

# Abstracts de publicaciones ISI 2018

## DEPARTAMENTO ANATOMÍA PATOLÓGICA

### INT J MOL SCI. 2018 MAY 2;19(5). PII: E1339.

SOMATOTROPIC AXIS DYSFUNCTION IN NON-ALCOHOLIC FATTY LIVER DISEASE: BENEFICIAL HEPATIC AND SYSTEMIC EFFECTS OF HORMONE SUPPLEMENTATION.

Cabrera D, Cabello-Verrugio C, Solís N, San Martín D, Cofré C, Pizarro M, Arab JP, Abrigo J, Campos F, Irigoyen B, Carrasco-Avino G, Bezares K, Riquelme V, Riquelme A, Arrese M, Barrera F.

BACKGROUND: Somatotropic axis dysfunction associated with non-alcoholic fatty liver disease (NAFLD) has potential multisystemic detrimental effects. Here, we analysed the effects of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) supplementation on liver histology, adipokine profile and muscle function in an NAFLD model. METHODS: C57BL/6 mice were fed with a high fat diet (HFD) for 12 weeks and were separated into three groups treated for 4 weeks with: (1) High fat diet (HFD) (n = 10); (2) HFD + GH 9  $\mu\text{g/g/d}$  (n = 10); (3) HFD + IGF-1 0.02  $\mu\text{g/g/d}$  (n = 9). A control group fed a chow diet was included (n = 6). Liver histology, liver triglycerides content, serum alanine aminotransferase (ALT) activity, adiponectin and leptin serum levels, in vivo muscle strength, tetanic force and muscle fibre cross-sectional area (CSA) were measured. RESULTS: HFD + GH and HFD + IGF-1 groups showed significantly lower ALT activity compared to HFD (p < 0.01). Liver triglyceride content in HFD + GH was decreased compared to HFD (p < 0.01). Histologic steatosis score was increased in HFD and HFD + GH group (p < 0.01), whereas HFD + IGF-1 presented no difference compared to the chow group (p = 0.3). HFD + GH group presented lower serum leptin and adiponectin levels compared to HFD. GH and IGF-1 supplementation therapy reverted HFD-induced reduction in muscle strength and CSA (sarcopenia). CONCLUSIONS: GH and IGF-1 supplementation induced significant improvement in liver steatosis, aminotransferases and sarcopenia in a diet-induced NAFLD model.

### CELL ADH MIGR. 2018 AUG 30:1-8.

THE NETRIN-4/LAMININ  $\gamma$ 1/NEOGENIN-1 COMPLEX MEDIATES MIGRATION IN SK-N-SH NEUROBLASTOMA CELLS.

Villanueva AA, Puvogel S, Lois P, Muñoz-Palma E, Ramírez Orellana M, Lubieniecki F, Casco Claro F, Gallegos I, García-Castro J, Sanchez-Gomez P, Torres VA, Palma V.

Neuroblastoma (NB) is the most common pediatric extracranial solid tumor. It arises during development of the sympathetic nervous system. Netrin-4 (NTN4), a laminin-related protein, has been proposed as a key factor to target NB metastasis, although there is controversy about its function. Here, we show that NTN4 is broadly expressed in tumor, stroma and blood vessels of NB patient samples. Furthermore, NTN4 was shown to act as a cell adhesion molecule required for the migration induced by Neogenin-1 (NEO1) in SK-N-SH neuroblastoma cells. Therefore, we propose that NTN4, by forming a ternary complex with Laminin  $\gamma$ 1 (LM $\gamma$ 1) and NEO1, acts as an essential extracellular matrix component, which induces the migration of SK-N-SH cells.

### CANCER IMMUNOL IMMUNOTHER. 2018 DEC;67(12):1897-1910.

TUMOR LYSATE-BASED VACCINES: ON THE ROAD TO IMMUNOTHERAPY FOR GALLBLADDER CANCER.

Rojas-Sepúlveda D, Tittarelli A, Gleisner MA, Ávalos I, Pereda C, Gallegos I, González FE, López MN, Butte JM, Roa JC, Fluxá P, Salazar-Onfray F.

Immunotherapy based on checkpoint blockers has proven survival benefits in patients with melanoma and other malignancies. Nevertheless, a significant proportion of treated patients remains refractory, suggesting that in combination with active immunizations, such as cancer vaccines, they could be helpful to improve response rates. During the last decade, we have used dendritic cell (DC) based vaccines where DCs loaded with an allogeneic heat-conditioned melanoma cell lysate were tested in a series of clinical trials. In these studies, 60% of stage IV melanoma DC-treated patients showed immunological responses correlating with improved survival. Further studies showed that an essential part of the clinical efficacy was associated with the use of conditioned lysates. Gallbladder cancer (GBC) is a high-incidence malignancy in South America. Here, we evaluated the feasibility of producing effective DCs using heat-conditioned cell lysates derived from gallbladder cancer cell lines (GBCCL). By characterizing nine different GBCCLs and several fresh tumor tissues, we found that they expressed some tumor-associated antigens such as CEA, MUC-1, CA19-9, Erb2, Survivin, and several carcinoembryonic antigens. Moreover, heat-shock treatment of GBCCLs induced calreticulin translocation and release of HMGB1 and ATP, both known to act as danger signals. Monocytes stimulated with combinations of conditioned lysates exhibited a potent increase of DC-maturation markers. Furthermore, conditioned lysate-matured DCs were capable of strongly inducing CD4+ and CD8+ T cell activation, in both allogeneic and autologous cell co-cultures. Finally, in vitro stimulated CD8+ T cells recognize HLA-matched GBCCLs. In summary, GBC cell lysate-loaded DCs may be considered for future immunotherapy approaches.

**ONCOTARGET. 2018 FEB 5;9(16):12853-12867.****INVERSE EXPRESSION OF SURVIVIN AND REPRIMO CORRELATES WITH POOR PATIENT PROGNOSIS IN GASTRIC CANCER.**

Cerda-Opazo P, Valenzuela-Valderrama M, Wichmann I, Rodríguez A, Contreras-Reyes D, Fernández EA, Carrasco-Aviño G, Corvalán AH, Quest AFG.

**BACKGROUND:** The objective of the study was to determine the relationship between Survivin and Reprimo transcript/protein expression levels, and gastric cancer outcome. **METHODS:** In silico correlations between an agnostic set of twelve p53-dependent apoptosis and cell-cycle genes were explored in the gastric adenocarcinoma TCGA database, using cBioPortal. Findings were validated by regression analysis of RNAseq data. Separate regression analyses were performed to assess the impact of p53 status on Survivin and Reprimo. Quantitative reverse-transcription PCR (RT-qPCR) and immunohistochemistry confirmed in silico findings on fresh-frozen and paraffin-embedded gastric cancer tissues, respectively. Wild-type (AGS, SNU-1) and mutated p53 (NCI-N87) cell lines transfected with pEGFP-Survivin or pCMV6-Reprimo were evaluated by RT-qPCR and Western blotting. Kaplan-Meier method and Long-Rank test were used to assess differences in patient outcome. **RESULTS:** BioPortal analysis revealed an inverse correlation between Survivin and Reprimo expression (Pearson's  $r = -0.3$ , Spearman's  $\rho = -0.55$ ). RNAseq analyses confirmed these findings (Spearman's  $\rho = -0.37$ ,  $p < 4.2 \times 10^{-9}$ ) and revealed p53 dependence in linear regression models ( $p < 0.05$ ). mRNA and protein levels validated these observations in clinical samples ( $p < 0.001$ ). In vitro analysis in cell lines demonstrated that increasing Survivin reduced Reprimo, while increasing Reprimo reduced Survivin expression, but only did so in p53 wild-type gastric cells ( $p < 0.05$ ). Survivin-positive but Reprimo-negative patients displayed shorter overall survival rates ( $p = 0.047$ , Long Rank Test) (HR=0.32; 95%CI: 0.11-0.97;  $p = 0.044$ ). **CONCLUSIONS:** TCGA RNAseq data analysis, evaluation of clinical samples and studies in cell lines identified an inverse relationship between Survivin and Reprimo. Elevated Survivin and reduced Reprimo protein expression correlated with poor patient prognosis in gastric cancer.

**ONCOLOGY. 2018 NOV 26;1-10.****MOLECULAR EPIDEMIOLOGY OF ALK REARRANGEMENTS IN ADVANCED LUNG ADENOCARCINOMA IN LATIN AMERICA.**

Arrieta O, Cardona AF, Bramuglia G, Cruz-Rico G, Corrales L, Martín C, Imaz-Olguín V, Castillo O, Cuello M, Rojas-Bilbao É, Casas G, Fernández C, Arén Frontera O, Denninghoff V, Recondo G, Avilés-Salas A, Mas-Lopez LA, Oblitas G, Rojas L, Piottante A, Jiménez-García E, Sánchez-Sosa S, Sáenz-Frias J, Lupera H, Ramírez-Tirado LA, Vargas C, Carranza H, Astudillo H, Wills LB, Pichelbauer E, Raez LE; on behalf of the CLICaP.

**OBJECTIVE:** Latin American countries are heterogeneous in terms of lung cancer incidence and exposure to potential carcinogens. We evaluated the frequency and clinical characteristics of ALK rearrangements (ALKr) in Latin America. **METHODS:** A total of 5,130 lung cancer patients from 10 Latin American countries were screened for inclusion. ALKr detection was performed by fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) to assess method variability. Demographic and clinicopathologic characteristics were analyzed. **RESULTS:** Among the 5,130 patients screened, 8.4% ( $n = 433$ ) had nonevaluable FISH tests. Evaluable FISH analyses revealed positive ALKr in 6.8% (320/4,697) of the study population, which included patients from 9 countries. ALKr distribution for each country was: Mexico 7.6% (79/1,034), Colombia 4.1% (10/242), Argentina 6.0% (153/2,534), Costa Rica 9.5% (13/137), Panama 4.4% (5/114), Uruguay 5.4% (2/37), Chile 8.6% (16/185), Venezuela 8.9% (13/146), and Peru 10.8% (29/268). RT-PCR showed high positive (83.6%) and negative (99.7%) predictive values when compared to the gold standard FISH. In contrast, IHC only showed a high negative predictive value (94.6%). **CONCLUSIONS:** Although there is a clear country and continental variability in terms of ALKr frequency, this difference is not significant and the overall incidence of ALKr in Latin America does not differ from the rest of the world.

**MOL NEUROBIOL. 2018 DEC;55(12):9169-9187.****LONG-TERM, FRUCTOSE-INDUCED METABOLIC SYNDROME-LIKE CONDITION IS ASSOCIATED WITH HIGHER METABOLISM, REDUCED SYNAPTIC PLASTICITY AND COGNITIVE IMPAIRMENT IN OCTODON DEGUS.**

Rivera DS, Lindsay CB, Codocedo JF, Carreño LE, Cabrera D, Arrese MA, Vio CP, Bozinovic F, Inestrosa NC.

There has been a progressive increase in the incidence of fructose-induced metabolic disorders, such as metabolic syndrome (MetS). Moreover, novel evidence reported negative effects of high-fructose diets in brain function. This study was designed to evaluate for the first time the effects of long-term fructose consumption (LT-FC) on the normal ageing process in a long-lived animal model rodent, Octodon degus or degu. Moreover, we could replicate human sugar consumption behaviour over time, leading us to understand then the possible mechanisms by which this MetS-like condition could affect cognitive abilities. Our results support that 28 months (from pup to adulthood) of a 15% solution of fructose induced clinical conditions similar to MetS which includes an insulin-resistance scenario together with elevated basal metabolic rate and non-alcoholic fatty liver disease. Additionally, we extended our analysis to evaluate the impact of this MetS-like condition on the functional and cognitive brain processes. Behavioural test suggests that fructose-induced MetS-like condition impair hippocampal-dependent and independent memory performance. Moreover, we also reported several neuropathological events as impaired hippocampal redox balance, together with synaptic protein loss. These changes might be responsible for the alterations in synaptic plasticity and transmitter release observed in these cognitively impaired animals. Our results indicate that LT-FC induced several facets of MetS that eventually could trigger brain disorders, in particular, synaptic dysfunction and reduced cognition.

**GENE. 2018 NOV 14;687:228-237.****DICKKOPF-1 REDUCES HYPERTROPHIC CHANGES IN HUMAN CHONDROCYTES DERIVED FROM BONE MARROW STEM CELLS.**

Rojas A, Mardones R, Pritzker K, van Wijnen AJ, Galindo MA, Las Heras F.

The in vitro process of chondrogenic differentiation of mesenchymal stem cells (MSCs) induces a pre-apoptotic hypertrophic phenotype, guided by the active status of the WNT/ $\beta$ -catenin pathway. To achieve a stable chondrocyte phenotype for cartilage tissue engineering, it is necessary to gain a better understanding of specific genes that regulate the cartilage tissue phenotype. RNA sequencing (RNA-seq) analysis of tissue samples from bone, cartilage,

growth plate and muscle show that Dickkopf-1 (DKK1), a natural WNT canonical signaling inhibitor, is expressed in cartilage tissue. This observation reinforces the concept that inhibition of the WNT/ $\beta$ -catenin pathway is critical for preventing avoid chondrocyte hypertrophy in vitro. We used two doses of DKK1 in a pellet cell culture system to inhibit the terminal differentiation of chondrocytes derived from bone marrow mesenchymal stem cells (MSCs). Bone marrow MSCs were cultured in chondrogenic induction medium with 50 and 200 ng/ml of DKK1 for 21 days. The highest doses of DKK1 reduce  $\beta$ -catenin expression and nuclear localization at day 21, concomitant with reduced expression and activity of hypertrophy markers collagen type X (COL10A1) and alkaline phosphatase (ALPL), thus decreasing the pre-hypertrophic chondrocyte population. Furthermore, DKK1 stimulated expression of collagen type II (COL2A1) and glycosaminoglycans (GAGs), which represent healthy articular cartilage markers. We conclude that exogenous DKK1 impedes chondrocyte progression into a prehypertrophic stage and stimulates expression of healthy articular cartilage markers by blocking the WNT/ $\beta$ -catenin pathway. Hence, DKK1 may promote a mature healthy articular cartilage phenotype and facilitate cartilage tissue engineering for joint repair.

## DEPARTAMENTO DE ANESTESIOLOGÍA Y MEDICINA PERIOPERATORIA

### **J CLIN ANESTH. 2018 SEP 28;53:5-10.**

A SYSTEMATIC REVIEW OF DURAL PUNCTURE EPIDURAL ANALGESIA FOR LABOR.

Layera S, Bravo D, Aliste J, Tran Q.

**STUDY OBJECTIVE:** This systematic review aimed to summarize the evidence derived from randomized controlled trials (RCTs) comparing dural puncture epidural analgesia (DPEA) and conventional lumbar epidural analgesia (LEA) for women undergoing labor. **INTERVENTIONS:** The MEDLINE and EMBASE databases were searched from inception to July 2018 in order to find RCTs published in the English language, which investigated DPEA in laboring women. **MAIN RESULTS:** Six RCTs were included in the final analysis. Their collective results remain ambiguous. Dural puncture with small (i.e., 26- or 27-gauge) spinal needles seems to confer either minimal benefits or improved analgesic quality and lower pain scores in the first 10 min. Dural puncture with 25-gauge spinal needles has been reported to provide higher success rate than conventional LEA in one trial; however two other studies could only agree on the fact that DPEA results in improved sacral blockade and fewer unilateral blocks compared to LEA. **CONCLUSIONS:** The current evidence regarding DPEA for labor analgesia remains ambiguous. Future research should investigate the optimal (spinal) needle size for dural puncture as well as factors governing transmeningeal flux of local anesthetics and opioids in the presence of a dural hole.

### **SEMIN ONCOL. 2018 JUN;45(3):164-169.**

VIABLE PREGNANCY IN A PATIENT WITH METASTATIC MELANOMA TREATED WITH DOUBLE CHECKPOINT IMMUNOTHERAPY.

Burotto M, Gormaz JG, Samtani S, Valls N, Silva R, Rojas C, Portiño S, de la Jara C.

Metastatic cancers during pregnancy have historically been associated with dismal outcomes, with greater rates of tumor progression in part because of diminished treatment alternatives. Immunotherapy with T-cell checkpoint inhibitors has significantly impacted the survival of several metastatic tumors. However, given their mechanism of action, immune-related adverse events can occur, especially with combined immunotherapy treatments. During pregnancy, checkpoint pathways have a major role, providing immune tolerance to the fetal allograft. Furthermore, evidence suggests that inhibition of this pathway may be associated with an increased risk of miscarriage. We describe, to our knowledge, the first case reported in the literature of a patient 7 weeks pregnant, diagnosed with metastatic melanoma and treated with nivolumab plus ipilimumab. We also present the associated immune-related side effects and their treatment, as well as the oncologic results that lead to favorable pregnancy outcome.

### **AM J RESPIR CRIT CARE MED. 2018 SEP 14.**

NEAR-APNEIC VENTILATION DECREASES LUNG INJURY AND FIBROPROLIFERATION IN AN ARDS MODEL WITH ECMO.

Araos J, Alegria L, Garcia P, Cruces P, Soto D, Erranz B, Amthauer M, Salomon T, Medina T, Rodriguez F, Ayala P, Borzone GR, Meneses M, Damiani F, Retamal J, Cornejo R, Buggedo G, Bruhn A.

**RATIONALE:** There is wide variability in mechanical ventilation settings during ECMO in ARDS patients. Although lung rest is recommended to prevent further injury, there is no evidence to support it. **OBJECTIVES:** To determine whether near-apneic ventilation decreases lung injury in a pig model of ARDS supported with ECMO. **METHODS:** Pigs (26-36kg; n=24) were anesthetized and connected to mechanical ventilation. In 18 animals lung injury was induced by a double-hit consisting in repeated saline lavages followed by 2 hours of injurious ventilation. Then, animals were connected to high-flow veno-venous ECMO, and randomized into 3 groups: Non-protective (PEEP 5 cmH<sub>2</sub>O, tidal volume 10 ml/kg, respiratory rate 20 bpm); Conventional-protective (PEEP 10 cmH<sub>2</sub>O, tidal volume 6 ml/kg, respiratory rate 20 bpm); Near-apneic (PEEP 10 cmH<sub>2</sub>O, driving pressure 10 cmH<sub>2</sub>O, respiratory rate 5 bpm). Six other pigs were used as Sham. All groups were maintained during the 24-hour study period. **MEASUREMENTS AND MAIN RESULTS:** Minute ventilation and mechanical power were lower in the Near-apneic group, but no differences were observed in oxygenation or compliance. Lung histology revealed less injury in the Near-apneic group. Extensive immunohistochemical staining for myofibroblasts and pro-collagen III was observed in the Non-protective group, with the Near-apneic group exhibiting the least alterations. Near-apneic group showed significantly less matrix-metalloproteinase-2 and -9 activity. Histological lung injury and fibroproliferation scores were positively correlated with driving pressure and mechanical power. **CONCLUSIONS:** In an ARDS model supported with ECMO, near-apneic ventilation decreased histologic lung injury and matrix-metalloproteinase activity, and prevented the expression of myofibroblast markers.

### **CAN J ANAESTH. 2018 JUN;65(6):658-684.**

TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME: AN UPDATED SYSTEMATIC REVIEW AND NARRATIVE SYNTHESIS.

Duong S, Bravo D, Todd KJ, Finlayson RJ, Tran DQ.

**PURPOSE:** Although multiple treatments have been advocated for complex regional pain syndrome (CRPS), the levels of supportive evidence are

variable and sometimes limited. The purpose of this updated review is to provide a critical analysis of the evidence pertaining to the treatment of CRPS derived from recent randomized-controlled trials (RCTs). SOURCE: The MEDLINE, EMBASE, Psychinfo, and CINAHL databases were searched to identify relevant RCTs conducted on human subjects and published in English between 1 May 2009 and 24 August 2017. PRINCIPAL FINDINGS: The search yielded 35 RCTs of variable quality pertaining to the treatment of CRPS. Published trials continue to support the use of bisphosphonates and short courses of oral steroids in the setting of CRPS. Although emerging evidence suggests a therapeutic role for ketamine, memantine, intravenous immunoglobulin, epidural clonidine, intrathecal clonidine/baclofen/adenosine, aerobic exercise, mirror therapy, virtual body swapping, and dorsal root ganglion stimulation, further confirmatory RCTs are warranted. Similarly, trials also suggest an expanding role for peripheral sympathetic blockade (i.e., lumbar/thoracic sympathetic, stellate ganglion, and brachial plexus blocks). CONCLUSIONS: Since our prior systematic review article (published in 2010), 35 RCTs related to CRPS have been reported. Nevertheless, the quality of trials remains variable. Therefore, further research is required to continue investigating possible treatments for CRPS.

#### **CAN J ANAESTH. 2018 MAR;65(3):280-287.**

##### **A RANDOMIZED COMPARISON BETWEEN INTERSCALENE AND COMBINED INFRACLAVICULAR-SUPRASCAPULAR BLOCKS FOR ARTHROSCOPIC SHOULDER SURGERY.**

Aliste J, Bravo D, Finlayson RJ, Tran DQ.

**BACKGROUND:** This randomized trial aimed to evaluate combined infraclavicular-suprascapular blocks (ICB-SSBs) as a diaphragm-sparing alternative to interscalene blocks (ISBs) for arthroscopic shoulder surgery. We hypothesized that ICB-SSB would provide equivalent postoperative analgesia to ISB 30 min after surgery without the risk of hemidiaphragmatic paralysis. **METHODS:** Following research ethics board approval and written informed consent, participants in the ISB group received an ultrasound-guided ISB with 20 mL of levobupivacaine 0.25% and epinephrine 5 µg·mL<sup>-1</sup>. In the ICB-SSB group, ultrasound-guided ICB (20 mL) and SSB (10 mL) were carried out using the same local anesthetic. Thirty minutes after the block was performed, a blinded investigator assessed the presence of hemidiaphragmatic paralysis. Subsequently, all patients underwent general anesthesia. Postoperatively, a blinded investigator recorded pain scores at rest at 0.5, 1, 2, 3, 6, 12 and 24 hr. Consumption of intra- and postoperative narcotics was also tabulated. **RESULTS:** Compared to its ICB-SSB counterpart, the ISB group displayed non-equivalent (i.e., lower) postoperative pain scores at 30 min (difference of the medians, -4; 99% confidence interval [CI], -6 to -3), required less cumulative morphine iv at 24 hr (difference of the means, -6.1 mg; 95% CI, -10.5 to -1.6), and resulted in a higher incidence of hemidiaphragmatic paralysis (18/20 vs 0/20 patients, respectively;  $P < 0.001$ ). Although postoperative pain scores at one, two, and three hours appeared lower in the ISB group, the upper bounds of the 99% CIs did not exceed the equivalence margin. **CONCLUSION:** Compared with ICB-SSB, ISB provided non-equivalent (i.e., lower) postoperative pain scores 30 min after arthroscopic shoulder surgery. Thereafter, postoperative analgesia was comparable between the two groups. Further trials are required to compare ISB with ICB-SSB using a proximal (i.e., costoclavicular) technique for ICB.

## **DEPARTAMENTO CARDIOVASCULAR**

#### **INFLAMMOPHARMACOLOGY. 2018 OCT 13.**

##### **INTERLEUKIN-1BETA IN SYNERGISM GABAPENTIN WITH TRAMADOL IN MURINE MODEL OF DIABETIC NEUROPATHY.**

Miranda HF, Poblete P, Sierralta F, Noriega V, Prieto JC, Zepeda RJ.

Neuropathic pain is a complication of cancer and diabetes mellitus and the most commonly used drugs in the treatment of the diabetic neuropathic pain have only limited efficacy. The aim of this study was to evaluate the role of the biomarker interleukin-1beta (IL-1B) in the pharmacological interaction of gabapentin with tramadol in a model of diabetic neuropathic pain. CF-1 male mice, pretreated with 200 mg/kg i.p. of streptozocin (STZ), were used and at day 3 and 7 were evaluated by the hot plate test and the spinal cord level of IL-1B was determined. Antinociceptive interaction of the coadministration i.p. of gabapentin with tramadol, in basic of the fixed the ratio 1:1 of their ED<sub>50</sub> values alone, was ascertained by isobolographic analysis. Tramadol was 1.13 times more potent than gabapentin in saline control mice, 1.40 times in STZ mice at 3 days and 1.28 times in STZ at 7 days. The interaction between gabapentin and tramadol was synergic, with an interaction index of 0.30 and 0.22 for mice pretreated with STZ at 3 and 7 days. The combination of gabapentin with tramadol reversed the increased concentration of IL-1β induced by STZ in diabetic neuropathic mice. These findings could help clarify the mechanism of diabetic neuropathy.

## **DEPARTAMENTO DE CIRUGÍA**

#### **OBES SURG. 2018 NOV;28(11):3424-3430.**

##### **LOSS AND REGAIN OF WEIGHT AFTER LAPAROSCOPIC SLEEVE GASTRECTOMY ACCORDING TO PREOPERATIVE BMI : LATE RESULTS OF A PROSPECTIVE STUDY (78-138 MONTHS) WITH 93% OF FOLLOW-UP.**

Csendes A, Burgos AM, Martinez G, Figueroa M, Castillo J, Díaz JC.

**INTRODUCTION:** The long-term results in sleeve gastrectomy (SG) have been reported in few publications. None of them has evaluated the importance of preoperative BMI (kg/m<sup>2</sup>) in the final results. **OBJECTIVE:** To determine the loss and regain of weight after SG, determining the influence of preoperative BMI in final results. **MATERIAL AND METHODS:** This prospective study included all patients operated between 2006 and 2010. Exclusion criteria corresponded to patients with Barrett's esophagus, type 2 diabetes, and hiatal hernia greater than 3 cm. Patients were followed and controlled "face to face" by the main author. **RESULTS:** From 109 original patients included in this study, 102 (93.5%) completed the late follow-up. Patients were divided into four groups: (a) I-29 patients with BMI 32.1-34.9; (b) II-56 patients with BMI 35-39.9; (c) III-20 patients

with BMI 40-49.9; and (d) IV-4 patients with BMI >50. There was a significant decrease in the BMI 12 to 24 months after surgery. At the late control, patients in groups III and IV regained weight in 85 and 100%, respectively. Patients in groups I and II had 3.6 and 38% of weight regain. CONCLUSION: The changes in weight after SG are directly related to preoperative BMI: the higher this value, the higher the percentage of failure and weight regain late after surgery. Besides, laparoscopic SG seems to be an adequate operation at late control in terms of loose of weight after surgery in patients with a BMI less than 40 kg/m<sup>2</sup> before surgery.

#### **GENES (BASEL). 2018 DEC 28;10(1).**

##### **POLYMORPHISMS IN RAS/RAF/MEK/ERK PATHWAY ARE ASSOCIATED WITH GASTRIC CANCER.**

Gonzalez-Hormazabal P, Musleh M, Bustamante M, Stambuk J, Pisano R, Valladares H, Lanzarini E, Chiong H, Rojas J, Suazo J, Castro VG, Jara L, Berger Z.

The RAS/RAF/MEK/ERK pathway regulates certain cellular functions, including cell proliferation, differentiation, survival, and apoptosis. Dysregulation of this pathway leads to the occurrence and progression of cancers mainly by somatic mutations. This study aimed to assess if polymorphisms of the RAS/RAF/MEK/ERK pathway are associated with gastric cancer. A case-control study of 242 gastric cancer patients and 242 controls was performed to assess the association of 27 single nucleotide polymorphisms (SNPs) in the RAS/RAF/MEK/ERK pathway genes with gastric cancer. Analyses performed under the additive model (allele) showed four significantly associated SNPs: RAF1 rs3729931 (Odds ratio (OR) = 1.54, 95% confidence interval (CI): 1.20-1.98, p-value =  $7.95 \times 10^{-4}$ ), HRAS rs45604736 (OR = 1.60, 95% CI: 1.16-2.22, p-value =  $4.68 \times 10^{-3}$ ), MAPK1 rs2283792 (OR = 1.45, 95% CI: 1.12-1.87, p-value =  $4.91 \times 10^{-3}$ ), and MAPK1 rs9610417 (OR = 0.60, 95% CI: 0.42-0.87, p-value =  $6.64 \times 10^{-3}$ ). Functional annotation suggested that those variants or their proxy variants may have a functional effect. In conclusion, this study suggests that RAF1 rs3729931, HRAS rs45604736, MAPK1 rs2283792, and MAPK1 rs9610417 are associated with gastric cancer.

#### **AM J CLIN NUTR. 2018 JUL 1;108(1):24-32.**

##### **CALCIUM ABSORPTION MAY BE AFFECTED AFTER EITHER SLEEVE GASTRECTOMY OR ROUX-EN-Y GASTRIC BYPASS IN PREMENOPAUSAL WOMEN: A 2-Y PROSPECTIVE STUDY.**

Carrasco F, Basfi-Fer K, Rojas P, Csendes A, Papapietro K, Codoceo J, Inostroza J, Krebs NF, Westcott JL, Miller LV, Ruz M.

BACKGROUND: Although Roux-en-Y gastric bypass (RYGBP) is known to reduce calcium absorption (CA), the effects of vertical sleeve gastrectomy (SG) and its long-term implications on CA have not yet been studied. OBJECTIVE: The aim of this study was to evaluate changes in CA and its relation with modifications of bone mineral density (BMD), intakes of calcium and vitamin D, vitamin D status, and parathyroid hormone (PTH) concentrations  $\leq 24$  mo after SG and RYGBP, respectively. DESIGN: Twenty-six premenopausal women undergoing SG [mean  $\pm$  SD body mass index (BMI; kg/m<sup>2</sup>):  $37.3 \pm 3.2$ ; age:  $34.2 \pm 10.2$  y] and 32 undergoing RYGBP (BMI:  $42.0 \pm 4.2$ ; age:  $37.3 \pm 8.1$  y) were studied at baseline (presurgery) and followed up at 12 and 24 mo after surgery. BMD, bone alkaline phosphatase activity, and serum PTH, 25-hydroxyvitamin D [25(OH)D], calcium, magnesium, and phosphorus concentrations were determined. Food and supplement intakes were recorded. CA was measured by using a dual stable isotope method. RESULTS: In premenopausal women, CA was significantly reduced from  $36.5\% \pm 2.0\%$  preoperatively to  $21.0\% \pm 2.3\%$  and  $18.8\% \pm 3.4\%$  at 12 and 24 mo post-SG surgery, respectively. CA also decreased significantly from  $41.5\% \pm 2.8\%$  preoperatively to  $27.9\% \pm 3.8\%$  and  $18.5\% \pm 2.2\%$  12 and 24 mo after RYGBP, respectively. No difference was found between type of surgery (time  $\times$  group interaction,  $P = 0.60$ ). Considering both groups combined, 56.6% of the variance in CA at the 12-mo but not at the 24-mo follow-up was explained by serum PTH and 25(OH)D concentrations, together with vitamin D and calcium intakes. CONCLUSIONS: CA was similarly reduced in both SG and RYGBP compared with baseline, and it was not associated with changes in BMD or body weight loss. This reduction in CA could be explained only partially by calcium intake increase. This trial is registered at <http://www.isrctn.com> as ISRCTN31937503.

#### **SURG TODAY. 2018 MAY;48(5):558-565.**

##### **LAPAROSCOPIC SUBTOTAL GASTRECTOMY IN MORBID OBESE PATIENTS: A VALID OPTION TO LAPAROSCOPIC GASTRIC BYPASS IN PARTICULAR CIRCUMSTANCES (PROSPECTIVE STUDY).**

Braghetto I, Martinez G, Korn O, Zamorano M, Lanzarini E, Narbona E.

BACKGROUND: Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) without resection of the distal stomach is largely performed over the world for morbid obesity. Potential risk of gastric remnant carcinoma development has been suggested. PURPOSE: To present the results obtained after LRYGB with resection of distal stomach. METHOD: This prospective study includes 400 consecutive patients. The mean body weight was  $105.9 \pm 16.8$  Kg (range 83-145 kg), and body mass index (BMI) was  $38.5 \pm 4.4$  kg/m<sup>2</sup> (32.9-50.3). Postoperative morbidity and follow-up were analyzed. RESULTS: Operative time was  $128.5 \pm 18.7$  min, hospital discharge occurred at 3rd postoperative day, postoperative complications occurred in 9.25%, early surgical complications were observed in 3% and medical complications 4%, late surgical complications occurred 2.25%, no mortality was observed. At 1 year follow-up, BMI was  $25.3 \pm 2.7$  kg/m<sup>2</sup> with % of weight loss (%WL) of  $84.6 \pm 19.1\%$ . At five years follow-up very similar values were observed. CONCLUSION: The results obtained after LRYGB with resection of distal stomach are similar to results published after non resection LRYGB regarding early and late results and can be indicated in high risk areas of gastric carcinoma.

#### **TUMOUR BIOL. 2018 NOV;40(11):1010428318810059.**

##### **THE RELATIONSHIP BETWEEN CHEMOKINES CCL2, CCL3, AND CCL4 WITH THE TUMOR MICROENVIRONMENT AND TUMOR-ASSOCIATED MACROPHAGE MARKERS IN COLORECTAL CANCER.**

De la Fuente López M, Landskron G, Parada D, Dubois-Camacho K, Simian D, Martínez M, Romero D, Roa JC, Chahuán I, Gutiérrez R, Lopez-K F, Alvarez K, Kronberg U, López S, Sanguinetti A, Moreno N, Abedrapo M, González MJ, Quera R, Hermoso-R MA.

A complex network of chemokines can influence cancer progression with the recruitment and activation of hematopoietic cells, including macrophages to the supporting tumor stroma promoting carcinogenesis and metastasis. The aim of this study was to investigate the relation

between tissue and plasma chemokine levels involved in macrophage recruitment with tumor-associated macrophage profile markers and clinicopathological features such as tumor-node-metastases stage, desmoplasia, tumor necrosis factor- $\alpha$ , and vascular endothelial growth factor plasma content. Plasma and tumor/healthy mucosa were obtained from Chilean patients undergoing colon cancer surgery. Chemokines were evaluated from tissue lysates (CCL2, CCL3, CCL4, CCL5, and CX3CL1) by Luminex. Statistical analysis was performed using Wilcoxon matched-paired test ( $p < 0.05$ ). Macrophage markers (CD68, CD163, and iNOS) were evaluated by immunohistochemistry samples derived from colorectal cancer patients. Correlation analysis between chemokines and macrophage markers and clinicopathological features were performed using Spearman's test. Plasmatic levels of chemokines and inflammatory mediators' vascular endothelial growth factor and tumor necrosis factor- $\alpha$  were evaluated by Luminex. Tumor levels of CCL2 (mean  $\pm$  standard deviation =  $530.1 \pm 613.9$  pg/mg), CCL3 ( $102.7 \pm 106.0$  pg/mg), and CCL4 ( $64.98 \pm 48.09$  pg/mg) were higher than those found in healthy tissue ( $182.1 \pm 116.5$ ,  $26.79 \pm 22.40$ , and  $27.06 \pm 23.69$  pg/mg, respectively  $p < 0.05$ ). The tumor characterization allowed us to identify a positive correlation between CCL4 and the pro-tumor macrophages marker CD163 ( $p = 0.0443$ ), and a negative correlation of iNOS with desmoplastic reaction ( $p = 0.0467$ ). Moreover, we identified that tumors with immature desmoplasia have a higher CD163 density compared to those with a mature/intermediated stromal tissue ( $p = 0.0288$ ). Plasmatic CCL4 has shown a positive correlation with inflammatory mediators (tumor necrosis factor- $\alpha$  and vascular endothelial growth factor) that have previously been associated with poor prognosis in patients. In conclusion High expression of CCL4 in colon cancer could induce the infiltration of tumor-associated macrophages and specifically a pro-tumor macrophage profile (CD163+ cells). Moreover, plasmatic chemokines could be considered inflammatory mediators associated to CRC progression as well as tumor necrosis factor- $\alpha$  and vascular endothelial growth factor. These data reinforce the idea of chemokines as potential therapeutic targets or biomarker in CRC.

### **PLAST RECONSTR SURG GLOB OPEN. 2018 JUL 9;6(7):E1850.**

BONE RESORPTION AFTER USE OF SILICONE CHIN IMPLANTS, LONG-TERM FOLLOW-UP STUDY WITH LATERAL CHIN RADIOGRAPHY.  
Sciaraffia CE, Ahumada MF, Parada FJ, Gonzalez E, Prado A.

Silicone chin implants are frequently used in cosmetic surgery to enhance a harmonic face. Obtaining an aesthetically pleasing face is increasingly becoming more important for people, and a considerable part of this goal can be achieved through different aesthetic modifications of the chin. The purpose of this study was to analyze the presence of bone resorption after the insertion of silicone chin implants, with lateral chin radiographs. Fifteen patients were studied, all of whom had a chin silicone implant inserted at least 1 year ago using the same surgical technique. The surgery was done intraorally with insertion of the silicone implant under the periosteum of the chin. Fourteen patients presented bone erosion, with the maximum of 2.0mm erosion. However, none of them manifested any symptoms of this erosion. In conclusion, even though the majority of the patients presented with bone erosion, the results were minimal and completely asymptomatic; thus, this technique produced an excellent final result.

### **DIG SURG. 2018;35(5):461-468.**

NATIONAL TREND IN LAPAROSCOPIC GASTRECTOMY FOR GASTRIC CANCER: ANALYSIS OF THE NATIONAL REGISTER IN CHILE.

Norero E, Funke R, Garcia C, Fernandez JI, Lanzarini E, Rodriguez J, Ceroni M, Crovari F, Pinto G, Musleh M, Gonzalez P; Chilean Laparoscopic Gastrectomy Study Group (CHILAGAS).

INTRODUCTION: The laparoscopic approach for the treatment of gastric cancer has many advantages. However, outside Asia there are few large case series. AIM: To evaluate postoperative morbidity, long-term survival, changes in indication, and the results of laparoscopic gastrectomy. METHODS: We included all patients treated with a laparoscopic gastrectomy from 2005 to 2014. We compared results across 2 time periods: 2005-2011 and 2012-2014. Median follow-up was 39 months. RESULTS: Two hundred and eleven patients underwent a laparoscopic gastrectomy (median age 64 years, 55% male patients). In 135 (64%) patients, a total gastrectomy was performed. Postoperative morbidity occurred in 29%. A significant increase in the indication of laparoscopic surgery for stages II-III (32 vs. 45%;  $p = 0.04$ ) and higher lymph node count (27 vs. 33;  $p = 0.002$ ) were observed between the 2 periods. The 5-year overall survival was 72%. According to the stage, the 5-year overall survival was 85, 63, and 54% for stage I, II, and III respectively ( $p < 0.001$ ). CONCLUSIONS: There was an acceptable rate of postoperative complications and the long-term survival was in accordance with the disease stage. There was a higher indication of laparoscopic surgery in stages II-III disease, and higher lymph node count in the latter period of this study.

### **J RECONSTR MICROSURG. 2018 SEP 27.**

REDUCED ANTEROLATERAL THIGH FLAP DONOR-SITE MORBIDITY USING INCISIONAL NEGATIVE PRESSURE THERAPY.

Mangelsdorff G, Cuevas P, Rodriguez JR, Pereira N, Ramirez E, Yañez R.

BACKGROUND: Primary closure of the donor-site after harvest of a large anterolateral thigh flap (ALT) is associated with significant morbidity. Incisional negative pressure therapy (INPT) may decrease complications in high-risk incisions. This study assessed if the incidence of complications after primary closure of the ALT flap donor-site decreases with INPT. METHODS: Retrospective cohort study of a prospectively maintained database including patients who underwent upper and lower limb reconstruction, using an ALT free flap with primary closure of the donor-site. Two groups were defined: primary closure and INPT (study group) and primary closure with traditional dressings (control group). Nonparametric statistics were employed to identify prognostic factors,  $p < 0.05$ . RESULTS: Fifty-eight free ALT flaps in 58 patients (study group  $n = 28$ ; control group  $n = 30$ ) were included. Median flap width and length were 9 cm (range: 5-14) and 25 cm (range: 10-48), respectively. Median follow-up was 19 months (range: 3-78 months). No significant differences in age or flap size were identified in both groups ( $p > 0.05$ ). The global complication rate was 7.14% ( $n = 2$ ) in the INPT group, and 37% ( $n = 11$ ) in the control group ( $p = 0.007$ ). The study group had a lower dehiscence and skin necrosis rate ( $p < 0.05$ ). Multivariate logistic regression analysis showed IPNT was associated with a significant reduction of donor-site complications ( $p = 0.006$ ), especially in patients with defects  $> 8$  cm ( $p = 0.003$ ). CONCLUSIONS: In this cohort study the use of INPT significantly reduced the donor-site morbidity after ALT flap harvest.

**NUTRITION. 2018 MAY;49:7-12.****ASSESSMENT OF PARENTERAL NUTRITION PRESCRIPTION IN CANADIAN ACUTE CARE SETTINGS.**

Adjemian D, Arendt BM, Allard JP.

**BACKGROUND:** Parenteral nutrition (PN) prescription can be challenging in patients with complex conditions and has potential complications. **OBJECTIVE:** To assess PN prescription, monitoring, and PN-related complications in a Canadian acute care setting. **METHODS:** This was a prospective cohort study in which patients receiving PN were assessed by an auditor for nutritional status, PN-related prescription, monitoring, and complications. In addition, length of stay and mortality were recorded. **RESULTS:** 147 patients (mean  $\pm$  SD 56.1  $\pm$  16.4y) with complex diseases (Charlson comorbidity index, median [p25-p75] 2 [1-4]) were enrolled. Before starting PN, 18.6%, 63.9%, and 17.5% of patients were classified as subjective global assessment A, B, and C, respectively. Body mass index remained unchanged during the period on PN. On average, 89% and 73% of patients received <90% of their energy and protein requirements, respectively, but 65% received oral or enteral nutrition at some point during PN. The average daily energy provided by PN increased and stabilized on day 10, reaching 87.2  $\pm$  20.1% of the requirements. Line sepsis (6.8% of patients) and hyperglycemia (6.9%) were the most common complications. The overall mortality was 15.6%. For those alive, length of stay was 30 (range: 4-268) d. PN was discontinued because of transitioning to an oral diet (56.6%), enteral nutrition (17.6%), home PN (14.7%), palliative care (5.1%), death (4.4%), or other (1.5%). **CONCLUSION:** Most patients were malnourished at the start of PN. Energy and protein provided from PN were less than requirements, and the goals were reached with delay. Mortality was high, possibly as a result of complex diseases.

**J CRANIOMAXILLOFAC SURG. 2018 APR;46(4):594-599.****CHARACTERIZATION OF THE ORBITAL VOLUME IN NORMAL POPULATION.**

Andrades P, Cuevas P, Hernández R, Danilla S, Villalobos R.

**INTRODUCTION:** The aim of the study was to describe the normal orbital volume and its most important relationships with other clinical variables. **METHODS:** We designed a correlation study and consecutive normal CTs scans were included. Orbital volume and facial anthropometrics were measured and correlated between them. Two independent and blind observers made all the measurements. Uni and multivariate statistical analysis were performed in order to create a predicting model for orbital volume. **RESULTS:** A total of 199 consecutive patients were included in the study (398 orbits). The mean Orbital Volume (OV) was 24.5  $\pm$  3.08 cc. Adequate intra and interobserver reliability was observed. There were no differences between the right and left orbit ( $p=0.73$ ). The male average OV was 24.9  $\pm$  3.03 cc, the female OV was 23.9  $\pm$  3.08 cc. Age group analysis demonstrated a slow increase in OV beyond thirty years, but these differences were not significant ( $p=0.98$ ). Only the age, total facial height, facial width and the interorbital distance were significant and were included in the predictive model of OV. **CONCLUSION:** We have characterized the normal orbital volume, variations and associations. In order to further advance in the understanding of the clinical implications the abnormal orbital volume must be fully studied.

**AESTHET SURG J. 2018 FEB 15;38(3):279-288.****LONG-TERM QUALITY-OF-LIFE OUTCOMES AFTER BODY CONTOURING SURGERY: PHASE IV RESULTS FOR THE BODY-QoL® COHORT.**

Suijker J, Troncoso E, Pizarro F, Montecinos S, Villarroel G, Erazo C, Cisternas JP, Andrades P, Benítez S, Sepúlveda S, Danilla S.

**BACKGROUND:** Body contouring surgery (BCS) is becoming increasingly popular for aesthetic and reconstructive purposes, particularly among patients with massive weight loss (MWL). However, data on quality of life (QoL) following the surgery are limited, especially long-term QoL. **OBJECTIVES:** The authors evaluated the effect of BCS on QoL and the durability of this effect over time. **METHODS:** QoL was measured with the Body-QoL® instrument at 3 time points among consecutively treated patients: the day before BCS, 1 to 9 months postoperatively (short term), and 1 to 2.7 years postoperatively (long term). Total Body-QoL scores were compiled, as were scores for the instrument's main domains: body satisfaction, sex life, self-esteem and social performance, and physical symptoms. Scores were examined for the entire study population and separately for the cosmetic and MWL cohorts. **RESULTS:** Fifty-seven of the 112 patients participated in the short-term assessment and 84 in the long-term assessment. Total Body-QoL scores increased significantly ( $P < 0.0001$ ), from 44.0  $\pm$  14.1 preoperatively to 85.5  $\pm$  17.5 short-term postoperatively and to 84.4  $\pm$  12.7 long-term postoperatively. Scores for the 2 postoperative assessments did not differ significantly. Similar results were observed for scores on each separate domain. Although preoperative scores were lower for the MWL cohort than the cosmetic cohort (33.9  $\pm$  15.6 vs 46.1  $\pm$  12.8;  $P = 0.0002$ ), they improved substantially after BCS, approaching scores for the cosmetic cohort. **CONCLUSIONS:** QoL increases significantly after BCS. This favorable outcome remained stable throughout long-term follow-up and was true for the cosmetic and MWL cohorts.

**ANTICANCER RES. 2018 OCT;38(10):5703-5708.****IL-8-251T>A (RS4073) POLYMORPHISM IS ASSOCIATED WITH PROGNOSIS IN GASTRIC CANCER PATIENTS.**

Gonzalez-Hormazabal P, Romero S, Musleh M, Bustamante M, Stambuk J, Pisano R, Lanzarini E, Chiong H, Rojas J, Castro VG, Jara L, Berger Z.

**BACKGROUND/AIM:** Inflammation is a key process in gastric carcinogenesis. Cytokines are mediators of inflammation and are involved in metastasis and tumorigenicity. We previously assessed the role of cytokine gene polymorphisms in gastric cancer risk in Chile. In the present study, we aimed to analyze whether these polymorphisms are associated with overall survival (OS) in gastric cancer (GC) patients. **PATIENTS AND METHODS:** A total of 153 individuals with GC diagnosis were followed-up for at least 2 years. Hazard ratios (HR) were estimated from Cox regression models using SNPs as predictor variables. The following SNPs were genotyped for study using a TaqMan assay: rs16944 (IL1B -511C>T); rs4073 (IL8 -251 T>A); rs2275913 (IL17 -197G>A); rs1800872 (IL10 -592 C>A); rs1800896 (IL10 -1082A>G); rs28372698 (IL32). **RESULTS:** Interleukin-8 rs4073 (IL8 -251T>A) showed association with OS under the dominant model (TA + AA) only when adjusted by clinicopathological variables (HR=1.64, 95%CI=1.05-2.55,  $p=0.030$ ,  $q$ -value=0.18), but not with the univariate model (HR=1.51, 95%CI=0.98-2.31,  $p=0.062$ ,  $q$ -value=0.37). No significant differences were observed after adjusting for population stratification (PC1 and PC2 from Principal Component Analysis using genotypes from Infinium Global Screening Array). After stratification by clinicopathological variables, the association with shorter overall survival was higher among

patients with diffuse-type tumors (HR=2.24, 95%CI=1.16-4.45) and patients with tumor size >5 cm (HR=1.79, 95%CI=1.08-2.97). CONCLUSION: These results suggest a role of IL-8 rs4073 in cancer prognosis. Its use as a prognostic marker of GC survival warrants further investigation.

**ANTICANCER RES. 2018 JUL;38(7):3871-3877.**

**POLYMORPHISMS IN TWIST1 AND ZEB1 ARE ASSOCIATED WITH PROGNOSIS OF GASTRIC CANCER PATIENTS.**

Romero S, Musleh M, Bustamante M, Stambuk J, Pisano R, Lanzarini E, Chiong H, Rojas J, Castro VG, Jara L, Berger Z, Gonzalez-Hormazabal P.

BACKGROUND/AIM: Epithelial-mesenchymal transition (EMT) program has been linked as a driver of metastatic dissemination by conferring migratory and invasive capacity to cancer cells. Gastric cancer (GC) patients with tumors expressing altered levels of EMT markers have low survival. This study aimed to assess if polymorphisms of CDH1, TWIST1, SNAIL2, ZEB1 and ZEB2 genes are associated with survival in GC patients. PATIENTS AND METHODS: A total of 153 individuals with diagnosis of GC were recruited in Santiago, Chile. All patients were genotyped using Infinium Global Screening Array (GSA). Twenty Tag SNPs of the studied genes were retrieved. RESULTS: Three SNPs were associated with survival: rs2526614 (TWIST1) (genotype CA + AA, adjusted HR=0.58, 95%CI=0.37-0.93), rs6953766 (TWIST1) (genotype GG, crude HR=2.02, 95%CI=1.06-3.82, adjusted HR=2.14, 95%CI=1.07-4.25), and rs431073 (ZEB1) (genotype AC + CC, crude HR=1.62, 95%CI=1.01-2.59, adjusted HR=1.96, 95%CI=1.18-3.25). CONCLUSION: To the best of our knowledge, this is the first study proposing a role of these SNPs in cancer prognosis. Their use as prognostic markers of GC survival warrants further investigation.

**BMC GASTROENTEROL. 2018 JUN 20;18(1):91.**

**PREVALENCE OF CLARITHROMYCIN RESISTANCE IN HELICOBACTER PYLORI IN SANTIAGO, CHILE, ESTIMATED BY REAL-TIME PCR DIRECTLY FROM GASTRIC MUCOSA.**

Gonzalez-Hormazabal P, Musleh M, Escandar S, Valladares H, Lanzarini E, Castro VG, Jara L, Berger Z.

BACKGROUND: Current available treatments for Helicobacter pylori eradication are chosen according to local clarithromycin and metronidazole resistance prevalence. The aim of this study was to estimate, by means of molecular methods, both clarithromycin and metronidazole resistance in gastric mucosa from patients infected with H.pylori. METHODS: A total of 191 DNA samples were analyzed. DNA was purified from gastric mucosa obtained from patients who underwent an upper gastrointestinal endoscopy at an university hospital from Santiago, Chile, between 2011 and 2014. H.pylori was detected by real-time PCR. A 5'exonuclease assay was developed to detect A2142G and A2143G mutations among H.pylori-positive samples. rdxA gene was sequenced in samples harboring A2142G and A2143G mutations in order to detect mutations that potentially confer dual clarithromycin and metronidazole resistance. RESULTS: Ninety-three (93) out of 191 DNA samples obtained from gastric mucosa were H.pylori-positive (48.7%). Clarithromycin-resistance was detected in 29 samples (31.2% [95%CI 22.0-41.6%]). The sequencing of rdxA gene revealed that two samples harbored truncating mutations in rdxA, one sample had an in-frame deletion, and 11 had amino acid changes that likely cause metronidazole resistance. CONCLUSIONS: We estimated a prevalence of clarithromycin-resistance of 31.8% in Santiago, Chile. Three of them harbor inactivating mutations in rdxA and 11 had missense mutations likely conferring metronidazole resistance. Our results require further confirmation. Nevertheless, they are significant as an initial approximation in re-evaluating the guidelines for H.pylori eradication currently used in Chile.

## DEPARTAMENTO DERMATOLOGÍA

**J ULTRASOUND MED. 2018 DEC 20.**

**ULTRASOUND CHARACTERISTICS OF THE HAIR FOLLICLES AND TRACTS, SEBACEOUS GLANDS, MONTGOMERY GLANDS, APOCRINE GLANDS, AND ARRECTOR PILI MUSCLES.**

Wortsman X, Carreño L, Ferreira-Wortsman C, Poniachik R, Pizarro K, Morales C, Calderon P, Castro A.

OBJECTIVES: To explore the capability of very high-frequency ultrasound (US; 50-71 MHz) to detect the normal morphologic characteristics of the hair follicles and tracts, sebaceous glands, Montgomery glands, apocrine glands, and arrector pili muscles. METHODS: A retrospective study, approved by the Institutional Review Board, evaluated the normal US morphologic characteristics of the hair and adnexal structures in a database of very high-frequency US images extracted from the perilesional or contralateral healthy skin of 1117 consecutive patients who underwent US examinations for localized lesions of the skin and 10 healthy individuals from December 2017 to June 2018. These images were matched with their counterparts from the database of normal histologic images according to the corporal region. The Cohen concordance test and regional mean diameters of the hair follicles and adnexal structures were analyzed. RESULTS: The normal hair follicles and tracts, sebaceous glands, Montgomery glands, apocrine glands, and arrector pili muscles were observed on US images and matched their histological counterparts in all the corporal regions. There was significant US concordance ( $\kappa=0.82$ ;  $P=.0001$ ) among observers. Regional mean diameters (millimeters) of the hair follicles, sebaceous glands, and apocrine glands are provided. CONCLUSIONS: The hair follicles and tracts, sebaceous glands, Montgomery glands, apocrine glands, and arrector pili muscles are detectable with very high-frequency US, including some regional and anatomic variants. Knowledge of their normal US appearances is a requisite for detecting subclinical changes, understanding the physiopathologic characteristics, and supporting the early diagnosis and management of common dermatologic diseases.

**REV MED CHILE 2018; 146: 1334-1342**

**GUÍA CLÍNICA CHILENA DE URTICARIA CRÓNICA ESPONTÁNEA**

Raquel Aguilera-Insunza, Hernán Correa, Carolina Díaz, María Angélica Marinovic, Fernando Valenzuela

Chronic urticaria (CU) is characterized by itchy wheals, angioedema or both lasting six weeks or more. It is classified as spontaneous (CSU) and inducible urticaria (CIndU), depending whether there is an identifiable trigger or not. CSU is the predominant form, affecting more than 75% of

patients, although overlaps often occur. The prevalence of CSU throughout life is around 1.8% and predominates in women at a ratio of 2: 1. The higher incidence of CSU is between 20 and 40 years of age and lasts between one to five years. However, in up to 20% of patients the disease may last longer. CSU not only hampers quality of life, but also affect performance at work and school. The diagnosis of CSU is mainly clinical, and laboratory tests are required depending on the clinical history of the patient. Extensive laboratory tests are usually unnecessary. Second generation anti-histamines are used as first line treatment for CSU treatment. In refractory patients, systemic treatments, such as cyclosporine or omalizumab are suggested. We herein report the first Chilean CSU guidelines.

**J AM PODIATR MED ASSOC. 2018 MAR;108(2):178-181.**

**ACROKERATOELASTOIDOSIS OF THE FOOT WITH CLINICAL, DERMOSCOPIC, ULTRASONOGRAPHIC, AND HISTOPATHOLOGIC CORRELATION.**  
Uribe P, Ortiz E, Wortsman X, Gonzalez S.

Acrokeratoelastoidosis (AKE) is a rare form of focal acral keratoderma of unknown cause that typically begins during childhood and manifests with multiple, small, hyperkeratotic papules located over the lateral margins of the hands and feet. The purpose of this article is to report a pediatric case of AKE with dermoscopic, sonographic, and histopathologic descriptions, contributing to the awareness of this clinical diagnosis. We describe a 7-year-old girl with nonpainful yellowish papules on the lateral and medial aspects of both feet. Dermoscopy showed yellowish, structureless, linear areas. The sonographic appearance was suggestive of benignancy and ruled out the presence of piezogenic pedal papules and granulomas. Histopathology was consistent with AKE, showing acral skin with hyperorthokeratosis, hypergranulosis, and elastorrhexis in the reticular dermis. Acrokeratoelastoidosis may be difficult to recognize clinically because of its resemblance to other focal acral keratodermas. Color Doppler ultrasound can be a useful noninvasive tool for diagnosis and can confirm its benign appearance, although histopathology confirms the definitive diagnosis. To date, the dermoscopic description and ultrasound morphology of AKE have not been reported.

**CLIN RHEUMATOL. 2018 JUN;37(6):1555-1561.**

**ULTRASOUND CHARACTERIZATION OF CUTANEOUS ULCERS IN SYSTEMIC SCLEROSIS.**

Suliman Y, Kafaja S, Fitzgerald J, Wortsman X, Grotts J, Matucci-Cerrinic M, Ranganath VK, Furst DE.

Skin ulcers in scleroderma (SSc) patients are considered a major challenge, both in clinical assessment and treatment decisions. The objective of our study is to assess ultrasonographic (US) morphology of skin ulcers in SSc patients and evaluate if US will be of value in enhancing our clinical information and influence our management plans. We examined a convenience sample of 21 skin ulcers reported in 10 SSc patients by US. We used a previously published US definition of normal skin and developed a preliminary US definition of skin ulcer. Skin ulcers were evaluated by gray scale (GS) and power Doppler (PD) and separated into ulcer and non-ulcer lesions; pain and ulcer measures were obtained using visual analogue scales (VAS). Lesions were characterized and ulcers were clinically and sonographically measured. Ten patients presenting with 21 skin lesions were examined by US. Applying our US definition of skin ulcer, all ulcers were available to measure by ultrasound. Eight lesions were sonographically defined as ulcers, and 13 lesions as non-ulcer lesions. Three ulcers had high PD signals suggestive of infection requiring antibiotic treatment and were monitored for 2 weeks showing a decrease of the pain, VAS, and PD signals. Five lesions showed subclinical calcinosis. This is the first study to show the promising role of US in defining skin ulcers of SSc patients. US may support the assessment of morphology and extent of skin ulcers in SSc and can be a helpful tool for detecting underlying pathology.

**J ULTRASOUND MED. 2018 MAY;37(5):1201-1209.**

**ULTRASONOGRAPHIC CRITERIA FOR DIAGNOSING UNILATERAL AND BILATERAL RETRONYCHIA.**

Fernández J, Reyes-Baraona F, Wortsman X.

**OBJECTIVES:** To assess the main characteristics of retronychia on ultrasonography (US) and to propose US criteria for diagnosing unilateral and bilateral cases according to the digit. **METHODS:** We conducted a case-control study with retrospective, descriptive, and statistical analyses of the US images of 210 nails: 43 with retronychia and 167 normal nails. The Student t test, Fisher exact test, and Kruskal-Wallis test, among other tests, were performed.  $P < .05$  was considered significant. **RESULTS:** Seventy percent of the patients were females, and the most affected digit was the big toe. Significant US diagnostic criteria were as follows: criterion 1, hypoechoic halo surrounding the origin of the nail plate; criterion 2, distance between the origin of the nail plate and the base of the distal phalanx of 5.1 mm or less in big toes and thumbs and/or a difference of 0.5mm of this distance or greater between the affected nail and the contralateral healthy nail; and criterion 3, proximal nail fold thickness of 2.2mm or greater for male patients or 1.9mm or greater for female patients and/or a proximal nail fold 0.3mm thicker or greater in comparison with the contralateral healthy nail. Cutoff points, sensitivity, and specificity with a 95% confidence interval were defined for each criterion according to the digit in cases with unilateral and bilateral involvement. **CONCLUSIONS:** Ultrasonography can support the diagnosis of retronychia in unilateral and bilateral cases. © 2017 by the American Institute of Ultrasound in Medicine.

**J ULTRASOUND MED. 2018 MAR;37(3):793-801.**

**SONOGRAPHIC CHARACTERISTICS OF APOCRINE NODULAR HIDRADENOMA OF THE SKIN.**

Wortsman X, Reyes C, Ferreira-Wortsman C, Uribe A, Misad C, Gonzalez S.

Nodular hidradenomas are benign sweat gland-derived tumors that can produce clinical and dermatoscopic misdiagnoses. Histologically, these tumors can be classified into eccrine and apocrine subtypes. We present the sonographic characteristics of 6 cases of apocrine nodular hidradenomas, which, to our knowledge, is so far the largest series reported. A detailed sonographic analysis included layers, body location, shape, diameters, echostructure patterns, and vascularity. Two sonographic signs not previously reported in these or other common dermatologic lesions were detected: "snow falling" and "fluid-fluid level." The sonographic characteristics of apocrine nodular hidradenomas can support their earlier and more precise diagnosis.

**J ULTRASOUND MED. 2018 JAN;37(1):285-292.**

**COLOR DOPPLER SONOGRAPHY OF MERKEL CELL CARCINOMA.**

Catalano O, Alfageme Roldán F, Scotto di Santolo M, Solivetti FM, Wortsman X.

We illustrate the color Doppler sonographic findings in primary cutaneous Merkel cell carcinoma. Eight cases (4 female and 4 male; mean age, 75.4 years) were collected. The most common affected regions were the face (63%) and the hip/buttock (25%). The mean transverse diameter and thickness were 21 and 14mm, respectively. Fifty percent were oval, and 50% were dome shaped. All lesions were hypoechoic, with variable degrees of heterogeneity. All but 2 lesions were poorly defined. An acoustic reinforcement artifact was present in 3 and epidermal thickening in 2. All tumors had prominent and chaotic hypervascularity with arterial vessels (mean peak velocity, 11 cm/s; mean resistive index, 0.57).

**DERMATOL THER (HEIDELB). 2018 DEC 21.**

**CLINICAL GOALS AND BARRIERS TO EFFECTIVE PSORIASIS CARE.**

Strober BE, van der Walt JM, Armstrong AW, Bourcier M, Carvalho AVE, Chouela E, Cohen AD, de la Cruz C10, Ellis CN, Finlay AY, Gottlieb AB, Gudjonsson JE, Iversen L, Kleyn CE, Leonardi CL, Lynde CW, Ryan C, Theng CT, Valenzuela F, et al.

Engaging global key opinion leaders, the International Psoriasis Council (IPC) held a day-long roundtable discussion with the primary purpose to discuss the treatment goals of psoriasis patients and worldwide barriers to optimal care. Setting clear expectations might ultimately encourage undertreated psoriasis patients to seek care in an era in which great gains in therapeutic efficacy have been achieved. Here, we discuss the option for early treatment of all categories of psoriasis to alleviate disease impact while emphasizing the need for more focused attention for psoriasis patients with mild and moderate forms of this autoimmune disease. In addition, we encourage policy changes to keep pace with the innovative therapies and clinical science and highlight the demand for greater understanding of treatment barriers in resource-poor countries.

**BR J DERMATOL. 2018 OCT;179(4):853-862.**

**TOFACITINIB IN PATIENTS WITH MODERATE-TO-SEVERE CHRONIC PLAQUE PSORIASIS: LONG-TERM SAFETY AND EFFICACY IN AN OPEN-LABEL EXTENSION STUDY.**

Valenzuela F, Korman NJ, Bissonnette R, Bakos N, Tsai TF, Harper MK, Ports WC, Tan H, Tallman A, Valdez H, Gardner AC.

**BACKGROUND:** Tofacitinib is an oral Janus kinase inhibitor. Final safety and efficacy data from an open-label extension study of tofacitinib in psoriasis are reported. **OBJECTIVES:** To evaluate the long-term safety and durability of efficacy of tofacitinib in adults with moderate-to-severe chronic plaque psoriasis. **METHODS:** Eligible patients who completed qualifying phase II/III tofacitinib studies received tofacitinib 10 mg twice daily (q12h) until month 3; subsequently, the dose could be adjusted by investigators to either 5 or 10 mg q12h. Adverse events (AEs) are reported up to month 66 and laboratory data up to month 54. Efficacy end points up to month 54 included Physician's Global Assessment of 'clear' or 'almost clear' (PGA response) and 75% improvement in Psoriasis Area and Severity Index (PASI 75). **RESULTS:** Overall, 2867 patients received tofacitinib, with a median treatment duration of 35.6 months. Adverse events (AEs) and serious AEs were reported in 82.5% and 13.7% of patients, respectively; 13.9% of patients discontinued owing to AEs; and 29 patients died. Incidence rates (patients with event/100 patient-years) were 1.16 for serious infections, 0.67 for malignancies and 0.26 for major adverse cardiovascular events. After initial changes in qualifying studies, most laboratory parameters were generally stable over 54 months. PGA response was achieved by 52-62% of patients and PASI 75 by 56-74% of patients at each study visit through month 54. **CONCLUSIONS:** In patients with psoriasis, the safety profile of tofacitinib over 66 months was similar to previous reports in phase III studies and efficacy was sustained through 54 months (NCT01163253).

**AN BRAS DERMATOL. 2018 JUN;93(3):438-440.**

**ERYTHRODERMIC PSORIASIS AND HUMAN IMMUNODEFICIENCY VIRUS: ASSOCIATION AND THERAPEUTIC CHALLENGES.**

Valenzuela F, Fernández J, Sánchez M, Zamudio A.

Erythrodermic psoriasis is a rare but severe type of psoriasis that may be triggered by human immunodeficiency virus infection. We describe the case of a 65-year-old male patient with chronic psoriasis who presents an exacerbation of his condition over a period of two weeks. Because of the severity of his case and subsequent need for systemic therapy, human immunodeficiency virus enzyme immunoassay was performed and tested positive. He thus began antiretroviral therapy combined with acitretin, showing good clinical response after 8 weeks of treatment. There is little evidence regarding the management of erythrodermic psoriasis associated with HIV infection, so antiretroviral therapy and systemic retinoid remain as the first-line treatment.

## **DEPARTAMENTO DE MEDICINA**

### **ENDOCRINOLOGÍA Y DIABETES**

**REV MED CHIL. 2018 JUL;146(7):933-937.**

**REMISIÓN ESPONTÁNEA DE ACROMEGALIA Y ENFERMEDAD DE CUSHING EN ADULTOS MAYORES. CASOS CLÍNICOS**

Araya AV, Eugenin D, Lemp M.

Pituitary diseases such as acromegaly and Cushing's disease require surgical or medical therapy. In some functioning pituitary tumors, a spontaneous remission of hormonal hypersecretion is observed, mainly associated to apoplexy or pituitary infarction. We report the evolution of two female patients older than 70 years at the time of diagnosis, with multiple comorbidities. In case 1, acromegaly was diagnosed at 74 years of age. Sellar CT scan showed a 10-mm adenoma. During her follow-up, IGF1 levels remained normal. Nine years later, a magnetic resonance (MR)

showed a 7-mm adenoma. In case 2, clinical and biochemical diagnosis of Cushing's disease was done being 71 years old. Sellar MR showed a 6-mm adenoma. Three years later, urinary cortisol normalized with no changes in adenoma at MR. Seven years later, she remains without clinical or biochemical signs of hypercortisolism. In both cases, no signs of hemorrhage were observed at MR.

**REV MED CHIL. 2018 DEC;146(10):1175-1183.**

ROL DE LA CIRUGÍA BARIÁTRICA/METABÓLICA EN EL MANEJO DE LA DIABETES MELLITUS 2.

Consenso SOCHED/SCCBMSapunar J, Escalona A, Araya AV, Aylwin CG, Bastías MJ, Boza C, Cárcamo C, Csendes A A, Davidof F P, Funke R, Gómez P, González MI, Lahsen R, Lanzarini E, Maíz A, Mujica V, Muñoz R, Pérez G, Raimann F, Salman P, Sepúlveda M, Soto N, Villagrán R.

Diabetes Mellitus (DM) and obesity are a public health problem in Chile. Bariatric surgery is the most effective treatment alternative to achieve a significant and sustained weight reduction in patients with morbid obesity. The results of controlled clinical trials indicate that, compared to medical treatment, surgery for obese patients with DM2 allows a better control of blood glucose and cardiovascular risk factors, reduces the need for medications and increases the likelihood for remission. Consensus conferences and clinical practice guidelines support bariatric surgery as an option to treat DM2 in Class III Obesity (Body Mass Index (BMI) > 40) regardless of the glycemic control and the complexity of pharmacological treatment and in Class II Obesity (BMI 35-39,9) with inadequate glycemic control despite optimal pharmacological treatment and lifestyle. However, surgical indication for patients with DM2 and BMI between 30-34.9, the most prevalent sub-group, is only suggested. The Chilean Societies of Endocrinology and Diabetes and of Bariatric and Metabolic Surgery decided to generate a consensus regarding the importance of other factors related to DM2 that would allow a better selection of candidates for surgery, particularly when weight does not constitute an indication. Considering the national reality, we also need a statement regarding the selection and characteristics of the surgical procedure as well as the role of the diabetologist in the multidisciplinary team.

## **GASTROENTEROLOGÍA**

**REV CHILENA INFECTOL. 2018 AUG;35(4):455-457.**

SEROPREVALENCIA DE VIRUS HEPATITIS E EN DONANTES DE SANGRE EN UN HOSPITAL UNIVERSITARIO EN CHILE

Covarrubias N, Naveas P, Miranda J, Hurtado C, Vera DB, Larrondo M, Brahm J, Venegas M.

In Chile, there are few studies about seroprevalence of IgG antibodies against hepatitis E virus (HEV) in blood banks, between 4 and 8%. The development of new techniques with greater sensitivity and specificity, account for an increase in the seroprevalence of HEV in various countries, the current status in Chile being unknown. In the present study, we determined the seroprevalence of anti-HEV IgG in blood donors of the Clinical Hospital University of Chile, with last generation ELISA techniques. Out of a total of 186 samples, collected in 2014, 56 (30.1%) were positive, without gender differences, but with a significant increase with age ( $p < 0.001$ ). These results show an increase in the seroprevalence of HEV in blood donors performed with immunoassays of greater sensitivity.

**GASTROENTEROL HEPATOL. 2018 DEC 27. PII: S0210-5705(18)30317-0.**

EVALUATION OF DE-ESCALATION OF ANTI-TNF- $\alpha$  THERAPY IN INFLAMMATORY BOWEL DISEASE.

Sedano Muñoz R, Quera Pino R, Lubascher Correa J, Pizarro Jofré G, Simian Marín D.

Anti-tumour necrosis factor  $\alpha$  therapy in inflammatory bowel disease has been shown to be effective in clinical practice. After more than a decade using these therapies the question arises about whether there is an appropriate time to suspend these therapies, and how this should be done. This review aims to evaluate the current evidence on these topics concerning anti-tumour necrosis factor  $\alpha$  therapies, and eventually identify conditions and subgroups of patients that could potentially be candidates for withdrawal.

**REV MED CHIL. 2018 JUL;146(7):823-829.**

EL POLIMORFISMO RS12979860 C>T EN EL GEN INTERFERÓN LAMBDA 4 NO ESTÁ ASOCIADO A RIESGO DE FIBROSIS HEPÁTICA EN PACIENTES CHILENOS CON HEPATITIS CRÓNICA POR VIRUS C.

Brahm J, Urzúa A, Poniachik J, Cáceres DD, Carreño L, Venegas M.

BACKGROUND: Host genetic predispositions may be important determinants of liver fibrosis in patients with chronic hepatitis C (CHC). The association between Interferon-L 4 (IFNL4) rs12979860 C>T polymorphism and risk of liver fibrosis in CHC is contradictory. AIM:To evaluate the impact of IFNL4 rs12979860 polymorphism on the risk of fibrosis in patients with CHC.MATERIAL AND METHODS: One hundred fifty patients with CHC aged 50  $\pm$  11 years (89 females) were genotyped for IFNL4 rs12979860 using real time PCR. Fibrosis present in liver biopsies was assessed using the METAVIR score, comparing patients with either no fibrosis, mild fibrosis, or intermediate fibrosis (F0+F1+F2, n = 96), with patients with severe fibrosis or cirrhosis (F3+F4, n = 54). RESULTS: In F0-F2 patients the distribution of rs12979860 genotypes was 22 CC, 57 CT and 17 TT, whereas in patients F3-F4 the distribution was 10, 29 and 15, respectively. No association between IFNL4 rs12979860 genotype and risk of fibrosis was observed in uni or multivariate analyses. CONCLUSIONS: IFNL4 rs12979860 C>T polymorphism is not associated with risk of liver fibrosis in this group of patients with CHC.

**WORLD J GASTROENTEROL. 2018 OCT 7;24(37):4224-4229.**

HEPATOCELLULAR CARCINOMA IN LATIN AMERICA: DIAGNOSIS AND TREATMENT CHALLENGES.

Piñero F, Poniachik J, Ridruejo E, Silva M.

Latin America, a region with a population greater than 600000000 individuals, is well known due to its wide geographic, socio-cultural and economic heterogeneity. Access to health care remains as the main barrier that challenges routine screening, early diagnosis and proper treatment of hepatocellular carcinoma (HCC). Therefore, identification of population at risk, implementation of surveillance programs and access

to curative treatments has been poorly obtained in the region. Different retrospective cohort studies from the region have shown flaws in the implementation process of routine surveillance and early HCC diagnosis. Furthermore, adherence to clinical practice guidelines recommendations assessed in two studies from Brazil and Argentina demonstrated that there is also room for improvement in this field, similarly than the one observed in Europe and the United States. In summary, Latin America shares difficulties in HCC decision-making processes similar to those from developed countries. However, a transversal limitation in the region is the poor access to health care with the consequent limitation to standard treatments for overall population. Specifically, universal health care access to the different World Health Organization levels is crucial, including improvement in research, education and continuous medical training in order to expand knowledge and generation of data promoting a continuous improvement in the care of HCC patients.

#### **ANN HEPATOL. 2018 MAR 1;17(2):256-267.**

##### **RESULTS OF LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN A MULTICENTER LATIN AMERICAN COHORT STUDY.**

Piñero F, Costa P, Boteon YL, Duque SH, Marciano S, Anders M, Varón A, Zerega A, Poniachik J, Soza A, Machaca MP, Menéndez J, Zapata R, Vilatoba M, Muñoz L, Maraschio M, Fauda M, McCormack L, Gadano A, Boin IS, García JHP, Silva M.

**BACKGROUND AND AIMS:** Heterogeneous data has been reported regarding liver transplantation (LT) for hepatocellular carcinoma (HCC) in Latin America. We aimed to describe treatment during waiting list, survival and recurrence of HCC after LT in a multicenter study from Latin America. **MATERIAL AND METHODS:** Patients with HCC diagnosed prior to transplant (cHCC) and incidentally found in the explanted liver (iHCC) were included. Imaging-explanted features were compared in cHCC (non-discordant if pre and post-LT were within Milan, discordant if pre-LT was within and post-LT exceeding Milan). **RESULTS:** Overall, 435 patients with cHCC and 92 with iHCC were included. At listing, 81% and 91% of cHCC patients were within Milan and San Francisco criteria (UCSF), respectively. Five-year survival and recurrence rates for cHCC within Milan, exceeding Milan/within UCSF and beyond UCSF were 71% and 16%; 66% and 26%; 46% and 55%, respectively. Locoregional treatment prior to LT was performed in 39% of cHCC within Milan, in 53% beyond Milan/within UCSF and in 83% exceeding UCSF ( $p < 0.0001$ ). This treatment difference was not observed according to AFP values ( $\leq 100$ , 44%; 101-1,000, 39%, and  $> 1,000$  ng/mL 64%;  $p = 0.12$ ). Discordant imaging-explanted data was observed in 29% of cHCC, showing lower survival HR 2.02 (CI 1.29; 3.15) and higher recurrence rates HR 2.34 when compared to AFP  $< 100$  ng/mL. Serum AFP  $> 1,000$  ng/mL at listing was independently associated with a higher 5-year recurrence rate and a HR of 3.24 when compared to AFP  $< 100$  ng/mL. **CONCLUSION:** Although overall results are comparable to other regions worldwide, pre-LT treatment not only considering imaging data but also AFP values should be contemplated during the next years.

#### **REV MED CHIL. 2018 MAY;146(5):555-561.**

##### **DISMINUCIÓN EN LA FRECUENCIA DE INFECCIÓN POR HELICOBACTER PYLORI EN ENDOSCOPIAS DIGESTIVAS ALTAS.**

Da Costa D, Guidotti F, Cabello N, Trigo F, Contreras C, Vergara F, Miranda JP, Montenegro C, Muñoz P, Berger Z.

**BACKGROUND:** Helicobacter pylori (HP) is the most widespread chronic human infection worldwide and the most important pathogenic factor of gastric cancer. The calculated prevalence at the Clinical Hospital of the University of Chile from 2002 to 2005 was 44.9%. **AIM:** To determine the current prevalence of HP in patients undergoing an upper gastrointestinal endoscopy (UGI) and analyze its distribution according to age and endoscopic findings. **MATERIAL AND METHODS:** We reviewed 3,433 UGI performed during the year 2015, selecting those in which rapid urease test (RUT) was done. A positive RUT or a positive gastric biopsy (GB) were considered as HP infection. **RESULTS:** RUT was done in 1862 UGI (55%) performed in patients aged  $51 \pm 17$  years, (66% women). In 23% of these endoscopies, the RUT was positive. A GB was obtained 43% of endoscopies and 30% were positive for HP. In 105 patients the RUT was negative and the GB positive (rendering a 19.5% false negative rate). HP was detected by RUT and GB in 29% of endoscopies. The highest prevalence of infection (38.1%) was found between 40 and 49 years. HP infection had odds ratio of 4.24 for nodular gastropathy, 2.63 for gastric ulcer and 2.14 for duodenal ulcer ( $p < 0.05$ ). **CONCLUSIONS:** HP prevalence in our center decreased significantly from 44.9% to 28.9% in 11 years. False negative RUT results may bias this finding. The use of proton pump inhibitors and antimicrobials that can interfere with the detection of HP should be registered to properly analyze the results of the RUT.

#### **CLIN RES HEPATOL GASTROENTEROL. 2018 OCT;42(5):443-452.**

##### **A CHANGING ETIOLOGIC SCENARIO IN LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN A MULTICENTER COHORT STUDY FROM LATIN AMERICA.**

Piñero F, Costa P, Boteon YL, Duque SH, Marciano S, Anders M, Varón A, Zerega A, Poniachik J, Soza A, Padilla Machaca M, Menéndez J, Zapata R, Vilatoba M, Muñoz L, Maraschio M, Podestá LG, McCormack L, Gadano A, Boin ISFF, García P, Silva M; Latin American Liver Research, Education, Awareness Network (LALREAN).

**BACKGROUND AND AIM:** Non-alcoholic fatty liver disease (NAFLD) is an increasing cause of hepatocellular carcinoma (HCC) and liver transplantation (LT). Our study focused on changing trends of liver related HCC etiologies during the last years in Latin America. **METHODS:** From a cohort of 2761 consecutive adult LT patients between 2005 and 2012 in 17 different centers, 435 with HCC were included. Different periods including years 2005-2006, 2007-2008, 2009-2010 and 2011-2012 were considered. Etiology of liver disease was confirmed in the explant. **RESULTS:** Participating LT centers per country included 2 from Brazil (n=191), 5 transplant programs from Argentina (n=98), 2 from Colombia (n=65), 4 from Chile (n=49), 2 from Mexico (n=12), and 1 from Peru (n=11) and Uruguay (n=9). Chronic hepatitis C infection was the leading cause of HCC in the overall cohort (37%), followed by HBV (25%) and alcoholic liver disease (17%). NAFLD and cryptogenic cirrhosis accounted for 6% and 7%, respectively. While HCV decreased from 48% in 2005-06 to 26% in 2011-12, NAFLD increased from 1.8% to 12.8% during the same period, accounting for the third cause of HCC. This represented a 6-fold increase in NAFLD-HCC, whereas HCV had a 2-fold decrease. Patients with NAFLD were older, had lower pre-LT serum AFP values and similar 5-year survival and recurrence rates than non-NAFLD. **CONCLUSION:** There might be a global changing figure regarding etiologies of HCC in Latin America. This epidemiological change on the incidence of HCC in the world, although it has been reported, should still be confirmed in prospective studies.

## **GASTROINTEST ENDOSC. 2018 APR;87(4):986-993.**

USE OF N-ACETYLCYSTEINE PLUS SIMETHICONE TO IMPROVE MUCOSAL VISIBILITY DURING UPPER GI ENDOSCOPY: A DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL.

Monrroy H, Vargas JI, Glasinovic E, Candia R, Azúa E, Gálvez C, Rojas C, Cabrera N, Vidaurre J, Álvarez N, González J, Espino A, González R, Parra-Blanco A.

**BACKGROUND AND AIM:** Upper GI endoscopy (UGE) is essential for the diagnosis of gastrointestinal diseases. Mucus and bubbles may decrease mucosal visibility. The use of mucolytics could improve visualization. Our aim was to determine whether premedication with simethicone or simethicone plus N-acetylcysteine is effective in improving visibility during UGE. **METHODS:** This was a randomized, double-blinded, placebo-controlled trial with 2 control groups: no intervention and water 100 mL (W); and 3 intervention groups: simethicone 200 mg (S); S + N-acetylcysteine (NAC) 500 mg (S+NAC500); and S + NAC 1000 mg (S+NAC1000). The solution was ingested 20 minutes before UGE. Gastric visibility was evaluated in 4 segments with a previously described scale. A score of less than 7 points was defined as adequate visibility (AV). Water volume was used to improve visibility, and adverse reactions were evaluated as a secondary outcome. Multiple group comparison was performed using non-parametric one-way analysis of variance (ANOVA). **RESULTS:** Two hundred thirty patients were included in the study, 68% female, mean age 49 years. The most common indication for UGE was epigastric pain/dyspepsia (33%). AV was more frequent in the S+NAC500 and S+NAC1000 groups (65% and 67%) compared with no intervention (44%,  $P = .044$ ) and water (41%,  $P = .022$ ). The gastric total visibility scale (TVS) was significantly better in the S+NAC500 and S+NAC1000 groups compared with water ( $P = .03$  and  $P = .008$ ). Simethicone was not different from no intervention and water. S+NAC1000 required less water volume to improve visibility. No adverse reactions from the study drugs were observed. **CONCLUSIONS:** Premedication with S+NAC500 and S+NAC1000 improves visibility during UGE. The use of simethicone did not show improvements in gastric visibility. TVS was worse in patients using water alone. (Clinical trial registration number: NCT 01653171.).

## **GENÉTICA**

### **ARCH ORAL BIOL. 2018 JUL;91:91-95.**

GENE-GENE INTERACTION FOR NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN CHILEAN CASE-PARENT TRIOS.

Suazo J, Santos JL, Colombo A, Pardo R.

**OBJECTIVE:** Nonsyndromic cleft lip with or without cleft palate (NSCL/P) is a birth defect for which several genes susceptibility genes been proposed. Consequently, it has been suggested that many of these genes belong to common inter-related pathways during craniofacial development gene-gene interaction. We evaluated the presence of gene-gene interaction for single nucleotide polymorphisms within interferon regulatory factor 6 (IRF6), muscle segment homeobox 1 (MSX1), bone morphogenetic protein 4 (BMP4) and transforming growth factor 3 (TGFB3) genes in NSCL/P risk in Chilean case-parent trios. **DESIGN:** From previous studies, we retrieved genotypes for 13 polymorphic variants within these four genes in 152 case-parent trios. Using the trio package (R) we evaluate the gene-gene interaction in genetic markers pairs applying a 1°-of-freedom test (1df) and a confirmatory 4°-of-freedom (4df) test for epistasis followed by both a permutation test and a Benjamini-Hochberg test for multiple comparisons adjustment. **RESULTS:** We found evidence of gene-gene interaction for rs6446693 (MSX1) and rs2268625 (TGFB3) (4df  $p = 0.024$ ; permutation  $p = 0.015$ , Benjamini-Hochberg  $p = 0.001$ ). **CONCLUSIONS:** A significant gene-gene interaction was detected for rs6446693 (MSX1) and rs2268625 (TGFB3). This finding is concordant with research in animal models showing that MSX1 and TGFB3 are expressed in common molecular pathways acting in an epistatic manner during maxillofacial development

## **HEMATOLOGÍA**

### **CLIN LYMPHOMA MYELOMA LEUK. 2018 AUG 29. PII: S2152-2650(18)30361-6.**

ANALYSIS OF AVAILABILITY AND ACCESS OF ANTI-MYELOMA DRUGS AND IMPACT ON THE MANAGEMENT OF MULTIPLE MYELOMA IN LATIN AMERICAN COUNTRIES.

Pessoa de Magalhães Filho RJ, Crusoe E, Riva E, Bujan W, Conte G, Navarro Cabrera JR, Garcia DK, Vega GQ, Macias J, Oliveros Alvear JW, Royg M, Neves LA, Lopez Dopico JL, Espino G, Ortiz DR, Socarra Z, Fantl D, Ruiz-Arguelles GJ, Maiolino A, Hungria VTM, Harousseau JL, Durie B.

**INTRODUCTION:** Latin American countries (LATAMC) represent a large fraction of patients treated for multiple myeloma (MM) worldwide. In order to understand the difficulty of access to anti-myeloma therapy in LATAMC, we designed this study that explores areas involved in the availability of drugs, such as health care systems, approval times, coverage of new agents, old drugs, use of generics, and the first-line treatments. **MATERIAL AND METHODS:** We collected data from 16 countries in 2015. **RESULTS:** The majority of LATAMC (88%;  $n = 14$ ) had mixed public and private coverage, with patients with MM cared for in public institutions. Although bortezomib and lenalidomide were approved in 100% and 73% in LATAMC, these figures did not translate to real-world practice as one-half of the nations reported unequal access to the new agents (thalidomide, bortezomib, and lenalidomide) in both public and private systems. Conversely, cheaper old drugs, represented by melphalan, were not available commercially in 44% ( $n = 7$ ) of nations. Thus, first-line MM treatments for old and young patients in public practice were triplets with thalidomide-alkylating agent-steroid, whereas in private practice, treatments involved bortezomib-alkylating agent-steroid. An alarming rate of 30% of the nations reported suboptimal regimens (eg, VAD [vincristine, adriamycin, and dexamethasone]) or the impossibility of transplantation. **CONCLUSION:** Our data indicates that bortezomib and transplant are still an unmet medical necessity in public systems. In the complex puzzle of myeloma drug access in LATAMC, important issues, such as the adjustment of disparities between health systems, the incorporation of new drugs with an economic cost-effectiveness view, and the re-establishment of essential old drugs, can be a platform to the future.

## INFECTOLOGÍA

### REV CHILENA INFECTOL. 2018 AUG;35(4):448-452.

TRATAMIENTO EXITOSO DE UNA FUSARIOSIS DISEMINADA EN UN PACIENTE NEUTROPÉNICO FEBRIL CON TERAPIA ANTIFÚNGICA COMBINADA DE VORICONAZOL MÁS ANFOTERICINA B DEOXICOLATO.

Olivares R, Luppi M, Díaz MC.

We report a case of a patient with acute lymphoblastic leukemia (ALL), who developed a disseminated infection by *Fusarium verticillioides* during chemotherapy-induced neutropenia. He was successfully treated only after combination therapy with voriconazole plus amphotericin B deoxycolate was used, but not when these compounds were used in an isolated form.

### REV MED CHIL. 2018 SEP;146(9):1074-1078.

TROMBOCITOPENIA HEREDITARIA RELACIONADA A GEN MYH-9: PRIMERA FAMILIA REPORTADA EN CHILE CON DIAGNÓSTICO MOLECULAR. CASO CLÍNICO

Conte G, López M, Alarcón P.

We report a 51-year-old female who had a first episode of thrombocytopenia at 23 years of age during a pregnancy. At the age of fifty, a hysterectomy was indicated due to a metrorrhagia: a platelet count of 21,000/ul was detected. She was treated with eltrombopag with a good response. The family history of the patient revealed the presence of thrombocytopenia in several family members. Suspecting a hereditary thrombocytopenia, a genetic study revealed a mutation in the MYH-9 gene. This mutation can be suspected when there is a family history of thrombocytopenia with autosomal dominant inheritance, macrothrombocytopenia and in this particular case, due to the response to thrombopoietin receptor agonist, eltrombopag.

## INMNOLOGÍA

### REV MED CHIL. 2018 MAR;146(3):394-398.

DESENSIBILIZACIÓN A LEVOTIROXINA. CASO CLÍNICO

Guzmán MA, Sepúlveda C, Liberman C, Cornejo R, Roizen G, Cereceda D, Lara MF, Álvarez-Cuesta E.

We report a 39-year-old female who underwent a total thyroidectomy as treatment for a thyroid papillary cancer. She suffered several episodes of mild angioedema in lips and tongue, after using different commercial Levothyroxine formulations, with and without excipients. Given the need to use this drug, the patient was admitted in our hospital and we proceeded to desensitize her with oral Levothyroxine. The patient fasted throughout the whole procedure, was properly monitored and had an adequate peripheral venous access. On the first day of the procedure, a 15-step protocol was performed, first administering placebo and then, compounded formulations of Levothyroxine starting from 0.01 ug, followed by doubling doses every 15 minutes until the cumulative dose of 111.95 ug was completed, corresponding to the daily dose of Levothyroxine her endocrinologist prescribed (112 ug). The patient was monitored at baseline, between each dose and up to 3 hours after the procedure was completed. There were no incidents such as urticaria, angioedema, or others. On the second day, the patient received a single-full dose of 112 ug on an empty stomach. The medication was successfully tolerated and she was discharged. Thereafter, she tolerates daily Levothyroxine.

### ALLERGY. 2018 DEC 18.

ARIA PHARMACY 2018 "ALLERGIC RHINITIS CARE PATHWAYS FOR COMMUNITY PHARMACY".

Bosnic-Anticevich S, Costa E, Menditto E, Lourenço O, Novellino E, Bialek S, Briedis V, Buonaiuto R, Chrystyn H, Cvetkovski B, Capua SD, Kritikos V, Mair A, Orlando V, Paulino E12, Guzmán MA et al

Pharmacists are trusted health professionals. Many patients use over-the-counter (OTC) medications and are seen by pharmacists who are the initial point of contact of allergic rhinitis management in most countries. The role of pharmacists in integrated care pathways (ICPs) for allergic diseases is important. This paper builds on existing studies and provides tools intended to help pharmacists provide optimal advice/interventions/strategies to patients with rhinitis. The ARIA-pharmacy ICP includes a diagnostic questionnaire specifically focusing attention on key symptoms and markers of the disease, a systematic Diagnosis Guide (including differential diagnoses) and a simple flowchart with proposed treatment for rhinitis and asthma multimorbidity. Key prompts for referral within the ICP are included. The use of technology is critical to enhance the management of AR. However, the ARIA-pharmacy ICP should be adapted to local health care environments/situations as regional (national) differences exist in pharmacy care. This article is protected by copyright. All rights reserved.

### ALLERGOL IMMUNOPATHOL (MADR). 2018 DEC 27. PII: S0301-0546(18)30159-9.

TREATMENT, OUTCOMES AND COSTS OF ASTHMA EXACERBATIONS IN CHILEAN CHILDREN: A PROSPECTIVE MULTICENTER OBSERVATIONAL STUDY.

Herrera AM, Brand P, Cavada G, Koppmann A, Rivas M, Mackenney J, Sepúlveda H, Wevar ME, Cruzat L, Soto S, Pérez MA, León A, Contreras I, Alvarez C, Walker B, Flores C, Lezana V, Garrido C, Herrera ME, Rojas A, Andrades C, Chala E, Martínez RA, Vega M, Perillán JA, Seguel H, Przybyzsweski I.

OBJECTIVE: To describe potential regional variations in therapies for severe asthma exacerbations in Chilean children and estimate the associated health expenditures. METHODS: Observational prospective cohort study in 14 hospitals over a one-year period. Children five years of age or older were eligible for inclusion. Days with oxygen supply and pharmacological treatments received were recorded from the clinical chart. A basic asthma hospitalization basket was defined in order to estimate the average hospitalization cost for a single patient. Six months after discharge,

new visits to the Emergency Room (ER), use of systemic corticosteroids and adherence to the controller treatment were evaluated. RESULTS: 396 patients were enrolled. Patients from the public health system and from the north zone received significantly more days of oxygen, systemic corticosteroids and antibiotics. Great heterogeneity in antibiotic use among the participating hospitals was found, from 0 to 92.3% (ICC 0.34, 95% CI 0.16-0.52). The use of aminophylline, magnesium sulfate and ketamine varied from 0 to 36.4% between the different Pediatric Intensive Care Units (ICC 0.353, 95% CI 0.010-0.608). The average cost per inpatient was of \$1910 USD. 290 patients (73.2%) completed the follow-up six months after discharge. 76 patients (26.2%) were not receiving any controller treatment and nearly a fourth had new ER visits and use of systemic corticosteroids due to new asthma exacerbations. CONCLUSIONS: Considerable practice variation in asthma exacerbations treatment was found among the participating hospitals, highlighting the poor outcome of many patients after hospital discharge, with an important health cost.

## LABORATORIO CLÍNICO

### MOLECULES. 2018 JUL 19;23(7). PII: E1776.

A NEW KIND OF QUINONIC-ANTIBIOTIC USEFUL AGAINST MULTIDRUG-RESISTANT S. AUREUS AND E. FAECIUM INFECTIONS.

Campanini-Salinas J, Andrades-Lagos J, Gonzalez Rocha G, Choquesillo-Lazarte D, Bollo Dragnic S, Faúndez M, Alarcón P, Silva F, Vidal R, Salas-Huenuleo E, Kogan M, Mella J, Recabarren Gajardo G, Vásquez-Velásquez D.

A rapid emergence of resistant bacteria is occurring worldwide, endangering the efficacy of antibiotics and reducing the therapeutic arsenal available for treatment of infectious diseases. In the present study, we developed a new class of compounds with antibacterial activity obtained by a simple, two step synthesis and screened the products for in vitro antibacterial activity against ATCC® strains using the broth microdilution method. The compounds exhibited minimum inhibitory concentrations (MIC) of 1-32 µg/mL against Gram-positive ATCC® strains. The structure-activity relationship indicated that the thiophenol ring is essential for antibacterial activity and the substituents on the thiophenol ring module, for antibacterial activity. The most promising compounds detected by screening were tested against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF) clinical isolates. We found remarkable activity against VREF for compounds 7 and 16, where the MIC<sub>50/90</sub> were 2/4 µg/mL and 4/4 µg/mL, respectively, while for vancomycin the MIC<sub>50/90</sub> was 256/512 µg/mL. Neither compound affected cell viability in any of the mammalian cell lines at any of the concentrations tested. These in vitro data show that compounds 7 and 16 have an interesting potential to be developed as new antibacterial drugs against infections caused by VREF.

## MEDICINA FÍSICA Y REHABILITACIÓN

### MEDICINA INTERNA

#### REV MED CHIL. 2018 FEB;146(2):249-253.

NEUMONÍA BACTERÉMICA POR NEISSERIA MENINGITIDIS: PRIMER CASO REPORTADO EN CHILE Y REVISIÓN BIBLIOGRÁFICA.

Yubini MC, Contreras C, Díaz G, Cerda MA, Guiñez D, Rogers N, Silva F, Cornejo R.

Few cases of bacteremic pneumonia by *Neisseria meningitidis* (NM) have been described worldwide; mostly in elderly patients or those with comorbidities. They appear clinically indistinguishable from other acute infectious pneumonias, that do not develop the syndrome of meningococemia. We report a 17-years-old male, without prior medical history, consulting in the emergency department with a 7-day history of productive cough, right pleural pain, fever and dyspnea. He was admitted to the ICU due to septic shock and respiratory distress. He was managed with vasoactive drugs and prone positioning ventilation for 48 hours. Chest radiography showed a right superior lobe condensation. The electrocardiogram and echocardiogram suggested septic myocarditis. Blood cultures demonstrated the presence of serogroup W135-NM. A lumbar puncture ruled out meningitis, and a 10-day ceftriaxone therapy was completed favorably.

### MEDICINA NUCLEAR

#### REV MED CHIL. 2018 AUG;146(8):831-839.

ESTRATIFICACIÓN DE RIESGO DE MUERTE A MEDIANO PLAZO DE PACIENTES EVALUADOS POR ENFERMEDAD CORONARIA CON SPECT DE PERFUSIÓN MIOCÁRDICA BAJO EFECTO DE DIPYRIDAMOL

Alarcón L, Rau M, Prat H, Fernández R, Carmona J, Zhindon JP, González J, Massardo T.

BACKGROUND: Dipyridamole (DIP) is the most commonly employed pharmacological stressor for myocardial perfusion tomography (SPECT) in patients unable to reach an adequate work load. AIM: To assess the predictive capacity of DIP SPECT on survival. MATERIAL AND METHODS: We included 985 adults aged 66 ±11 years (45% women) with rest and DIP-SPECT. The main indications for the procedure were coronary artery disease (CAD) screening in 66% and known CAD in 33%. Participants were followed up for a median of 65 months (interquartile range 54 to 86 months). During the follow up, 261 deaths were recorded and 98% had a specified cause in their death certificate. RESULTS: Myocardial SPECT was abnormal in 44% of participants. Transient ischemic defects were observed in 34%, fixed defects concordant with infarction in 27% and post-stress systolic dysfunction in 23%. Twenty five percent of deaths were attributable to cardiac or ischemic cause and 22% to cancer. In a bivariate analysis, the hazard ratio (HR) of death of any cause was lower in females and higher in the presence of CAD. The multivariate analysis showed that being older than 46 years increased the HR of death of any cause. In a bivariate analysis, the HR for cardiac death was higher when the myocardial SPECT showed ischemia, necrosis or left ventricular dilation. In the multivariate analysis, post-stress left ventricular systolic function was associated with a lower risk of cardiac death. CONCLUSIONS: An abnormal myocardial SPECT, perfusion abnormalities, left ventricular systolic function or dilation are independent predictors of cardiac death in these participants.

## NEFROLOGÍA

### **KIDNEY INT. 2018 MAY;93(5):1131-1141.**

#### **ERYTHROPOIETIN INDUCES BONE MARROW AND PLASMA FIBROBLAST GROWTH FACTOR 23 DURING ACUTE KIDNEY INJURY.**

Toro L, Barrientos V, León P, Rojas M, Gonzalez M, González-Ibáñez A, Illanes S, Sugikawa K, Abarzúa N, Bascañán C, Arcos K, Fuentealba C, Tong AM, Elorza AA, Pinto ME, Alzamora R, Romero C, Michea L.

It is accepted that osteoblasts/osteocytes are the major source for circulating fibroblast growth factor 23 (FGF23). However, erythropoietic cells of bone marrow also express FGF23. The modulation of FGF23 expression in bone marrow and potential contribution to circulating FGF23 has not been well studied. Moreover, recent studies show that plasma FGF23 may increase early during acute kidney injury (AKI). Erythropoietin, a kidney-derived hormone that targets erythropoietic cells, increases in AKI. Here we tested whether an acute increase of plasma erythropoietin induces FGF23 expression in erythropoietic cells of bone marrow thereby contributing to the increase of circulating FGF23 in AKI. We found that erythroid progenitor cells of bone marrow express FGF23. Erythropoietin increased FGF23 expression in vivo and in bone marrow cell cultures via the homodimeric erythropoietin receptor. In experimental AKI secondary to hemorrhagic shock or sepsis in rodents, there was a rapid increase of plasma erythropoietin, and an induction of bone marrow FGF23 expression together with a rapid increase of circulating FGF23. Blockade of the erythropoietin receptor fully prevented the induction of bone marrow FGF23 and partially suppressed the increase of circulating FGF23. Finally, there was an early increase of both circulating FGF23 and erythropoietin in a cohort of patients with severe sepsis who developed AKI within 48 hours of admission. Thus, increases in plasma erythropoietin and erythropoietin receptor activation are mechanisms implicated in the increase of plasma FGF23 in AKI.

## NEUMOLOGÍA

### **INT J CHRON OBSTRUCT PULMON DIS. 2018 MAY 11;13:1545-1556.**

#### **RESPIRATORY MEDICATION USED IN COPD PATIENTS FROM SEVEN LATIN AMERICAN COUNTRIES: THE LASSYC STUDY.**

Casas A, Montes de Oca M, Menezes AM, Wehrmeister FC, Lopez Varela MV, Mendoza L, Ramirez L, Miravittles M.

**BACKGROUND:** Limited information is available regarding medication use in COPD patients from Latin America. This study evaluated the type of medication used and the adherence to different inhaled treatments in stable COPD patients from the Latin American region. **METHODS:** This was an observational, cross-sectional, multinational, and multicenter study in COPD patients attended by specialist doctors from seven Latin American countries. Adherence to inhaled therapy was assessed using the Test of Adherence to Inhalers (TAI) questionnaire. The type of medication was assessed as: short-acting  $\beta$ -agonist (SABA) or short-acting muscarinic antagonist (SAMA) only, long-acting muscarinic antagonist (LAMA), long-acting  $\beta$ -agonist (LABA), LABA/LAMA, inhaled corticosteroid (ICS), ICS/LABA, ICS/LAMA/LABA, or other. **RESULTS:** In total, 795 patients were included (59.6% male), with a mean age of 69.5 $\pm$ 8.7 years and post-bronchodilator FEV1 of 50.0% $\pm$ 18.6%. The ICS/LAMA/LABA (32.9%) and ICS/LABA (27.7%) combinations were the most common medications used, followed by LABA/LAMA (11.3%), SABA or SAMA (7.9%), LABA (6.4%), LAMA (5.8%), and ICS (4.3%). The types of medication most commonly used in each Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 category were ICS/LABA (A: 32.7%; B: 19.8%; C: 25.7%; D: 28.2%) and ICS/LAMA/LABA (A: 17.3%; B: 30.2%; C: 33%; D: 41.1%). The use of long-acting bronchodilators showed the highest adherence (good or high adherence >50%) according to the TAI questionnaire. **CONCLUSION:** COPD management in specialist practice in Latin America does not follow the current guideline recommendations and there is an overuse of ICSs in patients with COPD from this region. Treatment regimens including the use of long-acting bronchodilators are associated with the highest adherence.

### **RESPIR MED. 2018 JAN;134:62-69.**

#### **PREVALENCE AND IMPACT OF RESPIRATORY SYMPTOMS IN A POPULATION OF PATIENTS WITH COPD IN LATIN AMERICA: THE LASSYC OBSERVATIONAL STUDY.**

Miravittles M, Menezes A, López Varela MV, Casas A, Ugalde L, Ramirez-Venegas A, Mendoza L, López A, Wehrmeister FC, Surmont F, Montes de Oca M.

**BACKGROUND:** To analyse the relationship between symptoms at different times during the 24-hour day and outcomes in COPD. **METHODS:** Observational cross-sectional study in a patients from 7 Latin American countries. The frequency of symptoms in the morning, at night and during the day was explored by means of standardised and validated questionnaires, and the relationship between symptoms and exacerbations and quality of life were investigated. **RESULTS:** 734 patients (59.6% male, mean age 69.5 years, mean FEV1 50% predicted normal) were recruited. The most frequent symptoms during the day were dyspnea (75% of patients, of which 94% mild-moderate) and cough (72.2%, of which 93.4% mild-moderate). Highly symptomatic patients had a greater impairment in FEV1, more exacerbations and worse scores in COPD assessment test (CAT) and Body Mass Index, Obstruction, Dyspnoea and Exacerbations (BODEx) index (all  $p < 0.001$ ). Morning symptoms were more frequent than night-time symptoms, particularly cough and dyspnoea (morning: 50.1% and 45.7%; night-time: 33.2% and 24.4%, respectively), and mostly rated as mild or moderate. Patients with morning or night-time symptoms presented with worse severity of daytime symptoms. There was a strong correlation between intensity of daytime with morning or night-time symptoms, as well as with CAT score ( $r = 0.715$ ;  $p < 0.001$ ), but a weak correlation with FEV1 ( $r = -0.205$ ;  $p < 0.001$ ). **CONCLUSION:** Morning symptoms were more frequent than night-time symptoms, and having either morning and/or night-time symptoms was associated with worse severity of daytime symptoms. Increased symptoms were strongly associated with worse quality of life and more frequent exacerbations, but weakly associated with airflow limitation.

## REUMATOLOGÍA

### **REV MED CHIL. 2018 FEB;146(2):241-248.**

#### **COMPROMISO RENAL EN VASCULITIS ASOCIADAS A ANTICUERPOS ANTICITOPLASMA DE NEURÓFILOS. RECOMENDACIONES DE CONSENSO DE LAS SOCIEDADES CHILENAS DE NEFROLOGÍA Y REUMATOLOGÍA.**

Aguirre V, Alvo M, Ardiles L, Fierro A, Goecke A, Iruetagoiena M, Jaiil R, Massardo L, Méndez GP, Palma S, Roessler E, Silva F, Wurgaft A. Renal involvement is a frequent complication in antineutrophil cytoplasmic antibodies (ANCA) associated vasculitides, adding morbidity and

mortality, such as chronic kidney disease and the need for renal replacement therapy. With the aim of reaching a consensus on relevant issues regarding the diagnosis, treatment and follow-up of patients with these diseases, the Chilean Societies of Nephrology and Rheumatology formed a working group that, based on a critical review of the available literature and their experience, raised and answered consensually a set of questions relevant to the subject. This document includes aspects related to the clinical diagnosis, the histological characteristics, the therapeutic alternatives to induce and maintain the remission of the disease, relapse surveillance strategies and complementary therapies.

## UNIDAD PACIENTES CRÍTICOS

### ANN INTENSIVE CARE. 2018 AUG 4;8(1):80.

CHARACTERISTICS AND OUTCOME OF PATIENTS WITH NEWLY DIAGNOSED ADVANCED OR METASTATIC LUNG CANCER ADMITTED TO INTENSIVE CARE UNITS (ICUS).

Barth C, Soares M, Toffart AC, Timsit JF, Burghi G, Irrazabal C, Pattison N, Tobar E, Almeida BF, Silva UV, Azevedo LC, Rabbat A, Lamer C, Parrot A, Souza-Dantas VC, Wallet F, Blot F, Bourdin G, Piras C, Delemazure J, Durand M, Salluh J, Azoulay E, Lemiale V; Lung Cancer in Critical Care (LUCCA) Study Investigators.

BACKGROUND: Although patients with advanced or metastatic lung cancer have poor prognosis, admission to the ICU for management of life-threatening complications has increased over the years. Patients with newly diagnosed lung cancer appear as good candidates for ICU admission, but more robust information to assist decisions is lacking. The aim of our study was to evaluate the prognosis of newly diagnosed unresectable lung cancer patients. METHODS: A retrospective multicentric study analyzed the outcome of patients admitted to the ICU with a newly diagnosed lung cancer (diagnosis within the month) between 2010 and 2013. RESULTS: Out of the 100 patients, 30 had small cell lung cancer (SCLC) and 70 had non-small cell lung cancer. (Thirty patients had already been treated with oncologic treatments.) Mechanical ventilation (MV) was performed for 81 patients. Seventeen patients received emergency chemotherapy during their ICU stay. ICU, hospital, 3- and 6-month mortality were, respectively, 47, 60, 67 and 71%. Hospital mortality was 60% when invasive MV was used alone, 71% when MV and vasopressors were needed and 83% when MV, vasopressors and hemodialysis were required. In multivariate analysis, hospital mortality was associated with metastatic disease (OR 4.22 [1.4-12.4];  $p=0.008$ ), need for invasive MV (OR 4.20 [1.11-16.2];  $p=0.030$ ), while chemotherapy in ICU was associated with survival (OR 0.23, [0.07-0.81];  $p=0.020$ ). CONCLUSION: This study shows that ICU management can be appropriate for selected newly diagnosed patients with advanced lung cancer, and chemotherapy might improve outcome for patients with SCLC admitted for cancer-related complications. Nevertheless, tumors' characteristics, numbers and types of organ dysfunction should be taken into account in the decisional process before admitting these patients in ICU.

### REV BRAS ANESTESIOL. 2018 MAR - APR;68(2):135-141.

IMPACT OF HYPOTENSION AND GLOBAL HYPOPERFUSION IN POSTOPERATIVE DELIRIUM: A PILOT STUDY IN OLDER ADULTS UNDERGOING OPEN COLON SURGERY.

Tobar E, Abedrapo MA, Godoy JA, Llanos JL, Díaz MJ, Azolas R, Bocic GR, Escobar JA, Cornejo RA, Romero CM.

BACKGROUND: Post-operative delirium is a serious complication in patients undergoing major abdominal surgery. It remains unclear whether peri-operative hemodynamic and perfusion variables affect the risk for postoperative delirium. The objective of this pilot study was to evaluate the association between perfusion and hemodynamics peri-operative with the appearance of post-operative delirium. METHODS: Prospective cohort study of adults 60 years or older undergoing elective open colon surgery. Multimodal hemodynamic and perfusion variables were monitored, including central venous oxygenation (ScvO<sub>2</sub>), lactate levels, and non-invasive cerebral oxygenation (rSO<sub>2</sub>), according to a standard anesthesia protocol. Fisher's exact test or Student's t-test were used to compare patients who developed post-operative delirium with those who did not ( $p<0.05$ ). RESULTS: We studied 28 patients, age  $73\pm 7$  years, 60.7% female. Two patients developed post-operative delirium (7.1%). These two patients had fewer years of education than those without delirium ( $p=0.031$ ). None of the peri-operative blood pressure variables were associated with incidence of post-operative delirium. In terms of perfusion parameters, postoperative ScvO<sub>2</sub> was lower in the delirium than the non-delirium group, without reaching statistical significance ( $65\pm 10\%$  vs.  $74\pm 5\%$ ;  $p=0.08$ ), but the delta-ScvO<sub>2</sub> (the difference between means post-operative and intra-operative) was associated with post-operative delirium ( $p=0.043$ ). Post-operative lactate and rSO<sub>2</sub> variables were not associated with delirium. CONCLUSIONS: Our pilot study suggests an association between delta ScvO<sub>2</sub> and post-operative delirium, and a tendency to lower post-operative ScvO<sub>2</sub> in patients who developed delirium. Further studies are necessary to elucidate this association.

## DEPARTAMENTO DE NEUROLOGÍA Y NEUROCIRUGÍA

### J NEUROL NEUROSURG PSYCHIATRY. 2018 DEC 8. PII: JNNP-2018-319578.

MUSCLE MRI IN A LARGE COHORT OF PATIENTS WITH OCULOPHARYNGEAL MUSCULAR DYSTROPHY.

Alonso-Jimenez A, Kroon RHMJM, Alejandre-Monforte A, Nuñez-Peralta C, Horlings CGC, van Engelen BGM, Olivé M, González L, Verges-Gil E, Paradas C, Márquez C, Garibaldi M, Gallano P, Rodriguez MJ, Gonzalez-Quereda L, Dominguez Gonzalez C, Vissing J, Fornander F, Eisum AV, García-Sobrinho T, Pardo J, García-Figueiras R, Muelas N, Vilchez JJ, Kapetanovic S, Tasca G, Monforte M, Ricci E, Gomez MT, Bevilacqua JA, Diaz-Jara J *et al*

BACKGROUND AND OBJECTIVE: Oculopharyngeal muscular dystrophy (OPMD) is a genetic disorder caused by an abnormal expansion of GCN triplets within the *PABPN1* gene. Previous descriptions have focused on lower limb muscles in small cohorts of patients with OPMD, but larger imaging studies have not been performed. Previous imaging studies have been too small to be able to correlate imaging findings to genetic and clinical data. METHODS: We present cross-sectional, T1-weighted muscle MRI and CT-scan data from 168 patients with genetically confirmed OPMD. We

have analysed the pattern of muscle involvement in the disease using hierarchical analysis and presented it as heatmaps. Results of the scans were correlated with genetic and clinical data. RESULTS: Fatty replacement was identified in 96.7% of all symptomatic patients. The tongue, the *adductor magnus* and the *soleus* were the most commonly affected muscles. Muscle pathology on MRI correlated positively with disease duration and functional impairment. CONCLUSIONS: We have described a pattern that can be considered characteristic of OPMD. An early combination of fat replacement in the tongue, *adductor magnus* and *soleus* can be helpful for differential diagnosis. The findings suggest the natural history of the disease from a radiological point of view. The information generated by this study is of high diagnostic value and important for clinical trial development.

#### **J ALZHEIMERS DIS. 2018;62(4):1887-1900.**

##### **STRUCTURAL ANATOMICAL INVESTIGATION OF LONG-TERM MEMORY DEFICIT IN BEHAVIORAL FRONTOTEMPORAL DEMENTIA.**

Bertoux M, Flanagan EC, Hobbs M, Ruiz-Tagle A, Delgado C, Miranda M, Ibáñez A, Slachevsky A, Hornberger M.

Although a growing body of work has shown that behavioral variant frontotemporal dementia (bvFTD) could present with severe amnesia in approximately half of cases, memory assessment is currently the clinical standard to distinguish bvFTD from Alzheimer's disease (AD). Thus, the concept of "relatively preserved episodic memory" in bvFTD remains the basis of its clinical distinction from AD and a criterion for bvFTD's diagnosis. This view is supported by the idea that bvFTD is not characterized by genuine amnesia and hippocampal degeneration, by contrast to AD. In this multicenter study, we aimed to investigate the neural correlates of memory performance in bvFTD as assessed by the Free and Cued Selective Reminding Test (FCSRT). Imaging explorations followed a two-step procedure, first relying on a visual rating of atrophy of 35 bvFTD and 34 AD patients' MRI, contrasted with 29 controls; and then using voxel-based morphometry (VBM) in a subset of bvFTD patients. Results showed that 43% of bvFTD patients presented with a genuine amnesia. Data-driven analysis on visual rating data showed that, in bvFTD, memory recall & storage performances were significantly predicted by atrophy in rostral prefrontal and hippocampal/perihippocampal regions, similar to mild AD. VBM results in bvFTD ( $p_{FWE} < 0.05$ ) showed similar prefrontal and hippocampal regions in addition to striatal and lateral temporal involvement. Our findings showed the involvement of prefrontal as well as medial/lateral temporal atrophy in memory deficits of bvFTD patients. This contradicts the common view that only frontal deficits explain memory impairment in this disease and plead for an updated view on memory dysfunctions in bvFTD.

#### **CURR ALZHEIMER RES. 2018;15(6):561-569.**

##### **VITAMIN D INCREASES A $\beta$ 140 PLASMA LEVELS AND PROTECTS LYMPHOCYTES FROM OXIDATIVE DEATH IN MILD COGNITIVE IMPAIRMENT PATIENTS.**

San Martin CD, Henriquez M, Chacon C, Ponce DP, Salech F, Rogers NK, Behrens MI.

BACKGROUND: Mild cognitive impairment (MCI) has an increased rate of progression to dementia. Alterations of some metabolic factors, such as deficiency of vitamin D, are a risk factor for cognitive deterioration. Vitamin D is involved in the clearance of  $\beta$ -amyloid (A $\beta$ ) from the brain. We have reported that lymphocytes from Alzheimer's disease (AD) patients have an increased susceptibility to oxidative death by H<sub>2</sub>O<sub>2</sub> exposure, but currently it is unknown if this characteristic is modifiable in vivo. OBJECTIVE: To determine if correction of low vitamin D levels protects lymphocytes from oxidative death and increases A $\beta$ 1-40 plasma levels in MCI and very early AD (VEAD) patients. METHOD: Sixteen MCI, 11 VEAD and 25 healthy control (HC) volunteers were evaluated with the Clinical Dementia Rating (CDR), Montreal Cognitive assessment (MoCA), and Memory Index score (MIS). Lymphocyte death was measured by flow cytometry after 20h exposure to H<sub>2</sub>O<sub>2</sub>. In patients with low levels of vitamin D -11 MCI, 9 VEAD and 20 HC- lymphocyte H<sub>2</sub>O<sub>2</sub>-death, plasma A $\beta$ 1-40 levels and cognitive status were evaluated pre- and post-vitamin D supplementation for 6 months. RESULTS: Lymphocytes from MCI and VEAD patients showed increased susceptibility to oxidative death at study entry. In MCI, but not VEAD patients, lymphocyte susceptibility to death and A $\beta$ 1-40 levels plasma levels improved after 6 months of vitamin D supplementation. In addition, cognitive status on follow-up (18 months) improved in MCI patients after vitamin D supplementation. CONCLUSION: Vitamin D supplementation may be beneficial in MCI. The lack of effect in VEAD may be due to a more advanced stage or different characteristics of the neurodegenerative process.

#### **FRONT NEUROL. 2018 NOV 23;9:1011.**

##### **DEEP BRAIN STIMULATION SURGERY FOR PARKINSON DISEASE COEXISTING WITH COMMUNICATING HYDROCEPHALUS: A CASE REPORT.**

Guevara C, de Grazia J, Vazquez P, Baabor P, Garrido C, Martinez M, Fuentes J, Piedimonte F, Baabor M.

We report a successful bilateral globus pallidus internus-deep brain stimulation (GPI-DBS) for a Parkinson disease (PD) patient with idiopathic normal pressure hydrocephalus (INPH) and an unusually long anterior commissure-posterior commissure (AC-PC) line. A 54-year-old man presented with a history of 3 months of severe shuffling gait, rigidity, slow movements of the left side limbs, and difficulty managing finances. A brain MRI revealed marked ventriculomegaly (Evans index = 0.42). The patient was diagnosed with INPH and a ventriculoperitoneal shunt was placed. Cognitive impairment improved, but walking disturbances, slowness, and rigidity persisted. Then treatment with levodopa was added, and the patient experienced a sustained improvement. He was diagnosed with PD. After 7 years, the patient developed gait freezing and severe levodopa-induced dyskinesia. The patient underwent bilateral GPI-DBS. We used MRI/CT fusion techniques for anatomical indirect targeting. Indirect targeting is based on standardized stereotactic atlas and on a formula-derived method based on AC-PC landmarks. The AC-PC line was 40 mm (the usual length is between 19 and 32 mm). Intraoperative microelectrode recording was a non-expendable test, but multiple recordings were avoided to reduce the surgical risk of ventricular involvement. There was a 71% decrease in the UPDRS III score during the on-stimulation state (28 to 8). The patient's dyskinesias resolved dramatically with a UdysRS of 15 (88% improvement) during the on-stimulation condition. The observed motor benefits and the improvement of his daily activities have persisted 6 months after surgery. Deep brain stimulation surgery in PD with ventriculomegaly is a challenge. This procedure can result in a greater chance of breaching the ventricle, with risks of intraventricular hemorrhage and migration of cerebrospinal fluid into the brain parenchyma with target displacement. Furthermore, clinical judgment is paramount when recent onset of shuffling gait coexists with ventriculomegaly because the most common dilemma is differentiating between PD and INPH. For these reasons, neurologists and surgeons may refuse to operate on PD patients

with ventriculomegaly. However, DBS should be considered for PD patients with motor complications when responsiveness to levodopa is demonstrated, even in the context of marked ventriculomegaly.

**J NEUROL SCI. 2018 DEC 15;395:84-87.**

SPINAL CORD INFARCTION WITH IPSILATERAL SEGMENTAL NEUROPATHIC PAIN AND FLACCID PARALYSIS. A FUNCTIONAL ROLE FOR HUMAN AFFERENT VENTRAL ROOT SMALL SENSORY FIBRES.

Campero M, Hughes R, Orellana P, Bevilacqua JA, Guilloff RJ.

This paper illustrates the cases of two patients with an acute onset of right brachial neuropathic pain, flaccid paralysis and contralateral thermal and thermal pain hypoesthesia, without posterior column impairment nor pyramidal signs below the segmental lesion. MRI showed right sided spinal cord infarction, in the anterior spinal artery territory between C1 and C5 in one patient and between C3 and C7 in the other. Contact Heat Evoked Potentials and Quantitative Thermal Sensory testing are consistent with contralateral, but not ipsilateral, spinothalamic tract involvement. Electromyographic results established ipsilateral segmental denervation and somatosensory evoked responses were consistent with dorsal column sparing. Unilateral anterior cervical spinal cord infarction may present with acute ipsilateral segmental neuropathic pain, lower motor neurone-type weakness, contralateral thermoanalgesia and no pyramidal signs. The ipsilateral pain provides novel evidence that in some instances, ventral roots can play a role in nociception in humans. The infarcted territory may result from occlusion of a sulcal commissural artery or a number of more proximal vessels (including a single or duplicated anterior spinal artery, vertebral arteries or feeding radicular arteries).

**BIOL OPEN. 2018 SEP 5;7(9).**

CHARACTERIZATION OF DIABETIC NEUROPATHY PROGRESSION IN A MOUSE MODEL OF TYPE 2 DIABETES MELLITUS.

De Gregorio C, Contador D, Campero M, Ezquer M, Ezquer F.

Diabetes mellitus (DM) is one of most common chronic diseases with an increasing incidence in most countries. Diabetic neuropathy (DN) is one of the earliest and main complications of diabetic patients, which is characterized by progressive, distal-to-proximal degeneration of peripheral nerves. The cellular and molecular mechanisms that trigger DN are highly complex, heterogeneous and not completely known. Animal models have constituted a valuable tool for understanding diabetes pathophysiology; however, the temporal course of DN progression in animal models of type 2 diabetes (T2DM) is not completely understood. In this work, we characterized the onset and progression of DN in BKS diabetic (db/db) mice, including the main functional and histological features observed in the human disease. We demonstrated that diabetic animals display progressive sensory loss and electrophysiological impairments in the early-to-mid phases of the disease. Furthermore, we detected an early decrease in intraepidermal nerve fiber (IENF) density in 18-week-old diabetic mice, which is highly associated with sensory loss and constitutes a reliable marker of DN. Other common histological parameters of DN - like Schwann cells apoptosis and infiltration of CD3+ cells in the sciatic nerve - were altered in mid-to-late phases of the disease. Our results support the general consensus that DN evolves from initial functional to late structural changes. This work aimed to characterize the progression of DN in a reliable animal model sharing the main human disease features, which is necessary to assess new therapies for this complex disease. Finally, we also aimed to identify an effective temporal window where these potential treatments could be successfully applied.

**APPL NEUROPSYCHOL CHILD. 2018 OCT 8:1-13**

NEUROPSYCHOLOGICAL ASSESSMENT OF CHILEAN CHILDREN WITH A HISTORY OF EXTREME PREMATURITY: AN EXPLORATORY STUDY.

Varela V, Torres F, Rosselli M, Quezada C.

This study was conducted to explore the neuropsychological abilities of premature Chilean children. Two groups (Premature and Control, 10 children each, age ranging from 5 to 7.11) were established based on weeks of gestation and/or weight at birth. Relevant variables such as age, gender, schooling, and socioeconomic level were matched considering Chile's particular demographic context. Children were assessed by means of the Evaluación Neuropsicológica Infantil (ENI-2) battery, measuring nine cognitive domains encompassing 23 subscales. In turn, subscales are grouped in two scales: Cognitive Functions and Executive Functions. Since the ENI-2 battery provides norms for Spanish-speaking children, obtained data were inspected both for possible between-group differences and either adjustment or deviance from average range. Results show that premature children perform within typical ranges in all subscales except for Visual attention and Graphic fluency. When comparing both groups, some differences emerged. These differences are most prominent in subscales related to visuo-perceptual skills. Interestingly, between-group linguistic performance is very similar. The point is made that early linguistic interventions conducted on premature children seem to positively impact on oral language expression and comprehension. On the contrary, early interventions focused on visuospatial abilities did not seem to attain the same impact. This may be a consequence of visual-information processing problems derived from cortical dorsal stream's vulnerability, which literature correlates with prematurity.

**REV MED CHIL. 2018 MAR;146(3):351-361.**

ENCEFALITIS AUTOINMUNES: CRITERIOS DIAGNÓSTICOS Y PAUTAS TERAPÉUTICAS.

Collao-Parra JP, Romero-Urra C, Delgado-Derio C.

Autoimmune encephalitis are one of the emergent causes of subacute changes in the level of consciousness, behavior, cognitive impairment and seizures, mainly in young people. They are a consequence of inflammation or dysfunction of parts of the brain caused by antibodies against specific brain antigens, usually located in the limbic system, resulting in clinical presentation as a limbic encephalitis. The objectives of this article are to show the clinical presentation, complementary studies and treatment of this entity, considering that the patient's prognosis depends on a high level of clinical suspicion, and on an early initiation of immunosuppressive therapy. We did a nonsystematic review of the literature on autoimmune encephalitis between 2005 and 2017. We conclude that the prevalence of autoimmune encephalitis is increasing, even surpassing infectious causes of encephalitis in developed countries. Clinical presentation includes sub-acute cognitive and behavioral impairment, with or without alterations in consciousness and seizures. Fever and inflammation of the cerebrospinal fluid are less common than in the infectious

causes but psychiatric symptoms are more frequent. There are specific clinical presentations according to the particular type of antigen/antibody present, which also determines the association with cancer, constituting a paraneoplastic syndrome only in some cases. Immunosuppressive therapy has been standardized in steps, and should be initiated early to improve prognosis.

### **CEPHALALGIA, 38 (4): 794-797**

**LANGERHANS CELL HISTIOCYTOSIS (EOSINOPHILIC GRANULOMA) OF THE SKULL MIMICKING NUMMULAR HEADACHE. REPORT OF TWO CASES**  
Silva Rosas, Carlos; Angus Leppan, Heather; Bruno Lemp, Melchor; Rozas, Juan Pablo; Quijada, Alonso Humberto

**Background** Nummular headache is a rare, recently described topographic headache defined by the circumscribed coin-shaped area of pain. It is classified as a primary headache. There is debate about whether it is due to a peripheral or central disturbance, and its relationship to migraine. **Case reports** We report two patients with presumed nummular headache secondary to Langerhans cell histiocytosis, both with resolution of their headaches after surgical resection. **Conclusion** Imaging in patients with clinical features of nummular headache is recommended, as this and other cases highlight that it may be symptomatic. There are no distinguishing clinical features to separate nummular headache from secondary mimics, and treatment of the underlying cause may be curative.

## **DEPARTAMENTO DE OFTALMOLOGÍA**

### **INT OPHTHALMOL. 2018 JUN 18.**

**EFFECTIVENESS OF SAMPLING METHODS EMPLOYED FOR ACANTHAMOEBA KERATITIS DIAGNOSIS BY CULTURE.**

Muiño L, Rodrigo D, Villegas R, Romero P, Peredo DE, Vargas RA, Liempi D, Osuna A, Jercic MI.

**PURPOSE:** This retrospective, observational study was designed to evaluate the effectiveness of the sampling methods commonly used for the collection of corneal scrapes for the diagnosis of Acanthamoeba keratitis (AK) by culture, in terms of their ability to provide a positive result. **METHODS:** A total of 553 samples from 380 patients with suspected AK received at the Parasitology Section of the Public Health Institute of Chile, between January 2005 and December 2015, were evaluated. A logistic regression model was used to determine the correlation between the culture outcome (positive or negative) and the method for sample collection. The year of sample collection was also included in the analysis as a confounding variable. **RESULTS:** Three hundred and sixty-five samples (27%) from 122 patients (32.1%) were positive by culture. The distribution of sample types was as follows: 142 corneal scrapes collected using a modified bezel needle (a novel method developed by a team of Chilean corneologists), 176 corneal scrapes obtained using a scalpel, 50 corneal biopsies, 30 corneal swabs, and 155 non-biological materials including contact lens and its paraphernalia. Biopsy provided the highest likelihood ratio for a positive result by culture (1.89), followed by non-biological materials (1.10) and corneal scrapes obtained using a modified needle (1.00). The lowest likelihood ratio was estimated for corneal scrapes obtained using a scalpel (0.88) and cotton swabs (0.78). **CONCLUSION:** Apart from biopsy, optimum corneal samples for the improved diagnosis of AK can be obtained using a modified bezel needle instead of a scalpel, while cotton swabs are not recommended.

## **DEPARTAMENTO DE OBSTETRICIA Y GINECOLOGÍA**

### **GYNECOL OBSTET INVEST. 2018 NOV 2:1-5.**

**CHORIONIC BUMP: AN EARLY ULTRASOUND MARKER FOR ADVERSE OBSTETRIC OUTCOME.**

Silva MC, Sepúlveda-Martínez A, Guíñez R, Haye MT, Parra-Cordero M.

**BACKGROUND/AIMS:** To assess the perinatal outcome of pregnancies with chorionic bump detected at the first trimester of pregnancy. **METHODS:** This was a nested case-control study of pregnancies with chorionic bump identified at the first trimester ultrasound that was performed from October 2014 and October 2016. The control group consisted of the following 5 unaffected pregnancies after each case. From the first trimester ultrasound, maternal and perinatal characteristics were obtained and stored in a dedicated database. The primary outcome was defined as the presence of an alive new-born. Secondary outcome was defined as the presence of a composite adverse obstetric outcome. **RESULTS:** Eleven first trimester pregnancies affected by a chorionic bump and 55 controls were identified. The primary outcome was observed in 72.7 and 89.1% of chorionic bump and controls respectively ( $p = 0.2$ ). The secondary outcome was observed in 45.5% of pregnancies with a chorionic bump versus 12.7% in the unaffected group ( $p = 0.01$ ). First trimester uterine artery Doppler demonstrated a non-significant trend to be higher in the chorionic bump group. **CONCLUSIONS:** The presence of a chorionic bump is associated with a significant higher risk of adverse perinatal outcome.

### **THE ADV MED ONCOL. 2018 MAY 4;10:1758835918770984.**

**METFORMIN PREVENTS NERVE GROWTH FACTOR-DEPENDENT PROLIFERATIVE AND PROANGIOGENIC EFFECTS IN EPITHELIAL OVARIAN CANCER CELLS AND ENDOTHELIAL CELLS.**

Garrido MP, Vera C, Vega M, Quest AFG, Romero C.

**BACKGROUND:** Epithelial ovarian cancer (EOC) is characterized by exacerbated angiogenesis regulated by proangiogenic and growth factors. Nerve growth factor (NGF) is overexpressed in EOC where it promotes proliferation as well as survival and is considered a proangiogenic factor. Metformin, a drug commonly used in the treatment of diabetes, is attributed to antineoplastic effects, but the underlying mechanisms remain unknown. Given that current therapies yield modest results in EOC patients, the aim of this study was to determine the effects of metformin on NGF-enhanced proliferation of EOC cells and the angiogenic potential of endothelial cells. **METHODS:** A2780 (EOC), HOSE (human ovarian surface

epithelial) and EA.hy926 (endothelial) cells were treated with NGF and metformin. Cell viability, cell proliferation and cell cycle were evaluated in all three cell lines, and the angiogenic potential in endothelial EA.hy926 cells. RESULTS: NGF enhanced cell proliferation in A2780, HOSE and EA.hy926 cells ( $p < 0.05$ ), while metformin treatment decreased cell proliferation in A2780 and EA.hy926 cells ( $p < 0.05$ ). Moreover, the NGF-enhanced angiogenic score in EA.hy926 cells was prevented by metformin ( $p < 0.05$ ). CONCLUSIONS: Given that NGF plays a significant role in EOC progression, our current findings suggest that metformin holds considerable promise as an adjuvant treatment in ovarian cancer.

### **BJOG. 2019 JAN;126(2):291-298.**

**POSTNATAL PERSISTENCE OF FETAL CARDIOVASCULAR REMODELLING ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGIES: A COHORT STUDY.**

Valenzuela-Alcaraz B, Serafini A, Sepulveda-Martínez A, Casals G, Rodríguez-López M, García-Otero L, Cruz-Lemini M, Bijns B, Sitges M, Balasch J, Gratacós E, Crispi F.

**OBJECTIVE:** To assess the postnatal persistence of fetal cardiovascular remodelling associated with assisted reproductive technologies (ART) in children at 3 years of age. **DESIGN:** A cohort study of children conceived by ART. **SETTING:** Maternal-Fetal Medicine Unit, Hospital Clinic Barcelona, Spain. **POPULATION SAMPLE:** Eighty singleton pregnancies conceived by ART and 80 spontaneously conceived (controls) followed from fetal life up to childhood. **METHODS:** Cardiovascular evaluation was performed at 3 years of corrected age, including echocardiography, carotid intima-media (cIMT) by ultrasound, and blood pressure. **MAIN OUTCOME MEASURES:** Postnatal persistence of cardiovascular changes in children conceived by ART. **RESULTS:** Compared with controls, children conceived by ART showed larger atria (right atrial area: control 4.9 cm<sup>2</sup> (0.9) versus ART 5.5 cm<sup>2</sup> (0.9),  $P < 0.001$ ), more globular ventricles (right ventricular sphericity index: control mean 1.8 (SD 0.5) versus ART 1.6 (0.2),  $P < 0.001$ ), and signs of systolic (tricuspid annular plane systolic excursion: control 18 mm (2) versus ART 16 mm (3),  $P < 0.001$ ) and diastolic dysfunction (isovolumic relaxation time: control 68 ms (12) versus ART 79 ms (12),  $P < 0.001$ ). ART children also presented increased systolic blood pressure (control 90 mmHg (6) versus ART 94 mmHg (5),  $P < 0.003$ ) and cIMT (control 0.52  $\mu$ m (0.14) versus ART 0.60  $\mu$ m (0.16),  $P < 0.001$ ) as compared with those spontaneously conceived. **CONCLUSIONS:** Cardiovascular changes previously reported in ART fetuses persist postnatally at 3 years of age. These results underscore the importance of future studies for assessing the long-term cardiovascular health associated with ART. **TWEETABLE ABSTRACT:** Cardiovascular changes described in fetuses conceived by ART, persist in children at 3 years of age.

### **J OBSTET GYNAECOL RES. 2018 SEP 19.**

**FIRST TRIMESTER SCREENING FOR PRETERM AND TERM PRE-ECLAMPSIA BY MATERNAL CHARACTERISTICS AND BIOPHYSICAL MARKERS IN A LOW-RISK POPULATION.**

Sepúlveda-Martínez A, Rencoret G, Silva MC, Ahumada P, Pedraza D, Muñoz H, Valdés E, Parra-Cordero M.

**AIM:** To develop a combined predictive model for preterm and term pre-eclampsia (PE) during the first trimester of pregnancy. **METHODS:** This investigation was a nested case-control study in singleton pregnancies at the Maternal-Fetal Medicine Unit, University of Chile Hospital. A priori risks for preterm and term PE were calculated by multivariate logistic regression analyses. Biophysical markers were log<sub>10</sub>-transformed and expressed as multiples of the median. A multivariate logistic regression analysis was used to estimate a combined predictive model of preterm and term PE. Detection rates at different cut-off points were determined by a receiver operator curve analysis of a posteriori risks. **RESULTS:** First trimester mean arterial pressure and uterine artery Doppler pulsatility index were significantly higher in women who develop PE than in the unaffected group. The detection rate of preterm PE based on maternal characteristics and biophysical markers was 72% at a 10% false-positive rate, corresponding to a cut-off risk of 1 in 50. The detection rate for term PE was 30% at a 10% false-positive rate. **CONCLUSION:** Preterm PE can be predicted by a combination of maternal characteristics and biophysical markers. However, first trimester screening is less valuable for term PE.

### **ULTRASOUND OBSTET GYNECOL. 2018 SEP 11.**

**TRANSGENERATIONAL TRANSMISSION OF SMALL FOR GESTATIONAL AGE.**

Sepúlveda-Martínez Á, Rodríguez-López M, Paz-Y-Miño F, Casu G, Crovetto F, Gratacós E, Crispi F.

**OBJECTIVE:** To evaluate the transgenerational transmission of small for gestational age. **METHODS:** Cohort study including a random sample of 2,043 offspring of deliveries occurring from 1975 to 1993. Of 623 offspring -now adults- that agreed to participate, 152 adults (72 born small-for-gestational age (SGA) and 80 with appropriate intrauterine growth) reported to have at least one child. Multiple regression analysis was used to determine the presence of SGA (defined as a birthweight < 10th percentile) or placental mediated disease (defined as the presence of SGA, preeclampsia or gestational hypertension) in the following generation. **RESULTS:** Descendants from SGA adults presented lower birthweight percentile (median 26 [interquartile range 7-52] vs. 43 [19-75];  $p < 0.001$ ) and higher prevalence of SGA (40.3% vs. 16.3%;  $p = 0.001$ ) and placental mediated disease (43.1% vs. 17.5%;  $p = 0.001$ ). After adjustment for confounder variables, parental SGA background was associated with an almost three-fold increased risk of subsequent SGA or any placental mediated disease in the following generation. This association was stronger in SGA mothers as compared to fathers. **CONCLUSIONS:** Our data provides evidence suggesting a transgenerational transmission of SGA highlighting the importance of public health strategies for preventing intrauterine growth impairment. This article is protected by copyright. All rights reserved.

### **INT UROGYNECOL J. 2018 AUG 1.**

**COMPARISON OF TRANSPERINEAL ULTRASOUND WITH POP-Q FOR ASSESSING SYMPTOMS OF PROLAPSE.**

Volløyhaug I, Rojas RG, Mørkved S, Salvesen KÅ.

**INTRODUCTION:** Our aim was to study any correlation between pelvic organ prolapse quantification (POP-Q) and ultrasound measurement of prolapse in women from a normal population and to identify the method with a stronger association with prolapse symptoms. **METHODS:** A cross-sectional study of 590 parous women responding to the Pelvic Floor Distress Inventory was carried out. They were examined using POP-Q and transperineal ultrasound, and correlation was tested using Spearman's rank test. Numerical measurements and significant prolapse (POP-Q  $\geq 2$  in

any compartment or bladder  $\geq 10$  mm, cervix  $\geq 0$  mm or rectal ampulla  $\geq 15$  mm below the symphysis on ultrasound) were compared in symptomatic and asymptomatic women (Mann-Whitney U and Chi-squared tests). RESULTS: A total of 256 women had POP-Q $\geq 2$  and 209 had significant prolapse on ultrasound. The correlation (rs) between POP-Q and ultrasound was 0.69 (anterior compartment), 0.53 (middle), and 0.39 (posterior),  $p < 0.01$ . Women with a "vaginal bulge" (n=68) had greater descent on POP-Q and ultrasound in the anterior and middle compartments than asymptomatic women,  $p < 0.01$ . For women with a symptomatic bulge, the odds ratio was 3.8 (95% CI 2.2-6.7) for POP-Q $\geq$  grade 2 and 2.4 (95% CI 1.4-3.9) for prolapse on ultrasound. A sensation of heaviness (n=90) and incomplete bladder emptying (n=4) were more weakly associated with ultrasound ( $p = 0.03$  and  $0.04$ ), and splinting (n=137) was associated with POP-Q Bp,  $p = 0.02$ . CONCLUSION: POP-Q and ultrasound measurement of prolapse had moderate to strong correlation in the anterior and middle compartments and weak correlation in the posterior compartment. Both methods were strongly associated with the symptom "vaginal bulge," but POP-Q had a stronger association than ultrasound.

#### **AM J OBSTET GYNECOL. 2018 OCT;219(4):379.E1-379.E8.**

##### **ATRAUMATIC NORMAL VAGINAL DELIVERY: HOW MANY WOMEN GET WHAT THEY WANT?**

Caudwell-Hall J, Kamisan Atan I, Guzman Rojas R, Langer S, Shek KL, Dietz HP.

BACKGROUND: Trauma to the perineum, levator ani complex, and anal sphincter is common during vaginal childbirth, but often clinically underdiagnosed, and many women are unaware of the potential for long-term damage. OBJECTIVE: In this study we use transperineal ultrasound to identify how many women will achieve a normal vaginal delivery without substantial damage to the levator ani or anal sphincter muscles, and to create a model to predict patient characteristics associated with successful atraumatic normal vaginal delivery. STUDY DESIGN: This is a retrospective, secondary analysis of data sets gathered in the context of an interventional perinatal imaging study. A total of 660 primiparas, carrying an uncomplicated singleton pregnancy, underwent an antepartum and postpartum interview, vaginal exam (Pelvic Organ Prolapse Quantification), and 4-dimensional translabial ultrasound. Ultrasound data were analyzed for levator trauma and/or overdistention and residual sphincter defects. Postprocessing analysis of ultrasound volumes was performed blinded against clinical data and analyzed against obstetric data retrieved from the local maternity database. Levator avulsion was diagnosed if the muscle insertion at the inferior pubic ramus at the plane of minimal hiatal dimensions and within 5 mm above this plane on tomographic ultrasound imaging was abnormal, ie the muscle was disconnected from the inferior pubic ramus. Hiatal overdistensibility (microtrauma) was diagnosed if there was a peripartum increase in hiatal area on Valsalva by  $>20\%$  with the resultant area  $\geq 25$  cm<sup>2</sup>. A sphincter defect was diagnosed if a gap of  $>30$  degrees was seen in  $\geq 4$  of 6 tomographic ultrasound imaging slices bracketing the external anal sphincter. Two models were tested: a first model that defines severe pelvic floor trauma as either obstetric anal sphincter injury or levator avulsion, and a second, more conservative model, that also included microtrauma. RESULTS: A total of 504/660 women (76%) returned for postpartum follow-up as described previously. In all, 21 patients were excluded due to inadequate data or intercurrent pregnancy, leaving 483 women for analysis. Model 1 defined nontraumatic vaginal delivery as excluding operative delivery, obstetric anal sphincter injuries, and sonographic evidence of levator avulsion or residual sphincter defect. Model 2 also excluded microtrauma. Of 483 women, 112 (23%) had a cesarean delivery, 103 (21%) had an operative vaginal delivery, and 17 (4%) had a third-/fourth-degree tear, leaving 251 women who could be said to have had a normal vaginal delivery. On ultrasound, in model 1, 27 women (6%) had an avulsion and 31 (6%) had a residual defect, leaving 193/483 (40%) who met the criteria for atraumatic normal vaginal delivery. In model 2, an additional 33 women (7%) had microtrauma, leaving only 160/483 (33%) women who met the criteria for atraumatic normal vaginal delivery. On multivariate analysis, younger age and earlier gestation at time of delivery remained highly significant as predictors of atraumatic normal vaginal delivery in both models, with increased hiatal area on Valsalva also significant in model 2 (all  $P \leq .035$ ). CONCLUSION: The prevalence of significant pelvic floor trauma after vaginal child birth is much higher than generally assumed. Rates of obstetric anal sphincter injury are often underestimated and levator avulsion is not included as a consequence of vaginal birth in most obstetric text books. In this study less than half (33-40%) of primiparous women achieved an atraumatic normal vaginal delivery.

#### **J MATERN FETAL NEONATAL MED. 2018 FEB 11:1-9.**

##### **COMPARISON OF 2D VERSUS M-MODE ECHOCARDIOGRAPHY FOR ASSESSING FETAL MYOCARDIAL WALL THICKNESS.**

Sepúlveda-Martínez A, García-Otero L, Soveral I, Guirado L, Valenzuela-Alcaraz B, Torres X, Rodríguez-Lopez M, Gratacos E, Gómez O, Crispi F.

OBJECTIVE: M-mode and 2D have been proposed for evaluating fetal myocardial thickness. However, studies comparing the performance of both modalities are lacking. We aimed to compare 2D versus M-mode reproducibility for assessing myocardial wall thicknesses. METHODS: A prospective study including 45 healthy fetuses from low-risk pregnancies evaluated between 18 and 41 weeks of gestation. Left and right ventricular free-wall and septal myocardial thicknesses were measured at end-diastole (ED) and end-systole (ES) in transverse 4-chamber view using 2D and M-mode. Intra- and interobserver reproducibility was evaluated by the concordance correlation coefficient (CCC). Both techniques were compared by t-test of the CCC. RESULTS: 2D and M-mode demonstrated excellent and similar intraobserver repeatability, with the best concordance in ES septal thickness (M-mode CCC 0.956 versus 2D-mode CCC 0.914). Interobserver reproducibility demonstrated also a high concordance, optimal in ES left ventricular free wall (M-mode 0.925 versus 2 D 0.855). Comparison of both techniques demonstrated a high concordance in all measurements, except for ED septal thickness with better reproducibility using M-mode (CCC 0.954 versus 0.847,  $p = .017$ ). CONCLUSIONS: 2D and M-mode can be used in a reproducible manner for measuring fetal myocardial thickness, with a slightly better performance of M-mode for assessing ED septal wall thickness.

#### **ULTRASOUND OBSTET GYNECOL. 2018 MAY;51(5):677-683.**

##### **ANAL SPHINCTER DEFECTS AND FECAL INCONTINENCE 15-24 YEARS AFTER FIRST DELIVERY: A CROSS-SECTIONAL STUDY.**

Guzmán Rojas RA, Salvesen KÅ, Volløyhaug I.

OBJECTIVES: To establish the prevalence of external (EAS) and internal (IAS) anal sphincter defects present 15-24 years after childbirth according to mode of delivery, and their association with development of fecal incontinence (FI). The study additionally aimed to compare the proportion

of women with obstetric anal sphincter injuries (OASIS) reported at delivery with the proportion of women with sphincter defect detected on ultrasound 15-24 years later. **METHODS:** This was a cross-sectional study including 563 women who delivered their first child between 1990 and 1997. Women responded to a validated questionnaire (Pelvic Floor Distress Inventory) in 2013-2014, from which the proportion of women with FI was recorded. Information about OASIS was obtained from the National Birth Registry. Study participants underwent four-dimensional transperineal ultrasound examination. Defect of EAS or IAS of  $\geq 30^\circ$  in at least four of six slices on tomographic ultrasound was considered a significant defect and was recorded. Four study groups were defined based on mode of delivery of the first child. Women who had delivered only by Cesarean section (CS) constituted the CS group. Women in the normal vaginal delivery (NVD) group had NVD of their first child and subsequent deliveries could be NVD or CS. The forceps delivery (FD) group included women who had FD, NVD or CS after FD of their first born. The vacuum delivery (VD) group included women who had VD, NVD or CS after VD of their first born. Multiple logistic regression was used to calculate adjusted odds ratios (aORs) for comparison of prevalence of an EAS defect following different modes of delivery and to test its association with FI. Fisher's exact test was used to calculate crude odds ratios (ORs) for IAS defects. **RESULTS:** Defects of EAS and IAS were found after NVD (n=201) in 10% and 1% of cases, respectively, after FD (n=144) in 32% and 7% of cases and after VD (n=120) in 15% and 4% of cases. No defects were found after CS (n=98). FD was associated with increased risk of EAS defect compared with NVD (aOR=3.6; 95% CI, 2.0-6.6) and VD (aOR=3.0; 95% CI, 1.6-5.6) and with increased risk of IAS defect compared with NVD (OR=7.4; 95% CI, 1.5-70.5). The difference between VD and NVD was not significant for EAS or IAS. FI was reported in 18% of women with an EAS defect, in 29% with an IAS defect and in 8% without a sphincter defect. EAS and IAS defects were associated with increased risk of FI (aOR=2.5 (95% CI, 1.3-4.9) and OR=4.2 (95% CI, 1.1-13.5), respectively). Of the ultrasonographic sphincter defects, 80% were not reported as OASIS at first or subsequent deliveries. **CONCLUSIONS:** Anal sphincter defects visualized on transperineal ultrasound 15-24 years after first delivery were associated with FD and development of FI. Ultrasound revealed a high proportion of sphincter defects that were not recorded as OASIS at delivery.

### **J OBSTET GYNAECOL RES. 2018 JAN;44(1):81-86.**

#### **METFORMIN AS A PROPHYLACTIC TREATMENT OF GESTATIONAL DIABETES IN PREGNANT PATIENTS WITH PREGESTATIONAL INSULIN RESISTANCE: A RANDOMIZED STUDY.**

Valdés E, Sepúlveda-Martínez A, Candia P, Abusada N, Orellana R, Manukian B, Cuellar E.

**AIM:** We aimed to assess the use of metformin (MTF) in the prevention of gestational diabetes mellitus (GDM) in patients with pregestational insulin resistance (PIR). **METHODS:** A double blind, multicenter, randomized trial was carried out in patients with a history of PIR and pregestational MTF treatment. Groups were allocated either to MTF 1700mg/day or placebo. Patients were recruited between 12+0 and 15+6 gestational weeks, and treatment was extended until week 36. A multiple logistic regression analysis was applied to determine the relation between the use of metformin and the development of GDM. **RESULTS:** One hundred and forty one patients were randomized (68 patients in the MTF group and 73 in the placebo group). A total of 30 patients withdrew from the study during follow-up. Administration of MTF was not associated with a decrease in the incidence of GDM as compared to placebo (37.5% vs 25.4%, respectively; P=0.2). Moreover, MTF administration was associated with a significant increase in drug intolerance as compared to placebo (14.3% vs 1.8%, respectively; P=0.02). **CONCLUSION:** The use of MTF is not effective in prevention of GDM in populations with PIR. The use of MTF shows a significantly higher frequency of drug intolerance than placebo.

### **INT UROGYNECOL J. 2018 AUG;29(8):1129-1134.**

#### **OBESITY: HOW MUCH DOES IT MATTER FOR FEMALE PELVIC ORGAN PROLAPSE?**

Young N, Atan IK, Rojas RG, Dietz HP.

**INTRODUCTION AND HYPOTHESIS:** The objective was to determine the association between body mass index (BMI) and symptoms and signs of female pelvic organ prolapse (POP). **METHODS:** An observational cross-sectional study of 964 archived datasets of women seen for symptoms and signs of lower urinary tract and pelvic organ dysfunction between September 2011 and February 2014 at a tertiary urogynaecology centre in Australia was carried out. An in-house standardised interview, the International Continence Society Pelvic Organ Prolapse Quantification (ICS POP-Q) and 4-D translabial ultrasound, followed by analysis of ultrasound volumes for pelvic organ descent and hiatal area on Valsalva, were performed, blinded against other data. **RESULTS:** There is a positive association between BMI and posterior compartment prolapse on clinical examination and ultrasound imaging, but not for the anterior and central compartments. There was no association with prolapse symptom bother and a negative association with symptoms of prolapse. **CONCLUSIONS:** In this observational study, we found a strong association between all tested measures of posterior compartment descent and BMI, both clinical and on imaging.

### **ULTRASOUND OBSTET GYNECOL. 2018 JUN;51(6):775-782.**

#### **PERINATAL OUTCOME AND PLACENTAL APOPTOSIS IN PATIENTS WITH LATE-ONSET PRE-ECLAMPSIA AND ABNORMAL UTERINE ARTERY DOPPLER AT DIAGNOSIS.**

Rodríguez M, Couve-Pérez C, San Martín S, Martínez F, Lozano C, Sepúlveda-Martínez A.

**OBJECTIVE:** To determine the rate of placental apoptosis and adverse perinatal outcome in patients with late-onset pre-eclampsia (PE) and abnormal uterine artery (UtA) Doppler at diagnosis. **METHODS:** This was a prospective cohort study of women with singleton pregnancy diagnosed with late PE, performed between August 2011 and January 2014 at the Maternal-Fetal Medicine Unit of Hospital Carlos Van Buren. Patients were stratified according to UtA Doppler status at diagnosis (pulsatility index (PI)  $\leq$  or  $>$  95th percentile). Logistic regression analysis was performed to identify associations between abnormal UtA Doppler and adverse maternal and perinatal outcomes. In a subset of this cohort for whom placental samples were available, immunohistochemical analysis of the placenta was performed to identify the rate of apoptosis and its association with UtA Doppler by comparing samples from those with normal and those with abnormal UtA Doppler and normotensive controls. Non-parametric linear trend analysis was performed for assessment of the apoptotic index. **RESULTS:** Eighty-six patients were included in the final analysis. Of these, UtA-PI was above the 95th percentile in 33 (38.4%) patients. Gestational age at diagnosis and delivery were significantly lower in this group

compared with patients with normal UtA Doppler. Abnormal UtA Doppler was associated with increased risk of severe PE (odds ratio (OR)=7.5; 95% CI, 2.76-20.46; P<0.001), late preterm delivery (OR=13.7; 95% CI, 4.53-41.46; P<0.001), small-for-gestational age at birth (OR=12.3; 95% CI, 3.17-47.57; P<0.001) and admission to the neonatal intensive care unit (OR=12.8; 95% CI, 2.61-62.36; P=0.002). Moreover, UtA Z-score demonstrated a significant inverse correlation with birth-weight Z-score ( $r=-0.34$ ; P=0.0013). Mean placental apoptotic index demonstrated an ascending linear trend according to UtA Doppler status (P=0.04). CONCLUSIONS: In patients with late PE, UtA Doppler was useful for clinical classification and as an indicator of placental histological findings. Correlation between UtA Doppler and the apoptotic index provides new evidence of a subgroup of late PE with a placental origin.

#### **ACTA OBSTET GYNECOL SCAND. 2018 JUN;97(6):751-757.**

##### **CAN PELVIC FLOOR TRAUMA BE PREDICTED ANTENATALLY?**

Caudwell-Hall J, Kamisan Atan I, Brown C, Guzman Rojas R, Langer S, Shek KL, Dietz HP.

**INTRODUCTION:** Levator trauma is a risk factor for the development of pelvic organ prolapse. We aimed to identify antenatal predictors for significant damage to the levator ani muscle during a first vaginal delivery. **MATERIAL AND METHODS:** A retrospective observational study utilizing data from two studies with identical inclusion criteria and assessment protocols between 2005 and 2014. A total of 1148 primiparae with an uncomplicated singleton pregnancy were recruited and assessed with translabial ultrasound at 36 weeks antepartum and 871 (76%) returned for reassessment 3-6 months postpartum. The ultrasound data of vaginally parous women were analyzed for levator avulsion and microtrauma. The former was diagnosed if the muscle insertion at the inferior pubic ramus in the plane of minimal hiatal dimensions and within 5 mm above were abnormal on tomographic ultrasound imaging. Microtrauma was diagnosed in women with an intact levator and if there was a postpartum increase in hiatal area on Valsalva by >20% with the resultant area  $\geq 25$  cm<sup>2</sup>. **RESULTS:** The complete datasets of 844 women were analyzed. Among them, 609 delivered vaginally: by normal vaginal delivery in 452 (54%), a vacuum birth in 102 (12%) and a forceps delivery in 55 (6%). Levator avulsion was diagnosed in 98 and microtrauma in 97. On multivariate analysis, increasing maternal age, lower body mass index and lower bladder neck descent were associated with avulsion. Increased bladder neck descent and a family history of cesarean section (CS) were associated with microtrauma. **CONCLUSIONS:** Maternal age, body mass index, bladder neck descent and family history of CS are antenatal predictors for levator trauma.

#### **REPRODUCTION. 2018 FEB;155(2):173-181.**

##### **EFFECTS OF SYMPATHECTOMY ON OVARIAN FOLLICULAR DEVELOPMENT AND STEROID SECRETION.**

Garrido MP, Fernandois D, Venegas M, Paredes AH.

Recently, the influence of adrenergic activity over ovarian function, and thus fertility, has begun to gain importance. Previous studies have shown that adrenergic activity through norepinephrine (NE) participates in the control of follicular development and steroidal secretion from the ovary, among other functions. To examine this phenomenon, the denervation of the gonad has been widely used to observe changes in the ovary's performance. Nevertheless, the effect of the absence of adrenergic nerves in the ovary has only been studied in short times periods. In the present work, we used guanethidine (a drug that produces an irreversible sympathectomy) during the infantile period of rats, and we observed its effects in the adult rat (6 months old). Our results indicate that ovarian NE content is recovered at 6 months old, alongside with an increase of the adrenal content of NE and a dysfunctional celiac ganglion. Together, these results suggest that the recovery of ovarian NE does not come from a neural origin. In addition, ovarian performance was impaired because the changes in follicular development and steroidal secretion are not recovered despite the recovery of ovarian NE content. In conclusion, these results suggest that the nerve-ovarian connections, which are established during infantile development, are necessary for the accurate response of the ovary to sympathetic stimulation.

## **DEPARTAMENTO DE ORTOPEDIA Y TRAUMATOLOGÍA**

#### **CASE REP ORTHOP. 2018 OCT 25;2018:3808362.**

##### **SURGICAL TREATMENT OF INTRAPELVIC PSEUDOTUMOUR AFTER HIP RESURFACING ARTHROPLASTY: CASE REPORT AND LITERATURE REVIEW.**

Barrientos C, Brañes J, Llanos JL, Martínez A, Barahona M.

Hip replacement is the surgery of the last century due to its impact on the quality of life. A pseudotumour is a rare complication of hip arthroplasty, and it is related to a metal-bearing surface. Pseudotumour is a challenging scenario for hip surgeons due to poor clinical outcomes. The patient consulted for hip pain and paresthesia in the left lower extremity, and analyses showed that the cause was a sizeable intrapelvic pseudotumour. A multidisciplinary team surgery was planned. At first, an infraumbilical approach was made to resect the intrapelvic-retroperitoneum portion of the pseudotumour. Then, a posterolateral hip approach was performed, to resect the remaining portion of the pseudotumour and revision arthroplasty. At five years of follow-up, there are no clinical or imaging signs of recurrence of the pseudotumour. Treatment evidence is limited to a series of cases and expert opinions; we encourage complete resection and revision arthroplasty.

#### **FOOT ANKLE SURG. 2018 NOV 5. PII: S1268-7731(18)30120-6.**

##### **CHRONIC DELTOID LIGAMENT INSUFFICIENCY REPAIR WITH INTERNAL BRACE™ AUGMENTATION.**

Pellegrini MJ, Torres N, Cuchacovich NR, Huertas P, Muñoz G, Carcuro GM.

**BACKGROUND:** Patients with chronic deltoid ligament insufficiency (CDLI) present a challenging situation. Although numerous procedures have been described, optimal treatment is still a matter of debate. While the treatment armamentarium ranges from simple ligament repair to complex reconstructions with or without realignment osteotomies, direct repair augmented with an Internal Brace™ device appears to be an attractive intermediate option. We investigated functional outcomes and complications in patients with CDLI operated on using Internal Brace™

augmentation. **METHODS:** A prospective study was conducted. Patients were included if they presented medial ankle pain and/or giving way, exhibited asymmetric flexible hindfoot valgus, failed conservative treatment, and had a positive MRI evaluated by an independent radiologist. Patients with stage IV flatfoot deformity, neuropathy and/or inflammatory arthritis were excluded. CDLI was confirmed intraoperatively with the arthroscopic drive-through sign. Patients were evaluated preoperatively and postoperatively using FAAM, SF-36 and grade of satisfaction. Paired t-tests were used to assess FAAM and SF-36 scores variation. **RESULTS:** Thirteen patients met inclusion criteria. No patient was lost to follow-up, with a mean follow-up time of 13.5 months (range 6-21). Preoperative FAAM and SF-36 scores improved from 58.7 to 75.3 and from 60.2 to 84.4 postoperatively, respectively ( $p<.01$ ). Two implant failures were observed, with no apparent compromise of construct stability. No patient was re-operated. **CONCLUSIONS:** Our results suggest that deltoid ligament repair with Internal Brace™ augmentation in patients with CDLI is a reliable option with good functional outcomes and high satisfaction grade in short term follow-up.

#### **FOOT ANKLE CLIN. 2018 DEC;23(4):659-678.**

##### **SPRING LIGAMENT INSTABILITY.**

Bastias GF, Dalmáu-Pastor M, Astudillo C, Pellegrini MJ.

The crucial role of the spring ligament complex within the pathologic process that leads to flatfoot deformity has evolved recently. There has been improvement in the anatomic knowledge of the spring ligament and understanding of its complex relationship to the deltoid complex and outstanding advances in biomechanics concepts related to the spring ligament. Optimization of flatfoot treatment strategies are focused on a renewed interest in the spring ligament and medial soft tissue reconstruction in concert with bony correction to obtain an adequate reduction of the talonavicular deformity and restoration of the medial longitudinal arch.

#### **KNEE SURG RELAT RES. 2018 SEP 1;30(3):255-260.**

##### **KNEE EXAMINATION UNDER ANESTHESIA: DEVELOPMENT OF A PREDICTIVE SCORE FOR PARTIAL ANTERIOR CRUCIATE LIGAMENT TEARS.**

Ekdahl M, Acevedo M, Dominguez C, Barahona M, Hernandez R, Mujica I.

**PURPOSE:** To determine the accuracy of knee examination under anesthesia (EUA) and develop a prognostic score for partial anterior cruciate ligament (ACL) tears. **MATERIALS AND METHODS:** A total of 229 patients with an ACL injury were included. Knee EUA was performed using the Lachman test, pivot shift test and arthrometric maximum manual side-to-side difference (AMMD) test. The arthroscopic examination is the gold standard for the diagnosis of partial and complete ACL tears, which was compared with EUA findings. Multivariate logistic regression was estimated, and the significant variables were used to develop a predictive score. **RESULTS:** The relative risk for a complete tear with Lachman 2+ was 8.55 (range, 3.5 to 20.7) and 53.04 (range, 6.7 to 417) with Lachman 3+, compared to Lachman 1+. Negative pivot shift was reported in 23 cases in the partial tear group (76.7%) and in 22 in the complete tear group (11.1%). The AMMD was 3.5 mm in the partial tear group and 5.4 mm in the complete tear group ( $p<0.05$ ). A prognostic score of less than five suggested the presence of a partial ACL tear. The score showed 81.1% sensitivity and 68.7% specificity. **CONCLUSIONS:** Partial ACL tears can be differentiated from complete tears with Lachman test, pivot shift test, and AMMD test.

#### **J PSYCHOSOM RES. 2018 JAN;104:48-54.**

##### **FOOD ALLERGY: CHILDREN'S SYMPTOM LEVELS ARE ASSOCIATED WITH MOTHERS' PSYCHO-SOCIO-ECONOMIC VARIABLES.**

Cortes A, Castillo A, Sciaraffia A.

**BACKGROUND:** Allergies affect children's health as well as their quality of life, stress levels, and family budget. The available literature suggests that family, social and psychological factors are affected by allergic pathologies such as rhinitis, asthma and atopic dermatitis. However, few studies have focused on quantifying such association in child food allergy. This study aims to enhance the understanding of the associations between caregiver variables and children's Food Allergy (FA). **METHODS:** The study involved 206 participants: 103 mothers plus 103 children with IgE mediated FA. The analyses excluded two outliers comprising 101 subjects. For statistical analyses, each dyad -mother/child- was considered to be one subject unit. A between-subjects one-way ANOVA determined the association of children's cutaneous, gastric and respiratory symptoms with anxiety, depression, perceived social support and socioeconomic factors in the mothers. **RESULTS:** There are significant associations between children's allergic symptoms (gastric and cutaneous) and mothers' psychological state (anxiety and depression); family budget; social interactions (with friends, family and partner); understanding of health care required by their child; and sleep disorders. Respiratory symptoms did not show any significant associations with the dependent variables. **CONCLUSION:** FA is a process in which children's symptoms are significantly associated with socioeconomic and psychological variables of the mothers. The presence or absence of some specific symptoms is directly associated with specific impacts on the mothers. An understanding of such dynamics supports the consideration of a comprehensive and multidisciplinary therapeutic approach to offer more ecological healthcare for "families living with FA."

#### **FOOT ANKLE SURG. 2018 FEB 16. PII: S1268-7731(18)30032-8.**

##### **TIBIOTALOCALCANEAL ARTHRODESIS WITH DISTAL TIBIAL ALLOGRAFT FOR MASSIVE BONE DEFICITS IN THE ANKLE.**

Escudero MI, Poggio D, Alvarez F, Barahona M, Vivar D, Fernandez A.

**BACKGROUND:** The purpose of this study was to assess the outcomes of distal tibial structural allograft to obtain a stable TTC fusion. **METHODS:** Retrospectively, ten patients were carried out with a minimum one year follow-up. The median age was 72 (33-81). The median BMI was 28 (24-33). Indications for TTC arthrodesis included failed total ankle arthroplasty ( $n=7$  patients), prior nonunion ( $n=2$  patients), and a trauma injury. **RESULTS:** Union rate was 80%. The median initial height of the distal tibial allograft was 19mm (14-24mm). In seven cases the allograft did not lose height. The AOFAS score median was 69 (31-84). SF-12 median physical component was 39 (30-53), and 59 (23-62) for mental component. The VAS median was 2 (0-8). **CONCLUSIONS:** TTC using distal tibial allograft shows a lower rate of collapse than other structural grafts and provides a fusion rate higher or in accordance with the literature. **LEVEL OF EVIDENCE:** Level IV, retrospective case series.

## DEPARTAMENTO DE PSIQUIATRÍA Y SALUD MENTAL

### AM J MED GENET A. 2018 OCT;176(10):2172-2181.

VARIANCE OF IQ IS PARTIALLY DEPENDENT ON DELETION TYPE AMONG 1,427 22Q11.2 DELETION SYNDROME SUBJECTS.

Zhao Y, Guo T, Fiksinski A, Breetvelt E, McDonald-McGinn DM, Crowley TB, Diacou A, Schneider M, Eliez S, Swillen A, Breckpot J, Vermeesch J, Chow EWC, Gothelf D, Duijff S, Evers R, van Amelsvoort TA, van den Bree M, Owen M, Niarchou M, Bearden CE, Ornstein C et al.

The 22q11.2 deletion syndrome is caused by non-allelic homologous recombination events during meiosis between low copy repeats (LCR22) termed A, B, C, and D. Most patients have a typical LCR22A-D (AD) deletion of 3 million base pairs (Mb). In this report, we evaluated IQ scores in 1,478 subjects with 22q11.2DS. The mean of full scale IQ, verbal IQ, and performance IQ scores in our cohort were 72.41 (standard deviation-SD of 13.72), 75.91(SD of 14.46), and 73.01(SD of 13.71), respectively. To investigate whether IQ scores are associated with deletion size, we examined individuals with the 3 Mb, AD (n = 1,353) and nested 1.5 Mb, AB (n = 74) deletions, since they comprised the largest subgroups. We found that full scale IQ was decreased by 6.25 points (p = .002), verbal IQ was decreased by 8.17 points (p = .0002) and performance IQ was decreased by 4.03 points (p = .028) in subjects with the AD versus AB deletion. Thus, individuals with the smaller, 1.5 Mb AB deletion have modestly higher IQ scores than those with the larger, 3 Mb AD deletion. Overall, the deletion of genes in the AB region largely explains the observed low IQ in the 22q11.2DS population. However, our results also indicate that haploinsufficiency of genes in the LCR22B-D region (BD) exert an additional negative impact on IQ. Furthermore, we did not find evidence of a confounding effect of severe congenital heart disease on IQ scores in our cohort.

### NEURO ENDOCRINOL LETT. 2018 OCT;39(4):288-293.

DEPRESSIVE SYMPTOMS ARE ASSOCIATED WITH HIGHER MORNING PLASMA CORTISOL IN PRIMARY CARE SUBJECTS.

Capponi V, Carrasco C, Macchiavello S, Undurraga J, Campino C, Carvajal C, Gomez T, Weiss C, Aedo I, Vecchiola A, Allende F, Solari S, Fardella C, Baudrand R.

BACKGROUND: Cortisol dysregulation has a potential role in depression. AIM AND METHODS: We evaluated depressive symptoms using the Hamilton Rating Scale for Depression in 48 primary care subjects without history of previous or current depression and its association with cortisol dysregulation (morning plasma cortisol, 24-hour urinary free cortisol and cortisol metabolites). Presence of metabolic syndrome and inflammatory parameters were also assessed. RESULTS: Hamilton Rating Scale for Depression correlated significantly with morning cortisol, but not with urinary free cortisol or metabolites. A significant increase in morning cortisol by Hamilton groups (asymptomatic  $\leq 8$ ; mild to moderate: 9-18; moderate to severe:  $\geq 19$ ) was observed even when adjusted by age/gender. We observed no association of depressive symptoms with metabolic or inflammatory parameters. CONCLUSION: Depressive symptoms in primary care subjects not consulting for their mood are associated with higher morning plasma cortisol, but not urinary cortisol or its metabolites. These observations suggest that systemic hypercortisolism and related metabolic disorders are not observed in mild/initial states of depressive disorders.

### J MED INTERNET RES. 2018 APR 30;20(4):E158.

A REMOTE COLLABORATIVE CARE PROGRAM FOR PATIENTS WITH DEPRESSION LIVING IN RURAL AREAS: OPEN-LABEL TRIAL.

Rojas G, Guajardo V, Martínez P, Castro A, Fritsch R, Moessner M, Bauer S.

BACKGROUND: In the treatment of depression, primary care teams have an essential role, but they are most effective when inserted into a collaborative care model for disease management. In rural areas, the shortage of specialized mental health resources may hamper management of depressed patients. OBJECTIVE: The aim was to test the feasibility, acceptability, and effectiveness of a remote collaborative care program for patients with depression living in rural areas. METHODS: In a nonrandomized, open-label (blinded outcome assessor), two-arm clinical trial, physicians from 15 rural community hospitals recruited 250 patients aged 18 to 70 years with a major depressive episode (DSM-IV criteria). Patients were assigned to the remote collaborative care program (n=111) or to usual care (n=139). The remote collaborative care program used Web-based shared clinical records between rural primary care teams and a specialized/centralized mental health team, telephone monitoring of patients, and remote supervision by psychiatrists through the Web-based shared clinical records and/or telephone. Depressive symptoms, health-related quality of life, service use, and patient satisfaction were measured 3 and 6 months after baseline assessment. RESULTS: Six-month follow-up assessments were completed by 84.4% (221/250) of patients. The remote collaborative care program achieved higher user satisfaction (odds ratio [OR] 1.94, 95% CI 1.25-3.00) and better treatment adherence rates (OR 1.81, 95% CI 1.02-3.19) at 6 months compared to usual care. There were no statically significant differences in depressive symptoms between the remote collaborative care program and usual care. Significant differences between groups in favor of remote collaborative care program were observed at 3 months for mental health-related quality of life (beta 3.11, 95% CI 0.19-6.02). CONCLUSIONS: Higher rates of treatment adherence in the remote collaborative care program suggest that technology-assisted interventions may help rural primary care teams in the management of depressive patients. Future cost-effectiveness studies are needed.

### J MED INTERNET RES. 2018 JAN 31;20(1):E38.

REMOTE COLLABORATIVE DEPRESSION CARE PROGRAM FOR ADOLESCENTS IN ARAUCANÍA REGION, CHILE: RANDOMIZED CONTROLLED TRIAL.

Martínez V, Rojas G, Martínez P, Zitko P, Irrarázaval M, Luttgés C, Araya R.

BACKGROUND: Despite evidence on efficacious interventions, a great proportion of depressed adolescents do not receive evidence-based treatment and have no access to specialized mental health care. Remote collaborative depression care (RCDC) may help to reduce the gap between needs and specialized mental health services. OBJECTIVE: The objective of this study was to assess the feasibility, acceptability, and effectiveness of an RCDC intervention for adolescents with major depressive disorder (MDD) living in the Araucanía Region, Chile. METHODS: A cluster randomized, assessor-blind trial was carried out at 16 primary care centers in the Araucanía Region, Chile. Before randomization, all

participating primary care teams were trained in clinical guidelines for the treatment of adolescent depression. Adolescents (N=143; 13-19 years) with MDD were recruited. The intervention group (RCDC, N=65) received a 3-month RCDC treatment that included continuous remote supervision by psychiatrists located in Santiago, Chile's capital city, through shared electronic health records (SEHR) and phone patient monitoring. The control group (enhanced usual care or EUC; N=78) received EUC by clinicians who were encouraged to follow clinical guidelines. Recruitment and response rates and the use of the SEHR system were registered; patient adherence and satisfaction with the treatment and clinician satisfaction with RCDC were assessed at 12-week follow-up; and depressive symptoms and health-related quality of life (HRQoL) were evaluated at baseline and 12-weeks follow-up. RESULTS: More than 60.3% (143/237) of the original estimated sample size was recruited, and a response rate of 90.9% (130/143) was achieved at 12-week follow-up. A mean (SD) of 3.5 (4.0) messages per patient were written on the SEHR system by primary care teams. A third of the patients showed an optimal adherence to psychopharmacological treatment, and adolescents in the RCDC intervention group were more satisfied with psychological assistance than those in EUC group. Primary care clinicians were satisfied with the RCDC intervention, valuing its usefulness. There were no significant differences in depressive symptoms or HRQoL between groups. Satisfaction with psychological care, in both groups, was related to a significant change in depressive symptomatology at 12-weeks follow-up (beta=-4.3, 95% CI -7.2 to -1.3). CONCLUSIONS: This is the first trial of its kind in Latin America that includes adolescents from vulnerable backgrounds, with an intervention that proved to be feasible and well accepted by both patients and primary care clinicians. Design and implementation issues may explain similar effectiveness across arms. The effectiveness of the intervention seems to be comparable with an already nationwide established treatment program that proved to be highly efficacious under controlled conditions.

### **J ADOLESC. 2018 FEB;63:129-141.**

IS MATERNAL DEPRESSION RELATED TO MOTHER AND ADOLESCENT REPORTS OF FAMILY FUNCTIONING?

Pérez JC, Coó S, Irarrázaval M.

While adolescent-parent disagreements about family functioning are common, they may also be indicative of family members' health problems and may compromise adolescent adjustment. This study examines the association between maternal depressive symptoms and family functioning perceptions, considering both the adolescents' and their mothers' points of view. A sample of 943 Chilean dyads of adolescents (69% female, Mage = 14.43 years old) and their mothers (Mage = 43.20 years) reported their perceptions of family cohesion and adaptability. Mothers also reported their depressive symptoms. Results indicated that mothers perceived their family as more cohesive and more adaptable than their children. There was a negative association between maternal and adolescent reports of family cohesion and maternal depressive symptoms. In the mother' reports, this association depended on adolescent's age. In the case of adolescents' reports, this association depended on adolescent's gender. Finally, maternal depressive symptoms were a significant predictor of mother-adolescent agreement about family cohesion.

### **J AFFECT DISORD. 2018 MAY;232:9-16.**

THE KOUKOPOULOS MIXED DEPRESSION RATING SCALE (KMDRS): AN INTERNATIONAL MOOD NETWORK (IMN) VALIDATION STUDY OF A NEW MIXED MOOD RATING SCALE.

Sani G, Vöhringer PA, Barroilhet SA, Koukopoulos AE, Ghaemi SN.

BACKGROUND: It has been proposed that the broad major depressive disorder (MDD) construct is heterogenous. Koukopoulos has provided diagnostic criteria for an important subtype within that construct, "mixed depression" (MxD), which encompasses clinical pictures characterized by marked psychomotor or inner excitation and rage/anger, along with severe depression. This study provides psychometric validation for the first rating scale specifically designed to assess MxD symptoms cross-sectionally, the Koukopoulos Mixed Depression Rating Scale (KMDRS). METHODS: 350 patients from the international mood network (IMN) completed three rating scales: the KMDRS, Montgomery-Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS). KMDRS' psychometric properties assessed included Cronbach's alpha, inter-rater reliability, factor analysis, predictive validity, and Receiver Operator Curve analysis. RESULTS: Internal consistency (Cronbach's alpha = 0.76; 95% CI 0.57, 0.94) and interrater reliability (kappa = 0.73) were adequate. Confirmatory factor analysis identified 2 components: anger and psychomotor excitation (80% of total variance). Good predictive validity was seen (C-statistic = 0.82 95% CI 0.68, 0.93). Severity cut-off scores identified were as follows: none (0-4), possible (5-9), mild (10-15), moderate (16-20) and severe (> 21) MxD. LIMITATIONS: Non DSM-based diagnosis of MxD may pose some difficulties in the initial use and interpretation of the scoring of the scale. Moreover, the cross-sectional nature of the evaluation does not verify the long-term stability of the scale. CONCLUSIONS: KMDRS was a reliable and valid instrument to assess MxD symptoms.

### **REV MED CHIL. 2018 APR;146(4):479-486.**

TAMIZAJE DE EPISODIO DEPRESIVO EN ADOLESCENTES. VALIDACIÓN DEL INSTRUMENTO PHQ-9

Borghero F, Martínez V, Zitko P, Vöhringer PA, Cavada G, Rojas G.

BACKGROUND: There is a paucity of validated instruments for screening depression in adolescent populations in Chile. AIM: To determine the diagnostic accuracy of the adolescent version of Patient Health Questionnaire-9 (PHQ-9). MATERIAL AND METHODS: The PHQ-9 was transculturally adapted and administered to adolescents aged 15 to 19 years residing in Santiago de Chile, who were then evaluated with a semi structured interview (Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version or K-SADS-PL) and the Beck Depression Inventory. Internal validity, concurrent validity, and discriminatory power of the PHQ-9 were analyzed. RESULTS: We evaluated 245 adolescents aged 16.2 ± 1 years (71% females). Two hundred and ten presented with a depressive episode and 35 were healthy. The sensitivity and specificity of the scale were 86.2 and 82.9% for 11 points, with a positive likelihood ratio of 5.02. CONCLUSIONS: The PHQ-9 is sensitive and specific enough to be used as a screening tool in adolescents with suspected depression. At a 11-point cut-off score as proposed, the likelihood to find a positive result in a subject with depression is five times higher.

**BR J PSYCHIATRY. 2018 JUN;212(6):377-385.**

**PROBABILITY OF MAJOR DEPRESSION DIAGNOSTIC CLASSIFICATION USING SEMI-STRUCTURED VERSUS FULLY STRUCTURED DIAGNOSTIC INTERVIEWS.**

Levis B, Benedetti A, Riehm KE, Saadat N, Levis AW, Azar M, Rice DB, Chiovitti MJ, Sanchez TA, Cuijpers P, Gilbody S, Ioannidis JPA, Kloda LA, McMillan D, Patten SB, Shrier I, Vöhringer P *et al*.

**BACKGROUND:** Different diagnostic interviews are used as reference standards for major depression classification in research. Semi-structured interviews involve clinical judgement, whereas fully structured interviews are completely scripted. The Mini International Neuropsychiatric Interview (MINI), a brief fully structured interview, is also sometimes used. It is not known whether interview method is associated with probability of major depression classification. **Aims** To evaluate the association between interview method and odds of major depression classification, controlling for depressive symptom scores and participant characteristics. **METHOD:** Data collected for an individual participant data meta-analysis of Patient Health Questionnaire-9 (PHQ-9) diagnostic accuracy were analysed and binomial generalised linear mixed models were fit. **RESULTS:** A total of 17 158 participants (2287 with major depression) from 57 primary studies were analysed. Among fully structured interviews, odds of major depression were higher for the MINI compared with the Composite International Diagnostic Interview (CIDI) (odds ratio (OR) = 2.10; 95% CI = 1.15-3.87). Compared with semi-structured interviews, fully structured interviews (MINI excluded) were non-significantly more likely to classify participants with low-level depressive symptoms (PHQ-9 scores  $\leq 6$ ) as having major depression (OR = 3.13; 95% CI = 0.98-10.00), similarly likely for moderate-level symptoms (PHQ-9 scores 7-15) (OR = 0.96; 95% CI = 0.56-1.66) and significantly less likely for high-level symptoms (PHQ-9 scores  $\geq 16$ ) (OR = 0.50; 95% CI = 0.26-0.97). **CONCLUSIONS:** The MINI may identify more people as depressed than the CIDI, and semi-structured and fully structured interviews may not be interchangeable methods, but these results should be replicated. **Declaration of interest** Drs Jetté and Patten declare that they received a grant, outside the submitted work, from the Hotchkiss Brain Institute, which was jointly funded by the Institute and Pfizer. Pfizer was the original sponsor of the development of the PHQ-9, which is now in the public domain. Dr Chan is a steering committee member or consultant of Astra Zeneca, Bayer, Lilly, MSD and Pfizer. She has received sponsorships and honorarium for giving lectures and providing consultancy and her affiliated institution has received research grants from these companies. Dr Hegerl declares that within the past 3 years, he was an advisory board member for Lundbeck, Servier and Otsuka Pharma; a consultant for Bayer Pharma; and a speaker for Medice Arzneimittel, Novartis, and Roche Pharma, all outside the submitted work. Dr Inagaki declares that he has received grants from Novartis Pharma, lecture fees from Pfizer, Mochida, Shionogi, Sumitomo Dainippon Pharma, Daiichi-Sankyo, Meiji Seika and Takeda, and royalties from Nippon Hyoron Sha, Nanzando, Seiya Shoten, Igaku-shoin and Technomics, all outside of the submitted work. Dr Yamada reports personal fees from Meiji Seika Pharma Co., Ltd., MSD K.K., Asahi Kasei Pharma Corporation, Seishin Shobo, Seiya Shoten Co., Ltd., Igaku-shoin Ltd., Chugai Igakusha and Sentan Igakusha, all outside the submitted work. All other authors declare no competing interests. No funder had any role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

**FRONT PSYCHIATRY. 2018 FEB 8;9:25.**

**ASSOCIATION BETWEEN SCHOOL MEMBERSHIP AND SUBSTANCE USE AMONG ADOLESCENTS.**

Gaete J, Rojas G, Fritsch R, Araya R.

**BACKGROUND:** Substance use among adolescents is a major problem worldwide, producing many health and economic consequences. Even though there are well-known personal, familial, and social factors associated with drug use, less is known about the effect of school-related factors. School membership is a recognized variable affecting academic performance among students; however, its effect on substance use is less understood. **AIMS:** The primary aim of this study was to explore the association between school membership and cigarette, alcohol, and cannabis use among a representative sample of secondary students from municipal state-funded schools in Santiago of Chile, and secondly, to test the hypothesis that depressive or anxiety symptoms mediate this association. **METHODS:** A total of 2,508 students from 22 state-funded schools in Santiago, Chile, answered a questionnaire. This instrument included an abbreviated version of the psychological sense of school membership (PSSM), questions regarding the use of alcohol, tobacco, and cannabis and scales of psychological functioning (depression, anxiety, self-concept, and problem-solving). The association analyses were performed using adjusted regression models for each outcome using all independent variables while controlling for gender and age. For the mediation effect, a combination of ordinary least square and logistic regression analyses was conducted. **RESULTS:** There was an association between a strong PSSM and low risk for smoking (OR 0.57; 95% CI 0.46-0.72), drinking (0.65; 95% CI: 0.51-0.83), and cannabis use (0.52; 95% CI 0.37-0.74). We also found that depressive and anxiety symptoms do not fully mediate the association between school membership and any substance use, and 73% of this effect in the case of smoking, 80% in the case of drinking, and 78.5% in the case of cannabis use, was direct. **CONCLUSION:** This is the first study in Latin America exploring the association between school membership and substance use among secondary students. School membership seems to be an important and independent factor to be included in preventive interventions. Therefore, these results support future research aiming to test interventions at increasing the sense of school membership to prevent substance use among adolescents.

**JOURNAL OF AFFECTIVE DISORDERS, 234 (2018): 193-200**

**INTERNET BASED INTERVENTIONS FOR THE PREVENTION AND TREATMENT OF DEPRESSION IN PEOPLE LIVING IN DEVELOPING COUNTRIES: A SYSTEMATIC REVIEW.**

Martínez, Pablo; Rojas Castillo, María Graciela; Martínez, Vania; Lara, María Asunción; Carola Perez, J.

**Background:** Internet-based interventions for depression may be a valuable resource to reduce the treatment gap for those living in developing countries. However, evidence comes mainly from developed countries. This systematic review summarized the evidence on preventive or therapeutic Internet-based interventions for depression for people who reside in developing countries. **Methods:** CINAHL, EMBASE, PubMed, SciELO Citation Indexes, the Journal of Medical Internet Research, and the Telemedicine and e-Health journal, were searched up to June 2017, to identify feasibility or effectiveness studies of preventive or therapeutic Internet-based interventions for depression, with or without human

support. Studies included subjects residing in developing countries, and were published in English or Spanish. Study protocols were included. Risk of bias and/or quality of the reporting of the studies included was assessed. Results: Five feasibility studies, aimed at the prevention of depression, and a study protocol were included in this systematic review. Reports came mostly from the Americas (n = 4). Internet-based interventions aimed at the prevention of depression presented low levels of human support, were useful and acceptable to their users, and require further design refinements to improve their use and retention. Limitations: No gray literature was searched or included in this systematic review. Searches were limited to English and Spanish languages. Discussions: Internet-based interventions aimed at the prevention of depression in people who reside in developing countries are in an early phase of development, limiting the generalizability of the results. Future studies must employ persuasive designs to improve user retention, incorporating larger samples and a control group to conclusively determine feasibility.

### **SCHIZOPHRENIA RESEARCH, 194 (2018): 13-17**

#### **THE RELATIVE PREVALENCE OF SCHIZOPHRENIA AMONG CANNABIS AND COCAINE USERS ATTENDING ADDICTION SERVICES**

Libuy Hidalgo, Nicolás; Angel, Valeria de; Ibáñez Berríos, Carlos; Murray, Robin M.; Mundt, Adrian P.

Background: Cannabis and cocaine are the most common illicit drugs for which people are treated in addiction services in Latin America. Much research has suggested that the use of cannabis increases the risk of schizophrenia; there is less evidence concerning cocaine. The aim of the present study was to establish the relative prevalence of schizophrenia in people treated for cannabis use and cocaine use disorders in Chile. Methods: A sample of 22,615 people treated for illicit drug use disorders was obtained from a national registry of addiction service users in Chile. Clinical diagnoses were established at admission to substance use treatment programs or at any point during the period of treatment. Prevalence rates of schizophrenia and related disorders, and affective disorders were calculated for the groups of people with cocaine use disorders, and cannabis use disorders. Odds ratios (OR) for schizophrenia and for affective disorders were calculated for cannabis users using the group of people treated for cocaine use disorders as reference category. Results: The prevalence of schizophrenia and related disorders was 1.1% in those with cocaine use disorders, but 5.2% in those with cannabis use disorders (OR 4.9;  $p < 0.01$ ). The prevalence of affective disorders was 9.3% in cocaine use disorders, and 13.2% in cannabis use disorders (OR 1.5;  $p < 0.01$ ). Conclusions: The prevalence of schizophrenia and to a lesser extent affective disorders is higher among people with cannabis use disorder than cocaine use disorder among those attending addiction services.

### **NEUROLOGIA. 2018 MAR;33(2):121-128.**

#### **PSYCHIATRIC MANIFESTATIONS OF 22Q11.2 DELETION SYNDROME: A LITERATURE REVIEW.**

Bertrán M, Tagle FP, Irarrázaval M.

INTRODUCTION: The 22q11.2 deletion syndrome is a genetic disorder with variable clinical manifestations. It affects one out of 5950 neonates and has an autosomal dominant inheritance pattern. The aim of this article is to review its psychiatric manifestations and any underlying genetic alterations. METHODS: We reviewed the scientific literature available as of October 2014 in the LILACS and Medline databases. RESULTS: Sixty per cent of these patients fulfilled diagnostic criteria for a mental disorder at some point in their lives, referring to psychotic disorders, attention deficit hyperactivity disorder, mood disorders, anxiety disorders, and autism spectrum disorders. Specific genes, such as COMT and PRODH, have been linked to these psychiatric manifestations. CONCLUSIONS: It is necessary to raise awareness among all health care professionals so that they understand the relevance of these manifestations, are able to anticipate them, and can provide appropriate information to patients and family members.

## **DEPARTAMENTO DE OTORRINOLARINGOLOGÍA**

### **EUR ARCH OTORHINOLARYNGOL. 2018 SEP;275(9):2403-2406.**

#### **EFFECT OF THE TEMPERATURE OF NASAL LAVAGES ON MUCOCILIARY CLEARANCE: A RANDOMISED CONTROLLED TRIAL.**

Sauvalle M, Alvo A.

BACKGROUND: The respiratory epithelium is mainly constituted by caliciform (produces mucus, responsible of keeping moisture and trapping particles) and ciliated cells (transports mucus into the pharynx, by the movement of multiple cilia). For centuries, nasal lavages have been used for different rhinosinusal conditions. Some studies suggest not only a direct effect on the mobilisation of secretions, but also an improvement in mucociliary clearance rates. To our knowledge, the impact of temperature in nasal lavages has been scarcely studied. METHODOLOGY/ PRINCIPAL: We used the saccharin test-applying it in the inferior turbinate and timing the detection of its taste-, to estimate mucociliary clearance rates before and after nasal lavages with saline solution at room (20 °C) or body (37 °C) temperatures. RESULTS: 78 healthy subjects were studied, with a mean saccharin test time of 13.88 min. Then, a nasal lavage was performed, half with 20 °C saline and the other with 37 °C. In both, times improved from baseline (from 13.66 to 11.59 and 14.06 to 9.4 min, respectively) with  $p$  values  $< 0.05$ . CONCLUSIONS: Nasal lavages with saline solution improve mucociliary clearance as measured by saccharin test. Temperature seems to matter, which should be taken into account when indicating nasal lavages to our patients

### **HEAR RES. 2018 DEC 6;373:10-22.**

#### **P27KIP1 DOWN-REGULATION AS ACHIEVED BY TWO CLINICALLY FEASIBLE MEANS DID NOT INDUCE PROLIFERATION OF SUPPORTING CELLS IN THE RAT NEONATAL COCHLEA IN VIVO.**

Silva SA, Maass JC.

In mammals, the cochlear sensory epithelium becomes quiescent early during development. After the first postnatal week, there is no cell replacement

or proliferation, and severe damage leads to permanent deafness. Supporting cells' trans-differentiation has been suggested as a way to regenerate cochlear hair cells after damage. However, they are also needed for proper functionality. *Cdkn1b* (p27Kip1) participates in the cochlear terminal mitosis state achieved during development. Its expression is maintained in adult supporting cells and its postnatal deletion has induced cochlear proliferation *in vitro* and *in vivo*. Therefore, its manipulation has been proposed as a feasible way to induce proliferation of supporting cells after birth. Nevertheless, the literature is scarce regarding feasible methods to directly decrease p27Kip1 in the clinical domain. The effects of p27Kip1 knockdown using viral vectors are not completely elucidated and no pharmacological approaches to decrease p27Kip1 in the cochlea have been tested *in vivo* before. This study explores the ability of p27Kip1 messenger knockdown and pharmacological transcriptional inhibition to induce proliferation of supporting cells in the PO neonatal rat cochlea *in vivo*. Respectively, lentiviral vectors transducing shRNA against p27Kip1 were administered into the scala media or Alsterpaullone 2-Cyanoethyl into the round window niche. Cell markers and gene expression were assessed through immunostaining and qRT-PCR. Despite both methods significantly decreasing p27Kip1 expression *in vivo*, signs of toxicity in the organ of Corti were not found; however, relevant proliferation was not found either. Finally, cochlear damage was added to increase the response *in vitro*, achieving only a mild to moderate proliferation induction. We conclude that our approaches were not able to stimulate the recall of supporting cell proliferation despite significantly decreased p27Kip1 levels *in vivo*. Considering the evaluation of the cochlea at a very responsive stage, we propose that the level of isolated modification of p27Kip1 expression in living mammals achievable through these approaches is insufficient to induce proliferation of supporting cells. Future proliferation induction experiments in the cochlea should study other methods and genes.

## DEPARTAMENTO DE RADIOLOGÍA

### MUSCLE NERVE. 2018 DEC 22.

DISEASE DURATION AND DISABILITY IN DYSFERLINOPATHY CAN BE DESCRIBED BY MUSCLE IMAGING USING HEATMAPS AND RANDOM FORESTS.

Gómez-Andrés D, Díaz J, Munell F, Sánchez-Montáñez Á, Pulido-Valdeolivas I, Suazo L, Garrido C, Quijano-Roy S, Bevilacqua JA.

INTRODUCTION: The manner in which imaging patterns change over the disease course and with increasing disability in dysferlinopathy is not fully understood. METHODS: Fibroadipose infiltration of 61 muscles was scored based on whole-body MRI of 33 patients with dysferlinopathy and represented in a heatmap. We trained random forests to predict disease duration, Motor Function Measure dimension 1 (MFM-D1), and modified Rankin scale (MRS) score based on muscle scoring and selected the most important muscle for predictions. RESULTS: The heatmap delineated positive and negative fingerprints in dysferlinopathy. Disease duration was related to infiltration of infraspinatus, teres major-minor, and supraspinatus muscles. MFM-D1 decreased with higher infiltration of teres major-minor, triceps, and sartorius. MRS related to infiltration of vastus medialis, gracilis, infraspinatus, and sartorius. DISCUSSION: Dysferlinopathy shows a recognizable muscle MRI pattern. Fibroadipose infiltration in specific muscles of the thigh and the upper limb appears to be an important marker for disease progression. Muscle Nerve 2019.

### TOP MAGN RESON IMAGING. 2018 AUG;27(4):179-196.

NEUROMETABOLIC DISORDERS OF THE NEWBORN.

Mankad K, Talenti G, Tan AP, Gonçalves FG, Robles C, Kan EYL, Siddiqui A.

There is an extensive and diverse set of medical conditions affecting the neonatal brain within the spectrum of neurometabolic disorders. As such, their clinical presentations can be rather nonspecific, and can often mimic acquired entities such as hypoxic-ischemic encephalopathy and sepsis. Similarly, the radiological findings in these entities can also be frequently nonspecific, but a more detailed analysis of imaging findings (especially magnetic resonance imaging) alongside the relevant clinical details can be a rewarding experience, thus enabling a timely and targeted diagnosis. Early diagnosis of an underlying neurometabolic disorder is vital, as some of these entities are potentially treatable, and laboratory and genetic testing can be precisely targeted. Further, their detection helps with counselling families for future pregnancies. We present a review of neurometabolic disorders specific to the newborns with a focus on how neuroimaging findings match their clinical presentation patterns.

## DEPARTAMENTO DE UROLOGÍA

### MOL HUM REPROD. 2018 APR 1;24(4):203-210.

LEYDIG CELL DYSFUNCTION IS ASSOCIATED WITH POST-TRANSCRIPTIONAL Deregulation OF CYP17A1 IN MEN WITH SERTOLI CELL-ONLY SYNDROME.

Lardone MC, Argandoña F, Lorca M, Piottante A, Flórez M, Palma C, Ebersperger M, Castro A.

STUDY QUESTION: Is the expression of steroidogenic enzyme 17 $\alpha$ -Hydroxylase/17,20-Lyase (CYP17A1) down-regulated in Leydig cells (LCs) of men with spermatogenic failure and compensated impairment of LC function, i.e. a low testosterone to LH (T/LH) ratio? SUMMARY ANSWER: Although the transcriptional expression of CYP17A1 is increased, its protein expression is decreased, in isolated LCs of men with spermatogenic failure and reduced serum T/LH. WHAT IS KNOWN ALREADY: Primary spermatogenic defects have been associated with functional and morphological abnormalities of LCs, characterized by decreased serum testosterone (T) levels, decreased T/LH, increased 17 $\beta$ -estradiol (E2) and E2/T ratio, and larger clusters of LCs (LC hyperplasia). CYP17A1 is a key enzyme in the testosterone pathway and has been implicated in the steroidogenic lesion produced by E2 stimulation. STUDY DESIGN, SIZE, DURATION: We studied 18 azoospermic patients with Sertoli cell-only syndrome (SCOS) and signs of LC dysfunction (cases) and 10 obstructive azoospermic/oligozoospermic men with normal spermatogenesis (controls). The SCOS patients were sub-grouped into 9 cases with T/LH <2 and 9 cases with T/LH  $\geq$ 2. All of the men underwent testicular biopsy for sperm retrieval

at the Reproductive Unit of a University Hospital. PARTICIPANTS/MATERIALS, SETTING, METHODS: The transcriptional expression of CYP17A1 and SF-1 (steroidogenic factor 1) was quantified by SYBR®Green-based qPCR in LCs isolated by laser capture microdissection (LCM), and relative expression to the control pool was assessed. CYP17A1 protein expression was semi-quantified by indirect immunofluorescence (IFI) using Image-Pro Plus v7.0 (Media Cybernetics) in testicular tissue. FSH and LH serum concentrations, and serum and intratesticular T (ITT) and E2 (ITE2) were measured by IRMA and RIA, respectively. MAIN RESULTS AND THE ROLE OF CHANCE: Relative CYP17A1 mRNA expression was increased in cases with T/LH <2 compared to cases with T/LH ≥2, by a mean of 3.3-fold (P = 0.002). No corresponding increase in protein expression was found; in fact, CYP17A1 immunostaining intensity assessed by the Integrated Optical Density (IOD) parameter was lower in the cases with T/LH <2 compared to controls (P = 0.008). Relative SF-1 mRNA expression was similar in both case subgroups. CYP17A1 mRNA expression correlated with ITE2 and intratesticular E2/T (r = 0.536; P = 0.026 and r = 0.542; P = 0.016, respectively), while an inverse association was observed for ITE2 and protein level expression (r = -0.421; P = 0.05). LARGE SCALE DATA: Not applicable. LIMITATIONS REASONS FOR CAUTION: We should interpret the results of the semi-quantification of immunofluorescent staining by Image-Pro Plus software with caution, because it is a semi-quantitative method that may have certain difficulties regarding the disposition of protein in the cells. However, it is not influenced by variations in the number of cells that express the protein, as could be the case of western blot analysis in testicular tissue. WIDER IMPLICATIONS OF THE FINDINGS: Dysfunctional LCs of men with SCOS show post-transcriptional deregulation of CYP17A1, with increased mRNA and decreased protein expression, which may be modulated by increased ITE2 levels. In addition, transcriptional expression of CYP17A1 was not associated with changes in SF-1 mRNA expression. STUDY FUNDING/COMPETING INTEREST(S): This work was supported by the National Fund for Scientific and Technological Development (FONDECYT) of Chile to A.C. [grant number 1120176]. The authors declare no conflict of interest.

## SERVICIO DE PEDIATRÍA

### ALLERGOL IMMUNOPATHOL (MADR). 2018 NOV - DEC;46(6):533-538.

#### HOSPITALIZATIONS FOR ASTHMA EXACERBATION IN CHILEAN CHILDREN: A MULTICENTER OBSERVATIONAL STUDY.

Herrera AM, Brand P, Cavada G, Koppmann A, Rivas M, Mackenney J, Sepúlveda H, Wevar ME, Cruzat L, Soto S, Pérez MA, León A, Contreras I, Alvarez C, Walker B, Flores C, Lezana V, Garrido C, Herrera ME, Rojas A, Andrades C, Chala E, Martínez RA, Vega M, Perillán JA, Seguel H, Przybyzswski I.

BACKGROUND: Asthma hospitalization rates in Chilean children have increased in the last 14 years, but little is known about the factors associated with this. OBJECTIVE: Describe clinical characteristics of children hospitalized for asthma exacerbation. METHODS: Observational prospective cohort study in 14 hospitals. Over a one-year period, children five years of age or older hospitalized with asthma exacerbation were eligible for inclusion. Parents completed an online questionnaire with questions on demographic information, about asthma, indoor environmental contaminant exposure, comorbidities and beliefs about disease and treatment. Disease control was assessed by the Asthma Control Test. Inhalation technique was observed using a checklist. RESULTS: 396 patients were enrolled. 168 children did not have an established diagnosis of asthma. Only 188 used at least one controller treatment at the time of hospitalization. 208 parents said they believed their child had asthma only when they had an exacerbation and 97 correctly identified inhaled corticosteroids as anti-inflammatory treatment. 342 patients used the wrong spacer and 73 correctly performed all steps of the checklist. CONCLUSIONS: Almost half of the patients were not diagnosed with asthma at the time of hospitalization despite having a medical history suggestive of the disease. In the remaining patients with an established diagnosis of asthma potentially modifiable factors like bad adherence to treatment and poor inhalation technique were found. Implementing a nationwide asthma program including continued medical education for the correct diagnosis and follow up of these patients and asthma education for patients and caregivers is needed to reduce asthma hospitalization rates in Chilean children.

## CENTRO INVESTIGACIÓN CLÍNICA AVANZADA - CICA

### REDOX BIOL. 2018 OCT;19:290-300.

#### MITOCHONDRIAL PERMEABILITY TRANSITION PORE CONTRIBUTES TO MITOCHONDRIAL DYSFUNCTION IN FIBROBLASTS OF PATIENTS WITH SPORADIC ALZHEIMER'S DISEASE.

Pérez MJ, Ponce DP, Aranguiz A, Behrens MI, Quintanilla RA.

In the last few decades, many reports have suggested that mitochondrial function impairment is a hallmark of Alzheimer's disease (AD). Although AD is a neurodegenerative disorder, mitochondrial damage is also present in patients' peripheral tissues, suggesting a target to develop new biomarkers. Our previous findings indicate that AD fibroblasts show specific defects in mitochondrial dynamics and bioenergetics, which affects the generation of adenosine triphosphate (ATP). Therefore, we explored the possible mechanisms involved in this mitochondrial failure. We found that compared with normal fibroblasts, AD fibroblasts had mitochondrial calcium dysregulation. Further, AD fibroblasts showed a persistent activation of the non-specific mitochondrial calcium channel, the mitochondrial permeability transition pore (mPTP). Moreover, the pharmacological blockage of mPTP with Cyclosporine A (CsA) prevented the increase of mitochondrial superoxide levels, and significantly improved mitochondrial and cytosolic calcium dysregulation in AD fibroblasts. Finally, despite the failure of CsA to improve ATP levels, the inhibition of mitochondrial calcium uptake by the mitochondrial calcium uniporter increased ATP production in AD fibroblasts, indicating that these two mechanisms may contribute to mitochondrial failure in AD fibroblasts. These findings suggest that peripheral cells present similar signs of mitochondrial dysfunction observed in the brain of AD patients. Therefore, our work creates possibilities of new targets to study for early diagnosis of the AD.

**FRONT NEUROSCI. 2018 FEB 8;12:58.**

**CANCER IMPRINTS AN INCREASED PARP-1 AND P53-DEPENDENT RESISTANCE TO OXIDATIVE STRESS ON LYMPHOCYTES OF PATIENTS THAT LATER DEVELOP ALZHEIMER'S DISEASE.**

Salech F, Ponce DP, San Martín CD, Rogers NK, Henríquez M, Behrens MI.

We have proposed that a common biological mechanism deregulated in opposite directions might explain the inverse epidemiological association observed between Alzheimer's disease (AD) and cancer. Accordingly, we showed that lymphocytes from AD patients have an increased susceptibility, whereas those from survivors of a skin cancer, an increased resistance to oxidative death induced by hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), compared to healthy controls (HC). We investigated the susceptibility to H<sub>2</sub>O<sub>2</sub>-induced death of lymphocytes in survivors of any type of cancer and in cancer survivors who later developed AD (Ca&AD). We also explored the involvement of Poly [ADP-ribose] polymerase-1 (PARP-1) and p53 pathways in the process, since both are involved in the increased susceptibility to death of AD lymphocytes. Lymphocytes from 11 cancer and 13 Ca&AD patients, and 12 HC were submitted to increasing concentrations of H<sub>2</sub>O<sub>2</sub> for 20 h. Cell death was determined by flow cytometry, in the presence or absence of PARP-1 inhibition (3-aminobenzamide, 3-ABA), or p53 inhibition (pifithrin- $\alpha$ ) or stabilization (Nut-3). PARP-1 and p53 mRNA levels were determined by Real-Time PCR. Lymphocytes from cancer and Ca&AD patients showed increased survival compared to HC, without differences between them, opposite to the increased susceptibility to death previously shown in AD. PARP-1 inhibition provided marked protection from H<sub>2</sub>O<sub>2</sub>-induced death in the two groups of patients, significantly greater than in HC. Pharmacological inhibition of p53 increased lymphocyte survival in Ca&AD patients, contrary to the effect previously reported in HC and AD. PARP-1 and p53 mRNA levels were elevated in Ca&AD lymphocytes compared with controls. In all, these results show that cancer imprints an increased resistance to H<sub>2</sub>O<sub>2</sub>-induced death in lymphocytes that persists after AD development, and is dependent on both PARP-1 and p53. p53 inhibition showed a differential role in cancer and Ca&AD compared to HC and AD lymphocytes, that could explain the inverse susceptibility to oxidative death in cancer and AD. These results are in agreement with the hypothesis of a common biological mechanism in AD and cancer. The similar cell death susceptibility and cell death pattern observed in cancer and Ca&AD lymphocytes suggests that cancer history leaves long term effects on lymphocyte cell death susceptibility.