deletion. Using whole-genome sequencing data from 519 unrelated individuals with 22q11.2DS, we conducted genome-wide comparisons of common and rare variants between those with schizophrenia and those with no psychotic disorder at age ≥ 25 years. Available microarray data enabled direct comparison of polygenic risk for schizophrenia between 22q11.2DS and independent population samples with no 22q11.2 deletion, with and without schizophrenia (total $n = 35,182$). Polygenic risk for schizophrenia within 22q11.2DS was significantly greater for those with schizophrenia ($p_{adj} = 6.73 \times 10^{-6}$). Novel reciprocal case-control comparisons between the 22q11.2DS and population-based cohorts showed that polygenic risk score was significantly greater in individuals with psychotic illness, regardless of the presence of the 22q11.2 deletion. Within the 22q11.2DS cohort, results of gene-set analyses showed some support for rare variants affecting synaptic genes. No common or rare variants within the 22q11.2 deletion region were significantly associated with schizophrenia. These findings suggest that in addition to the deletion conferring a greatly increased risk to schizophrenia, the risk is higher when the 22q11.2 deletion and common polygenic risk factors that contribute to schizophrenia in the general population are both present.

DEPRESS ANXIETY. 2021 APR;38(4):431-438. DOI: 10.1002/DA.23144.

THE CONTRIBUTION OF EARLY ADVERSE STRESS TO COMPLEX AND SEVERE DEPRESSION IN DEPRESSED OUTPATIENTS

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Background To assess whether linear effects or threshold effects best describe the association between early adverse stress (EAS) and complex and severe depression (i.e., depression with treatment resistance, psychotic symptoms, and/or suicidal ideation), and to examine the attributable risk of complex and severe depression associated with EAS. **Methods** A cross-sectional study was conducted using deidentified clinical data (on demographics, presence of complex and severe depression, and exposure to seven types of EAS) from 1,013 adults who were seen in an outpatient mental health clinic in Santiago, Chile, for a major depressive episode. Multivariate logistic regressions were fitted to estimate odds ratios (ORs), using a bootstrap approach to compute 95% bias-corrected confidence intervals (95% BC CIs). A detailed examination of the cumulative risk score and calculations of the attributable risk was conducted. **Results** Exposure to at least five EASs was reported by 3.6% of the sample. In the multivariate logistic regression models, there was a marked increase in the odds of having complex and severe depression associated with exposure to at least five EASs (OR = 4.24; 95% BC CI: 1.25 to 9.09), according to a threshold effect. The attributable risk of complex and severe depression associated with exposure to at least one EAS was 36.8% (95% BC CI: 17.7 to 55.9). **Conclusions** High levels of EAS distinctively contribute to complex clinical presentations of depression in adulthood. Patients with complex clinical presentations of depression and history of EAS should need a differentiated treatment approach, particularly those having high levels of EAS.

FRONT NEUROL. 2021 SEP 6;12:710332. DOI: 10.3389/FNEUR.2021.710332. ECOLLECTION 2021.

FRONTOTEMPORAL DEMENTIAS IN LATIN AMERICA: HISTORY, EPIDEMIOLOGY, GENETICS, AND CLINICAL RESEARCH

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Introduction: The historical development, frequency, and impact of frontotemporal dementia (FTD) are less clear in Latin America than in high-income countries. Although there is a growing number of dementia studies in Latin America, little is known collectively about FTD prevalence studies by country, clinical heterogeneity, risk factors, and genetics in Latin American countries. **Methods:** A systematic review was completed, aimed at identifying the frequency, clinical heterogeneity, and genetics studies of FTD in Latin American populations. The search strategies used a combination of standardized terms for FTD and related disorders. In addition, at least one author per Latin American country summarized the available literature. Collaborative or regional studies were reviewed during consensus meetings. **Results:** The first FTD reports published in Latin America were mostly case reports. The last two decades marked a substantial increase in the number of FTD research in Latin American countries. Brazil (165), Argentina (84), Colombia (26), and Chile (23) are the countries with the larger numbers of

FTD published studies. Most of the research has focused on clinical and neuropsychological features (n = 247), including the local adaptation of neuropsychological and behavioral assessment batteries. However, there are little to no large studies on prevalence (n = 4), biomarkers (n = 9), or neuropathology (n = 3) of FTD. Conclusions: Future FTD studies will be required in Latin America, albeit with a greater emphasis on clinical diagnosis, genetics, biomarkers, and neuropathological studies. Regional and country-level efforts should seek better estimations of the prevalence, incidence, and economic impact of FTD syndromes.

J AFFECT DISORD. 2022 JAN 15;297:381-385. DOI: 10.1016/J.JAD.2021.10.014.

STRUCTURAL GENDER INEQUALITIES AND SYMPTOMS OF POSTPARTUM DEPRESSION IN 40 COUNTRIES

Pablo Martínez, José Ignacio Nazif-Munoz, Graciela Rojas, Irene Magaña

Background: The role of structural gender inequality in macro-level differences in women's perinatal mental health remains largely unexplored. This short communication explores structural gender inequalities and their potential as a macro-level, upstream social determinant of postpartum depression (PPD). Methods: We compiled meta-analytically derived national-level prevalence estimates of PPD symptoms - based on the Edinburgh Postnatal Depression Scale - with economic (e.g., income inequality), health (e.g., infant mortality rate), sociodemographic (e.g., urban population), and structural gender inequality variables (e.g., abortion policies) for 40 countries. Meta-regression techniques and traditional p-value based stepwise procedures, complemented with a Bayesian model averaging approach, were used for a robust selection of variables associated with national-level PPD symptom prevalence. Results: Income inequality ($\beta = 0.04$, 95% CI = 0.02 to 0.07) and abortion policies ($\beta = 0.02$, 95% CI = 0.00 to 0.03) were the only variables selected in the final, adjusted model, accounting for 60.7% of cross-national variations in PPD symptoms. Limitations: Study quality of primary studies was not assessed and some national-level meta-analytical estimates were based on few primary studies. A fifth of world countries and territories could be included, with high-income regions overrepresented. High rate of missing national-level data for potential predictors of PPD. Cross-sectional analyses precludes causal inferences. Conclusions: Abortion policies are a significant macro-level social determinant of PPD, and its liberalization might be associated with women's mental health at a population level. Our findings should be a relevant argument for clinicians to advocate for changing discriminatory social norms against women.

AGING MENT HEALTH. 2021 AUG 11;1-22. DOI: 10.1080/13607863.2021.1958145.

IMPACT OF SOCIAL ISOLATION AND COPING STRATEGIES IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT DURING THE COVID-19 PANDEMIC: A QUALITATIVE STUDY

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Objectives: The objective of this study was to explore the experiences and feelings of older adults with MCI during the COVID-19 outbreak in Chile and to know what strategies they used to overcome social isolation. Method: A qualitative design was used. Ten participants with a diagnosis of MCI took part in this study. All interviews were recorded and coded using thematic analysis. Results: The thematic analysis identified three themes related to the quarantine experience of older adults with MCI diagnosis: (1) Effects of social isolation during the COVID-19 pandemic (2) Beliefs, feelings and behaviors about the SARS-CoV-2 virus (3) Coping with social isolation/response to difficulties during the pandemic. It was found that older adults with MCI have been mainly psychologically and socially affected by social distancing and isolation, particularly individuals who were alone during COVID-19 outbreak. The only physical dimension negatively affected was the level of activity. Social isolation led to a significant number of negative emotions such as anger, fear of contracting the virus or possibility of contagion for their families, worries and sadness as well as emotional loneliness. It is noteworthy that the majority of participants have used several coping strategies during this challenging time. Conclusion: Since social isolation and a sedentary life have been associated with poorer cognition and functionality in people with MCI, a rational plan to both prevent the progression of cognitive decline and to increase social contact, is essential. Special attention must be drawn to maintaining people physically active at home and keeping their daily routine (within the possibilities) and also to ensure social connectedness through technology. Implementation of these measures could potentially reduce negative emotions during the pandemic.

FRONT PSYCHIATRY. 2021 DEC 24;12:745247. DOI: 10.3389/FPSYT.2021.745247. ECOLLECTION 2021.

EXPERT ARGUMENTS FOR TRENDS OF PSYCHIATRIC BED NUMBERS: A SYSTEMATIC REVIEW OF QUALITATIVE DATA

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Introduction: Mental health policies have encouraged removals of psychiatric beds in many countries. It is under debate whether to continue those trends. We conducted a systematic review of expert arguments for trends of psychiatric bed numbers. Methods: We searched seven electronic databases and screened 15,479 papers to identify expert opinions, arguments and recommendations for trends of psychiatric bed numbers, published until December 2020. Data were synthesized using thematic analysis and classified into arguments to maintain or increase numbers and to reduce numbers. Results: One hundred six publications from 25 countries were included. The most common themes arguing for reductions of psychiatric bed numbers were inadequate use of inpatient care, better integration of care and better use of community care. Arguments to maintain or increase bed numbers included high demand of psychiatric beds, high occupancy rates, increasing admission rates, criminalization of mentally ill, lack of community care and inadequately short length of stay. Cost effectiveness and quality of care were used as arguments for increase or decrease. Conclusions: The expert arguments presented here may guide and focus future debate on the required psychiatric bed numbers. The recommendations may help policymakers to define targets for psychiatric bed numbers. Arguments need careful local evaluation, especially when supporting opposite directions of trends in different contexts.

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A COLLABORATIVE, COMPUTER-ASSISTED, PSYCHO-EDUCATIONAL INTERVENTION FOR DEPRESSED PATIENTS WITH CHRONIC DISEASE AT PRIMARY CARE: PROTOCOL FOR A CLUSTER RANDOMIZED CONTROLLED TRIAL

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Background Depression and chronic diseases are frequently comorbid public health problems. However, clinical guidelines often fail to consider comorbidities. This study protocol describes a cluster randomized trial (CRT) aimed to compare the effectiveness of a collaborative, computer-assisted, psycho-educational intervention versus enhanced usual care (EUC) in the treatment of depressed patients with hypertension and/or diabetes in primary care clinics (PCC) in Santiago, Chile. **Methods** Two-arm, single-blind, CRT carried out at two municipalities in Santiago, Chile. Eight PCC will be randomly assigned (1:1 ratio within each municipality, 4 PCC in each municipality) to the INTERVENTION or EUC. A total of 360 depressed patients, aged at least 18 years, with Patient Health Questionnaire-9 Item (PHQ-9) scores ≥ 15 , and enrolled in the Cardiovascular Health Program at the participating PCC. Patients with alcohol/substance abuse; current treatment for depression, bipolar disorder, or psychosis; illiteracy; severe impairment; and resident in long-term care facilities, will be excluded. Patients in both arms will be invited to use the Web page of the project, which includes basic health education information. Patients in the INTERVENTION will receive eight sessions of a computer-assisted, psycho-educational intervention delivered by trained therapists, a structured telephone calls to monitor progress, and usual medical care for chronic diseases. Therapists will receive biweekly and monthly supervision by psychologist and psychiatrist, respectively. A monthly meeting will be held between the PCC team and a member of the research team to ensure continuity of care. Patients in EUC will receive depression treatment according to clinical guidelines and usual medical care for chronic diseases. **Outcome assessments** will be conducted at 3, 6, and 12 months after enrollment. The primary outcome will be depression improvement at 6 months, defined as $\geq 50\%$ reduction in baseline PHQ-9 scores. **Intention-to-treat analyses** will be performed. **Discussion** This study will be one of the first to provide evidence for the effectiveness of a collaborative, computer-assisted, psycho-educational intervention for depressed patients with chronic disease at primary care in a Latin American country.

SOC PSYCHIATRY PSYCHIATR EPIDEMIOL. 2021 FEB;56(2):315-323. DOI: 10.1007/S00127-020-01871-3.

1324 PRISON SUICIDES IN 10 COUNTRIES IN SOUTH AMERICA: INCIDENCE, RELATIVE RISKS, AND ECOLOGICAL FACTORS

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Purpose: Although suicide rates of prison populations and incidence factors have been reported for high-income countries, data from low- and middle-income regions are lacking. The purpose of the study was to estimate suicide rates among prison populations in South America, to examine prison-related factors, and to compare suicide rates between prison and general populations. **Methods:** In this observational study, we collected the numbers of suicides in prison, rates of prison occupancy, and incarceration rates from primary sources in South America between 2000 and 2017. We compared suicide rates among prisoners with incidence rates in the general populations by calculating incidence rate ratios. We assessed the effect of gender, year, incarceration rates and occupancy on suicide rates in the prison populations using regression analyses. **Results:** There were 1324 suicides reported during 4,437,591 person years of imprisonment between 2000 and 2017 in 10 South American countries. The mean suicide rate was 40 (95% CI 16-65) per 100,000 person years for male and female genders combined. The pooled incidence rate ratio of suicide between prison and general populations was 3.9 (95% CI 3.1-5.1) for both genders combined, 2.4 (95% CI 1.9-3.1) for men and a higher ratio in women (13.5, 95% CI 6.9-26.9). High occupancies of prisons were associated with lower incidence of suicide ($\beta = - .58$, 95% CI - 108.5 to - 7.1). **Conclusions:** Suicides during imprisonment in South America are an important public health problem. Suicide prevention strategies need to target prison populations.

SCI REP. 2021 NOV 3;11(1):21623. DOI: 10.1038/S41598-021-00873-8.

ABNORMAL NODAL AND GLOBAL NETWORK ORGANIZATION IN RESTING STATE FUNCTIONAL MRI FROM SUBJECTS WITH THE 22Q11 DELETION SYNDROME

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The 22q11 deletion syndrome is a genetic disorder associated with a high risk of developing psychosis, and is therefore considered a neurodevelopmental model for studying the pathogenesis of schizophrenia. Studies have shown that localized abnormal functional brain connectivity is present in 22q11 deletion syndrome like in schizophrenia. However, it is less clear whether these abnormal cortical interactions lead to global or regional network disorganization as seen in schizophrenia. We analyzed from a graph-theory perspective fMRI data from 40 22q11 deletion syndrome patients and 67 healthy controls, and reconstructed functional networks from 105 brain regions. Between-group differences were examined by evaluating edge-wise strength and graph theoretical metrics of local (weighted degree, nodal efficiency, nodal local efficiency) and global topological properties (modularity, local and global efficiency). Connectivity strength was globally reduced in patients, driven by a large network comprising 147 reduced connections. The 22q11 deletion syndrome network presented with abnormal local topological properties, with decreased local efficiency and reductions in weighted degree particularly in hub nodes. We found evidence for abnormal integration but intact segregation of the 22q11 deletion syndrome network. Results suggest that 22q11 deletion syndrome patients present with similar aberrant local network organization as seen in schizophrenia, and this network configuration might represent a vulnerability factor to psychosis.

EXP GERONTOL. 2021 NOV;155:111592. DOI: 10.1016/J.EXGER.2021.111592.

EFFECT OF A 40-WEEKS MULTICOMPONENT EXERCISE PROGRAM AND BRANCHED CHAIN AMINO ACIDS SUPPLEMENTATION ON FUNCTIONAL FITNESS AND MENTAL HEALTH IN FRAIL OLDER PERSONS

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Background The ageing process implies several physiological and psychological changes that hence affect the general health, mood states, and quality of life of older persons. Exercise and adequate nutrition are renowned non-pharmacological strategies that significantly delay and alleviate the adverse consequences of the ageing process. This study aimed to evaluate the effects of branched-chain amino acid (BCAA) supplementation and a multicomponent exercise program (ME) on the physical frailty and mood states of older persons. **Methods** 35 participants (women and men; 83 ± 3 years old) from residential care homes were submitted to a 40-week exercise-washout-retraining intervention (16 weeks of the elastic band based exercise and/or supplementation, 8 weeks of washout, and 16 weeks of multicomponent exercise and/or resupplementing), with or without BCAA supplementation. The experimental groups were: (i) ME plus BCAA supplementation (ME+BCAA); (ii) ME; (iii) BCAA supplementation (BCAA), and (iv) control group (CG). Fried's phenotype was used to assess frailty prevalence. Geriatric Depression Scale (GDS), Profile of Mood State (POMS), Mini-Mental State Examination (MMSE), were used to assess mental health and cognition. The Short Physical Performance Battery (SPPB) was used to assess functional capacity. Salivary testosterone levels (ST) were also determined to assess the anabolic effects of the intervention. **Results** Exercise was effective in improving functional capacity and prevented the increase in frailty that occurred in the non-exercising CG, where the frailty scores increased over time ($p < 0.01$). BCAAs supplement alone had no impact on functional fitness, but in a short time (16 weeks) contributed to diminishing frailty and combined with exercise may have the potential to reduce the effect of a detraining period on functional capacity. Salivary testosterone levels correlated with handgrip strength and could be a useful indicator of susceptibility to frailty. No effects were found for mood states, cognition, and depression. **Conclusion** This study showed that a long-term exercise program, independent of being multicomponent or strength elastic band-based, was effective in improving functional capacity and prevented an increase in frailty in frail and pre-frail older persons living in residential care homes.

EUR J PSYCHOTRAUMATOL. 2021 FEB 19;12(1):1874600. DOI: 10.1080/20008198.2021.1874600.

POPULATION-ATTRIBUTABLE RISK OF ADVERSE CHILDHOOD EXPERIENCES FOR HIGH SUICIDE RISK, PSYCHIATRIC ADMISSIONS, AND RECURRENT DEPRESSION, IN DEPRESSED OUTPATIENTS

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Background: Population-attributable risk (PAR) may help estimate the potential contribution of adverse childhood experiences (ACEs) to serious clinical presentations of depression, characterized by suicidality, previous psychiatric admissions, and episode recurrence. **Objective:** To determine the PAR of ACEs for serious clinical presentations of depression (high suicide risk, previous psychiatric admissions, and recurrent depression) in outpatients with ICD-10 clinical depression. **Method:** Systematic chart review of 1,013 adults who were assessed and/or treated in a mental health clinic in Santiago, Chile for a major depressive episode. Data were collected on demographics and clinical characteristics of depression. Exposure to ACEs was determined with the Brief Physical and Sexual Abuse Questionnaire, assessing seven types of ACEs. Multivariable logistic regression analysis was used to assess the association between exposure to ACEs and suicidality, previous psychiatric admissions, and recurrence. Predicted probabilities were used for calculations of PAR. **Results:** Of the 1,001 study participants with complete data, 53.3% had recurrent depression, 13.5% had high suicide risk, and 5.0% had previous psychiatric admissions. Exposure to at least one ACE was recorded for 69.0% of the sample. Exposure to at least one ACE and specific types of ACEs (i.e. childhood sexual abuse and traumatic separation from caregiver) were associated with serious clinical presentations of depression. A dose-response relationship was observed between cumulative exposure to ACEs and the most serious clinical presentations of depression. ACEs were attributed to a significant proportion of disease: 61.6% of previous psychiatric admissions, 45.0% of high suicide risk, and 14.5% of recurrent depression. **Conclusions:** A substantial proportion of serious clinical presentations of depression among outpatients are associated with ACEs. Early detection of depressive episodes associated with ACEs, and tailored treatment for these patients, may potentially reduce the incidence of serious complications in this population.

SCHIZOPHR BULL. 2021 DEC 21;SBAB139. DOI: 10.1093/SCHBUL/SBAB139.

FUNCTIONAL DYSCONNECTIVITY IN VENTRAL STRIATOCORTICAL SYSTEMS IN 22Q11.2 DELETION SYNDROME

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22q11.2 deletion syndrome (22q11.2DS) is a genetic neurodevelopmental disorder that represents one of the greatest known risk factors for psychosis. Previous studies in psychotic subjects without the deletion have identified a dopaminergic dysfunction in striatal regions, and dysconnectivity of striatocortical systems, as an important mechanism in the emergence of psychosis. Here, we used resting-state functional MRI to examine striatocortical functional connectivity in 22q11.2DS patients. We used a 2×2 factorial design including 125 subjects (55 healthy controls, 28 22q11.2DS patients without a history of psychosis, 10 22q11.2DS patients with a history of psychosis, and 32 subjects with a history of psychosis without the deletion), allowing us to identify network effects related to the deletion and to the presence of psychosis. In line with previous results from psychotic patients without 22q11.2DS, we found that there was a dorsal to ventral gradient of hypo- to

hyperstriatocortical connectivity related to psychosis across both patient groups. The 22q11.2DS was additionally associated with abnormal functional connectivity in ventral striatocortical networks, with no significant differences identified in the dorsal system. Abnormalities in the ventral striatocortical system observed in these individuals with high genetic risk to psychosis may thus reflect a marker of illness risk.

INT J ENVIRON RES PUBLIC HEALTH. 2021 NOV 15;18(22):12000. DOI: 10.3390/IJERPH182212000.

TECHNOLOGY-ASSISTED COLLABORATIVE CARE PROGRAM FOR PEOPLE WITH DIABETES AND/OR HIGH BLOOD PRESSURE ATTENDING PRIMARY HEALTH CARE: A FEASIBILITY STUDY

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The comorbidity of depression with physical chronic diseases is usually not considered in clinical guidelines. This study evaluated the feasibility of a technology-assisted collaborative care (TCC) program for depression in people with diabetes and/or high blood pressure (DM/HBP) attending a primary health care (PHC) facility in Santiago, Chile. Twenty people diagnosed with DM/HBP having a Patient Health Questionnaire-9 score \geq 15 points were recruited. The TCC program consisted of a face-to-face, computer-assisted psychosocial intervention (CPI, five biweekly sessions), telephone monitoring (TM), and a mobile phone application for behavioral activation (CONEMO). Assessments of depressive symptoms and other health-related outcomes were made. Thirteen patients completed the CAPI, 12 received TM, and none tried CONEMO. The TCC program was potentially efficacious in treating depression, with two-thirds of participants achieving response to depression treatment 12 weeks after baseline. Decreases were observed in depressive symptoms and healthcare visits and increases in mental health-related quality of life and adherence to treatment. Patients perceived the CPI as acceptable. The TCC program was partially feasible and potentially efficacious for managing depression in people with DM/HBP. These data are valuable inputs for a future randomized clinical trial

LANCET REG HEALTH EUR. 2021 JUN 5;7:100137. DOI: 10.1016/J.LANEPE.2021.100137. ECOLLECTION 2021 AUG.

CHANGES IN NATIONAL RATES OF PSYCHIATRIC BEDS AND INCARCERATION IN CENTRAL EASTERN EUROPE AND CENTRAL ASIA FROM 1990-2019: A RETROSPECTIVE DATABASE ANALYSIS

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Background: Numbers of psychiatric beds (general, forensic, and residential) and prison populations have been considered to be indicators of institutionalisation of people with mental illnesses. The present study aimed to assess changes of those indicators across Central Eastern Europe and Central Asia (CEECA) over the last three decades to capture how care has developed during that historical period. Methods: We retrospectively obtained data on numbers of psychiatric beds and prison populations from 30 countries in CEECA between 1990 and 2019. We calculated the median of the percent changes between the first and last available data points for all CEECA and for groups of countries based on former political alliances and income levels. Findings: Primary national data were retrieved from 25 out of 30 countries. Data from international registries were used for the remaining five countries. For all of CEECA, the median decrease of the general psychiatric bed rates was 33•8% between 1990 and 2019. Median increases were observed for forensic psychiatric beds (24•7%), residential facility beds (12•0%), and for prison populations (36•0%). Greater reductions of rates of psychiatric beds were observed in countries with lower per capita income as well as in countries that were formerly part of the Soviet Union. Seventeen out of 30 countries showed inverse trends for general psychiatric beds and prison populations over time, indicating a possible shift of institutionalisation towards correctional settings. Interpretation: Most countries had decreased rates of general psychiatric beds, while there was an increase of forensic capacities. There was an increase in incarceration rates in a majority of countries. The large variation of changes underlines the need for policies that are informed by data and by comparisons across countries.

SLEEP. 2021 DEC 28;ZSAB300. DOI: 10.1093/SLEEP/ZSAB300.

ANALYSIS OF REM SLEEP WITHOUT ATONIA IN 22Q11.2 DELETION SYNDROME DETERMINED BY DOMICILIARY POLYSOMNOGRAPHY: A CROSS SECTIONAL STUDY

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Study Objectives Our aim is to evaluate the presence of REM sleep without atonia (RWA), the objective hallmark of REM sleep Behaviour Disorder (RBD), as prodromal marker of Parkinson's disease (PD), in an adult cohort of 22q11.2 deletion syndrome (22qDS). Methods Sleep quality was assessed by means of Pittsburgh quality scale index (PSQI), and RBD symptoms by means of RBD questionnaire-Hong-Kong (RBDQ-HK). Attended domiciliary video-Polysomnography (v-PSG) were performed in 26 adults (18–51 years, 14 females) 22qDS patients. Electromyogram during REM sleep was analyzed by means of SINBAR procedure at 3-second time resolution (miniepochs). Results An overall poor sleep quality was observed in the cohort and high RBDQ-HK score in 7 of the 26 patients, two additional patients with positive dream enactment reported by close relatives had low score of RBDQ-HK. Nevertheless, SINBAR RWA scores were lower than cut-off threshold for RWA (mean 5.5%, range 0–12.2%). TST and the percentage of light sleep (N1) were increased, with preserved proportions of N2 and N3. Participants reported poor quality of sleep (mean PSQI > 5), with prolonged sleep latency in the v-PSG. No subjects exhibit evident dream enactment episodes during recording sessions. Conclusions RWA was absent in the studied cohort of 22qDS adult volunteers according to validated polysomnographic criteria. High RBDQ-HK scores do not correlate with v-PSG results among 22qDS individuals.

FRONT PSYCHIATRY. 2021 JUN 16;12:662407. DOI: 10.3389/FPSYT.2021.662407. ECOLLECTION 2021.

BDNF AS A BIOMARKER OF COGNITION IN SCHIZOPHRENIA/PSYCHOSIS: AN UPDATED REVIEW

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Brain Derived Neurotrophic Factor (BDNF) has been linked to cognitive symptoms of schizophrenia, which has been documented in previous reviews by several authors. However, a trend has recently emerged in this field moving from studying schizophrenia as a disease to studying psychosis as a group. This review article focuses on recent BDNF studies in relation to cognition in human subjects during different stages of the psychotic process, including subjects at high risk of developing psychosis, patients at their first episode of psychosis, and patients with chronic schizophrenia. We aim to provide an update of BDNF as a biomarker of cognitive function on human subjects with schizophrenia or earlier stages of psychosis, covering new trends, controversies, current research gaps, and suggest potential future developments in the field. We found that most of current research regarding BDNF and cognitive symptoms in psychosis is done around schizophrenia as a disease. Therefore, it is necessary to expand the study of the relationship between BDNF and cognitive symptoms to psychotic illnesses of different stages and origins.

ACTA PSYCHIATR SCAND. 2021 SEP;144(3):259-276. DOI: 10.1111/ACPS.13312.

POLYPHARMACY AS MAINTENANCE TREATMENT IN BIPOLAR ILLNESS: A SYSTEMATIC REVIEW

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Objectives Polypharmacy is common in maintenance treatment of bipolar illness, but proof of greater efficacy compared to monotherapy is assumed rather than well known. We systematically reviewed the evidence from the literature to provide recommendations for clinical management and future research. Method A systematic review was conducted on the use of polypharmacy in bipolar prophylaxis. Relevant papers published in English through 31 December 2019 were identified searching the electronic databases MEDLINE, Embase, PsycINFO, and the Cochrane Library. Results Twelve studies matched inclusion criteria, including 10 randomized controlled trials (RCTs). The best drug combination in prevention is represented by lithium + valproic acid which showed a significant effect on time to mood relapses (HR = 0.57) compared to valproic acid monotherapy, especially for manic episodes (HR = 0.51). The effect was significant in terms of time to new drug treatment (HR = 0.51) and time to hospitalization (HR = 0.57). A significant reduction in the frequency of mood relapses was also reported for lithium + valproic acid vs. lithium monotherapy (RR=0.12); however, the trial had a small sample size. Lamotrigine + valproic acid reported significant efficacy in prevention of depressive episodes compared to lamotrigine alone. Conclusions The literature to support a generally greater efficacy with polypharmacy in bipolar illness is scant and heterogeneous. Within that limited evidence base, the best drug combination in bipolar prevention is represented by lithium + valproic acid for manic, but not depressive episodes. Clinical practice should focus more on adequate monotherapy before considering polypharmacy.

NEUROPSYCHOPHARMACOLOGY. 2021 JAN;46(2):455-461. DOI: 10.1038/S41386-020-00838-X.

PREDICTING CHANGE IN DIAGNOSIS FROM MAJOR DEPRESSION TO BIPOLAR DISORDER AFTER ANTIDEPRESSANT INITIATION

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We aimed to develop and validate classification models able to identify individuals at high risk for transition from a diagnosis of depressive disorder to one of bipolar disorder. This retrospective health records cohort study applied outpatient clinical data from psychiatry and nonpsychiatry practice networks affiliated with two large academic medical centers between March 2008 and December 2017. Participants included 67,807 individuals with a diagnosis of major depressive disorder or depressive disorder not otherwise specified and no prior diagnosis of bipolar disorder, who received at least one of the nine antidepressant medications. The main outcome was at least one diagnostic code reflective of a bipolar disorder diagnosis within 3 months of index antidepressant prescription. Logistic regression and random forests using diagnostic and procedure codes as well as sociodemographic features were used to predict this outcome, with discrimination and calibration assessed in a held-out test set and then a second academic medical center. Among 67,807 individuals who received at least one antidepressant medication, 925 (1.36%) subsequently received a diagnosis of bipolar disorder within 3 months. Models incorporating coded diagnoses and procedures yielded a mean area under the receiver operating characteristic curve of 0.76 (ranging from 0.73 to 0.80). Standard supervised machine learning methods enabled development of discriminative and transferable models to predict transition to bipolar disorder. With further validation, these scores may enable physicians to more precisely calibrate follow-up intensity for high-risk patients after antidepressant initiation.

SERVICIO DE TRAUMATOLOGÍA

J KNEE SURG. 2021 SEP 10. DOI: 10.1055/S-0041-1735312.

GONYAUTOXINS 2/3 LOCAL PERIARTICULAR INJECTION FOR PAIN MANAGEMENT AFTER TOTAL KNEE ARTHROPLASTY: A DOUBLE-BLIND, RANDOMIZED STUDY

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The purpose of this study was to compare the efficacy of periarticular infiltration of gonyautoxin 2/3 (GTX 2/3) and a mixture of levobupivacaine, ketorolac, and epinephrine for pain management after total knee arthroplasty (TKA). Forty-eight patients were randomly allocated to receive periarticular infiltration of 40 µg GTX 2/3 (n = 24) diluted in 30 mL of sodium chloride 0.9% (study group) or a combination of 300 mg of levobupivacaine, 1 mg of epinephrine, and 60 mg ketorolac (n = 24) diluted in 150 mL of sodium chloride 0.9% (control group). Intraoperative anesthetic and surgical techniques were identical for both groups. Postoperatively, all patients received patient-controlled analgesia (morphine bolus of 1 mg; lockout interval of 8 minutes), acetaminophen, and ketoprofen for 72 hours. A blinded investigator recorded morphine consumption, which was the primary outcome. Also, the range of motion (ROM) and static and dynamic pain were assessed at 6, 12, 36, and 60 hours after surgery. The incidence of adverse events, time to readiness for discharge, and length of hospital stay were also recorded. The median of total cumulative morphine consumption was 16 mg (range, 0-62 mg) in the GTX 2/3 group and 9 mg (range, 0-54 mg) in control group, which did not reach statistical difference (median test, $p = 0.40$). Furthermore, static and dynamic pain scores were similar at all time intervals. GTX 2/3 was inferior in range of motion at 6 and 12 hours; nevertheless, we noted no difference after 36 hours. No differences between groups were found in terms of complications, side effects, or length of hospital stay. No significant differences were found between groups in terms of breakthrough morphine requirement. However, local anesthetic use resulted in an increased ROM in the first 12 hours. This prospective randomized clinical trial shows that GTX 2/3 is a safe and efficient drug for pain control after TKA; nevertheless, more studies using GTX 2/3 with larger populations are needed to confirm the safety profile and efficiency. This is level 1 therapeutic study, randomized, double-blind clinical trial.

J FOOT ANKLE SURG. JAN-FEB 2021;60(1):80-84. DOI: 10.1053/J.JFAS.2020.08.031.

THE IMPACT OF CONCOMITANT LOW BACK PAIN (LBP) ON FUNCTIONAL OUTCOMES IN TOTAL ANKLE ARTHROPLASTY (TAA)

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Although numerous studies have demonstrated that concomitant low back pain (LBP) is associated with worse functional outcomes in patients undergoing total hip and knee arthroplasty, no study has analyzed its impact on patients undergoing total ankle arthroplasty (TAA). The aim of this study was to determine the prevalence of LBP in people undergoing TAA and analyze its impact on patient reported functional outcome measures (PROMs). A retrospective review was performed on data from the Vancouver End Stage Ankle Arthritis Database. In total, 87 patients undergoing TAA were studied, with patient demographics collected preoperatively, including the absence or presence of LBP. Postoperative follow-up was performed at 5 years, primarily analyzing disease-specific PROMs including the Ankle Osteoarthritis Score and Ankle Arthritis Score. The Short Form-36 was used as a secondary outcome measure to assess global function. Multivariable linear mixed-effects regression models were conducted to compare the PROM between patients with LBP with those without LBP. In total, 30 patients (35%) presented with concomitant LBP. There were no significant differences at baseline between the LBP group and no LBP group in terms of demographics or baseline primary disease-specific PROMs. At 5 years, the patients with LBP had significantly worse Ankle Arthritis Score (32 ± 23 vs 22 ± 17 , $p = .03$), Ankle Osteoarthritis Score Total (34 ± 23 vs 22 ± 16 , $p = .01$), and Short Form-36 physical (PCS) components summaries (33 ± 12 vs 44 ± 9 , $p = .001$) compared to the no-LBP group. Both groups improved significantly from baseline across all outcome measures. Our study demonstrated that the prevalence of concomitant LBP in end stage ankle arthritis undergoing TAA is similar to that described in arthritic knees and hips. If present, it can be associated with worse functional outcomes in the intermediate term. However it is not a contraindication to surgery, with patients still experiencing significant improvements from baseline. Further studies are needed to evaluate if LBP influences complications, implant failure rates and survival.

J ORTHOP SURG RES. 2021 AUG 20;16(1):517. DOI: 10.1186/S13018-021-02653-6.

VALIDATION OF THE SPANISH VERSION OF THE GOODMAN SCORE IN TOTAL HIP ARTHROPLASTY

Julián Brañes, Maximiliano Barahona, Sebastián Carvajal, Rodrigo Wulf, Cristián Barrientos

Purpose Currently, patient-reported outcome measures (PROMs) are the standard instruments used to compare arthroplasty results. Goodman *et al.* recently published a well-constructed scale with excellent psychometric properties that can be quickly administered. The main objective of our study was to translate, culturally adapt, and validate a Spanish version of the Goodman questionnaire in patients who underwent total hip arthroplasty (THA). Methods The original Goodman scale was translated into Spanish and cross-culturally adapted. Then, the data from this version were tested for psychometric quality. We designed a cross-sectional study for data collection. This study enrolled 2 institutions. Patients who underwent hip replacement due to primary osteoarthritis secondary to dysplasia between 1 January 2018 and 31 December 2019 were included. A total of 153 patients were contacted twice to record the Goodman and Oxford hip scales (OHS) to assess the validity of the questionnaire. Reliability was tested using the Cronbach's alpha, Concordance using 3 test: intraclass correlation coefficient (ICC),

Lin's concordance correlation coefficient (CCC), and the Bradley-Blackwood F test. The Spearman correlation was used to assess correlation between the OHS and the Spanish-adapted Goodman scale. Results The overall satisfaction after THA was reported to be "very satisfied" by 137 patients (75%), and only 14 patients reported some degree of dissatisfaction (6%). The improvement in quality of life was reported to be "more than I ever dreamed possible" by 41% patients. Cronbach's alpha was acceptable, reaching a coefficient of 0.95 (95% confidence interval, 0.82–1). No statistical difference (t test, $p = 0.55$) was found in the original version, with great internal validity. Test re-test concordance was optimal among the 3 tests used. A moderate correlation was found between the OHS and the Spanish-adapted Goodman scale. Conclusion The Spanish version of the Goodman questionnaire in THA is a reliable, consistent, and feasible scale to evaluate patient satisfaction and improvement in the quality of life in Spanish speakers.

J KNEE SURG. 2021 JUL;34(9):918-923. DOI: 10.1055/S-0039-3402077.

THE DISTANCE BETWEEN TIBIAL TUBERCLE AND TROCHLEAR GROOVE CORRELATES WITH KNEE ARTICULAR TORSION

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This study aims to correlate the tibial tubercle to trochlear groove (TT-TG) distance with knee axial alignment. The hypothesis is that as internal torsion of the distal femur or external torsion of the proximal tibia increases, the TT-TG distance increases. We designed a cross-sectional study approved by our institutional ethics review board. We reviewed 32 computed tomography angiographies of patients that have nonjoint or bone-related symptoms. Distal femoral torsion, proximal tibial torsion, knee articular torsion (AT), and TT-TG distance were measured. A regression analysis between the TT-TG distance and the AT was performed. A positive correlation between the TT-TG distance and the AT was found. An increase in external torsion of the proximal tibia or an increase in internal torsion of the distal femur increases the TT-TG distance. For a correct interpretation of the TT to trochlear groove distance, we propose that the axial alignment should be included in the regular analysis of patellofemoral disease.

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ROBOTIC-ASSISTED VS CONVENTIONAL SURGERY IN MEDIAL UNICOMPARTMENTAL KNEE ARTHROPLASTY: A CLINICAL AND RADIOLOGICAL STUDY

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Background The use of unicompartmental knee arthroplasty (UKA) has increased and new technologies have been developed to improve patient survival and satisfaction, soft tissue balance, alignment, and component size. Robot-assisted systems offer an increase in surgical precision and accuracy. The purpose of this study is to evaluate the precision of component position using five radiological parameters in conventional and robotic-assisted medial UKA using the NAVIO system. **Methods** A cohort study was designed for patients who underwent medial UKA between April 2017 and March 2019 in a single center. Patients were allocated in the conventional (UKA-C) or robotic-assisted (UKA-R) group. The variables analyzed were age, gender, affected knee side, length of hospital stay, surgical time, and radiological measurements such as anatomical medial distal femoral angle (aMDFA), anatomical medial proximal tibial angle (aMPTA), tibial slope, the sagittal femoral angle, and the component size. A target was defined for each measurement, and a successful UKA was defined if at least four radiological measures were on target after surgery. Also, patients' reported outcomes were evaluated using the Oxford Knee Score (OKS) and a numeric rating scale (NRS) for pain. **Results** Thirty-four patients were included, 18 of them underwent UKA-R. The success rate for UKA in the UKA-R group was 87%; meanwhile, in the UKA-C group this was 28%, this difference was significant and powered (Fisher's exact test, $p = 0.001$; $1 - \beta = 0.95$). Also, a 5-point difference in favor of the UKA-R group in the median OKS ($p = 0.01$), and a significantly lower median NRS for pain ($p < 0.000$) were found after surgery. **Conclusions** UKA-R achieved more precision in the radiological parameters' measure in this study. Also, UKA-R has a trend towards a better OKS and a lower NRS for pain at short-term follow-up.

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THE ROLE OF ANTERIOR SUPRA-ACETABULAR EXTERNAL FIXATOR AS DEFINITIVE TREATMENT FOR ANTERIOR RING FIXATION IN UNSTABLE PELVIC FRACTURES

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Purpose Management of anterior ring injuries is still a matter of discussion, and there are only few studies reporting anterior external fixator as definitive treatment for unstable pelvic injuries. This study aimed to describe the clinical and radiological outcomes of a consecutive series of mechanically unstable pelvic injuries that were treated with definitive anterior supra-acetabular external fixator for the anterior ring, and to identify risk factors for failure. **Methods** We included a consecutive series of patients with unstable pelvic ring fractures who underwent anterior supra-acetabular external fixation for definitive treatment, between January 2012 and January 2020. All demographics, associated injuries and procedures, injury mechanism, and complications were analysed. Pelvic fracture was classified based on Orthopaedic Trauma Association/Tile AO (OTA/AO) and Young-Burgess classifications. Complications associated with the external fixator were revised. All patients were functionally evaluated at final follow-up and asked to report their clinical outcomes using the Majeed score. **Results** A total of 47 patients were included, of which 25 were females. The median age was 44 years (interquartile range 23–59). Median follow-up duration was 14 months (interquartile range 6–31). The most frequent aetiology was motor vehicle accident (35), followed by fall from height (8). All fractures required posterior pelvic ring fixation. The median time during which patients had external fixation in situ was 11 weeks (interquartile range 9–13). All patients

achieved healing of pelvic fracture at median time of 10 weeks (interquartile range 8–12). At final follow-up, the median displacement of the anterior pelvis was 6 mm (interquartile range 0–11). Superficial infection was the most common complication (n = 7). No washout procedures were needed. No major complication was reported. No patient required reoperation for anterior ring fracture. The median Majeed score was 88 points (range 60–95; interquartile range 80–90) at final follow-up. Conclusion Our findings suggest that the use of supra-acetabular external fixator is safe and effective for definitive treatment of the anterior ring in unstable pelvic fractures. It is a method with high proportion of excellent results, regardless of the type of fracture. The rate of complications is low, and it does not compromise functional results.

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EJACULATION-SPARING THULIUM LASER ENUCLEATION OF THE PROSTATE (ES-THULEP): OUTCOMES ON A LARGE COHORT

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Purpose To assess the effects of a new ejaculation-sparing thulium laser enucleation of the prostate (ES-ThuLEP) technique on sexual functions and micturition, in patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) and to evaluate how the surgical technique of ES-ThuLEP can lead to ejaculation preservation. Methods A prospective study was carried out between January 2015 and January 2018 on patients with surgical indication for BPH, who wished to preserve ejaculation. The patients were treated with ES-ThuLEP and were evaluated before and 3 and 6 months after surgery. Three validated questionnaires (ICIQ-MLUTSsex, IIEF-5 and IPSS) were used to assess changes in ejaculation, erectile function and urinary symptoms. Uroflowmetry (Qmax and Qavg), post-void residual volume and voided volume were also evaluated, to assess micturition improvement. Patients with moderate to severe erectile dysfunction were excluded. Statistical analysis was performed with the Student's t test, Chi-square test and logistic regression analysis. Results Two hundred and eighty three patients were enrolled. Ejaculation was spared in 203 and 219 patients at 3 and 6 months after surgery. No significant differences were observed between erectile function before and after surgery: baseline IIEF-5 = 16.2 ± 4.47 vs 16.7 ± 2.9 ($p=0.419$) and 17.7 ± 3.2 ($p=0.410$) at 3 and 6 months. Significant improvement in urinary symptoms was achieved: baseline IPSS = 19.4 ± 7.24 vs 5.8 ± 4.3 ($p=0.032$) and 3.9 ± 4.1 ($p=0.029$) at 3 and 6 months. Conclusion ES-ThuLEP effectively preserved ejaculation in over two thirds of the patients without compromising micturition improvement or erectile function. ES-ThuLEP could be a valid treatment option for BPH in young and sexually active men.

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PRÓTESIS PENIANAS: DESCRIPCIÓN DE UNA SERIE DE IMPLANTES CON Y SIN DILATACIÓN DE CUERPOS CAVERNOSOS

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Introduction: Penile prosthesis (PP) implantation is the treatment of choice for refractory erectile dysfunction (ED). They show a high satisfaction rate (75%-100%) and a complication rate that varies between 2.1% and 28.8%. The standard surgical technique includes dilatation of the corpora cavernosa (CC) prior to the insertion of the cylinders. This step takes time and is critical for the occurrence of complications. The aim of this study is to describe the results of a series of PP implanted using the techniques with and without dilatation of the CC. Materials and methods: One-hundred and 20 patients with refractory ED in whom a PP was implanted by 2 surgeons in different centers. Comorbidities, operative characteristics, satisfaction and postoperative complications were evaluated. Results: The average age was 61 ± 9.6 years. The most prevalent comorbidities were: history of radical prostatectomy, high-blood pressure and diabetes mellitus. Forty-two malleable and 78 hydraulic prostheses were implanted. Eleven patients had a previous PP. The median operative time was 70minutes (35-140). The satisfaction reported was 95.8%. Ten patients presented complications. In the group in which the surgery was performed without dilatation of the CC (n=80), the operative time was shorter (62.5minutes [35-105] versus 90minutes [60-140] respectively, $p<0.0001$). There was no difference in complications ($p=0.73$) or levels of satisfaction ($p=0.196$) when comparing the technique with and without dilatation of the CC. Conclusion: In our series, a shorter operative time was observed with the technique without dilatation of the CC, but there were no differences in complications. A prospective and randomized study is required to make a stronger recommendation regarding to dilatation of the CC.

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PREVALENCE OF "UNCOMPLICATED" AND "COMPLICATED" STRESS URINARY INCONTINENCE IN ARGENTINIAN WOMEN: ASSESSING THE ROLE OF THE URODYNAMIC STUDY

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Objective: To determine the percentage of Argentinian patients with "uncomplicated" and "complicated" stress urinary incontinence (SUI) in whom preoperative urodynamics study (UDS) was performed. The secondary objective of the study was to evaluate differences between clinical observation and urodynamics in both groups of women. Methods: A retrospective study of women with IOE derivatives for UDS prior to surgical treatment is performed. The analyzed patients were classified in complicated and not complicated according to the criteria of the study VALUE. The prevalence of different urodynamics observations was assessed in patients with complicated and uncomplicated SUI. Results: We studied 792 patients with SUI derivatives for UDS. Of the patients studied, 313 (39.5%) were considered as uncomplicated SUI and

479 (60.5%) as complicated SUI. The Urodynamics observation was considered different from the clinical data in 415/792 (52.4%), although in greater proportion in SUI complicated (59.9% vs. 40.9%, $p < 0.001$). There was a higher incidence of voiding dysfunction in patients with complicated SUI (32.4% vs. 14.7%, $p < 0.001$). Conclusions: Patients with uncomplicated SUI represent 39% of patients studied with SUI. The differences between clinical evaluation and urodynamics are higher in patients with complicated SUI contributing new information in 60% of the cases.

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PENILE LOW INTENSITY SHOCK WAVE TREATMENT FOR PDE5I REFRACTORY ERECTILE DYSFUNCTION: A RANDOMIZED DOUBLE-BLIND SHAM-CONTROLLED CLINICAL TRIAL

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Purpose Over the last decade, penile low-intensity extracorporeal shockwave therapy (LI-ESWT) has emerged as a promising alternative for the treatment of erectile dysfunction (ED). The aim of this trial is to assess the effect of electromagnetic LI-ESWT on the erectile function of vascular phosphodiesterase type 5 inhibitor (PDE5I) refractory ED patients. **Methods** Randomized, double-blind, sham-controlled study. 76 patients with vascular PDE5I-refractory ED completed the study. 40 men were treated with LI-ESWT (1 session/week for 4 weeks, 5000 shocks/session, 0.09 mJ/mm² energy density) and 36 were treated with a sham probe. Baseline and post-treatment (1, 3 and 6 months) evaluations were performed using validated erectile function questionnaires (IIEF-EF, EHS, SEP2, SEP3 and GAQ1). The groups were compared using Mann-Whitney-Wilcoxon and chi-squared tests, with results considered statistically significant at $p < 0.05$. **Results** At the 3-month follow-up, median change in IIEF-EF score for active and sham groups was 3.5 (IQR 0–10) and –0.5 (IQR –11 to 1), respectively ($p < 0.05$). Six months after treatment, 52.5% of patients (21/40) in the active group and 27.8% of patients (10/36) in the sham group presented an EHS > 2 ($p < 0.05$). At the same evaluation, 40.0% (16/40) and 13.9% (5/36) of patients had positive answers to GAQ-1, in the treated and sham groups, respectively ($p < 0.05$). No adverse events were observed during the study. **Conclusion** This study showed that penile electromagnetic shockwave therapy may improve erectile function, to a modest extent, on certain patients that do not respond to PDE5I; making it an alternative for vascular ED patients that reject more invasive therapies.