El material que se presenta a continuación proviene de los datos proporcionados por la OAIC (Oficina de Apoyo a la Investigación Clínica) de nuestro Hospital, así como de los recolectados por nuestra Revista.

Abstracts de publicaciones internacionales ISI 2014

DEPARTAMENTO CARDIOVASCULAR

TRIALS. 2014 MAY 29;15:192.

THE EFFECTIVENESS OF ANTIOXIDANT VITAMINS C AND E IN REDUCING MYOCARDIAL INFARCT SIZE IN PATIENTS SUBJECTED TO PERCUTANEOUS CORONARY ANGIOPLASTY (PREVEC TRIAL): STUDY PROTOCOL FOR A PILOT RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL.

Rodrigo R, Hasson D, Prieto JC, Dussaillant G, Ramos C, León L, Gárate J, Valls N, Gormaz JG.

BACKGROUND: Acute myocardial infarction (AMI) is the leading cause of mortality worldwide. Oxidative stress has been involved in the ischemia-reperfusion injury in AMI. It has been suggested that reperfusion accounts for up to 50% of the final size of a myocardial infarct, a part of the damage likely to be prevented.Therefore, we propose that antioxidant reinforcement through vitamins C and E supplementation should protect against the ischemia-reperfusion damage, thus decreasing infarct size.The PREVEC Trial (Prevention of reperfusion damage associated with percutaneous coronary angioplasty following acute myocardial infarction) seeks to evaluate whether antioxidant vitamins C and E reduce infarct size in patients subjected to percutaneous coronary angioplasty after AMI. METHODS/DESIGN: This is a randomized, 1:1, double-blind, placebo-controlled clinical trial.The study takes place at two centers in Chile: University of Chile Clinical Hospital and San Borja Arriarán Clinical Hospital.The subjects will be 134 adults with acute myocardial infarction with indication for percutaneous coronary angioplasty.This intervention is being performed as a pilot study, involving high-dose vitamin C infusion plus oral administration of vitamin E (Vitamin-treatment group) or placebo (Control group) during the angioplasty procedure. Afterward, the Vitamin-treatment group receives oral doses of vitamins C and E, and the Control group receives placebo for 84 days after coronary angioplasty.Primary outcome is infarct size, assessed by cardiac magnetic resonance (CMR), measured 6 and 84 days after coronary angioplasty.Secondary outcomes are ejection fraction, measured 6 and 84 days after coronary angioplasty with CMR, and biomarkers for oxidative stress, antioxidant status, heart damage, and inflammation, which will be measured at baseline, at the onset of reperfusion, 6 to 8 hours after revascularization, and at hospital discharge. DISCUSSION: The ischemia-reperfusion event occurring during angioplasty is known to increase myocardial infarct size. The cardioprotective benefits of high doses of vitamin C combined with vitamin E have not been fully explored. The PREVEC Trial seeks to determine the suitability of the therapeutic use of vitamins C and E against the reperfusion damage produced during angioplasty.Patient recruitment opened in February 2013. The trial is scheduled to end in March 2016.

J CARD FAIL. 2014 MAR;20(3):149-54.

EFFECTS OF TRIMETAZIDINE IN NONISCHEMIC HEART FAILURE: A RANDOMIZED STUDY.

Winter JL, Castro PF, Quintana JC, Altamirano R, Enriquez A, Verdejo HE, Jalil JE, Mellado R, Concepción R, Sepúlveda P, Rossel V, Sepúlveda L, Chiong M, García L, Lavandero S.

OBJECTIVES: Heart failure (HF) is associated with changes in myocardial metabolism that lead to impairment of contractile function. Trimetazidine (TMZ) modulates cardiac energetic efficiency and improves outcomes in ischemic heart disease. We evaluated the effects of TMZ on left ventricular ejection fraction (LVEF), cardiac metabolism, exercise capacity, O2 uptake, and quality of life in

patients with nonischemic HF. METHODS AND RESULTS: Sixty patients with stable nonischemic HF under optimal medical therapy were included in this randomized double-blind study. Patients were randomized to TMZ (35 mg orally twice a day) or placebo for 6 months. LVEF, 6-minute walk test (6MWT), maximum O2 uptake in cardiopulmonary exercise test, different markers of metabolism, oxidative stress, and endothelial function, and quality of life were assessed at baseline and after TMZ treatment. Left ventricular peak glucose uptake was evaluated with the use of the maximum standardized uptake value (SUV) by 18-fluorodeoxyglucose positron emission tomography ((18)FDG-PET). Etiology was idiopathic in 85% and hypertensive in 15%. Both groups were similar in age, functional class, LVEF, and levels of N-terminal pro-B-type natriuretic peptide at baseline. After 6 months of TMZ treatment, no changes were observed in LVEF (31 ± 10% vs 34 ± 8%; P = .8), 6MWT (443 ± 25 m vs 506 ± 79 m; P = .03), maximum O2 uptake (19.1 ± 5.0 mL kg(-1) min(-1) vs 23.0 ± 7.2 mL kg(-1) min(-1); P = .11), functional class (percentages of patients in functional classes I/II/III/IV 10/3753/0 vs 7/40/50/3; P = .14), or quality of life (32 ± 26 points vs 24 ± 18 points; P = .25) in TMZ versus placebo, respectively. In the subgroup of patients evaluated with (18)FDG-PET, no significant differences were observed in SUV between both groups (7.0 ± 3.6 vs 8.2 ± 3.4 respectively; P = .47). CONCLUSIONS: In patients with nonischemic HF, the addition of TMZ to optimal medical treatment does not result in significant changes of LVEF, exercise capacity, O2 uptake, or quality of life.

J BIOMED SCIENCE 2014; 21: 62-66

ISOBOLOGRAPHIC ANALYSIS OF THE OPIOID-OPIOID INTERACTIONS IN A TONIC AND A PHASIC MOUSE MODEL OF INDUCED NOCICEPTIVE PAIN

Hugo F Miranda, Viviana Noriega, Pilar Zanetta, Juan Carlos Prieto, Juan Carlos Prieto-Rayo, Nicolás Aranda and Fernando Sierralta

Background: Opioids have been used for the management of pain and coadministration of two opioids may induce synergism. In a model of tonic pain, the acetic acid writhing test and in a phasic model, the hot plate, the antinociceptive interaction between fentanyl, methadone, morphine, and tramadol was evaluated. Results: The potency of opioids in the writhing test compared to the hot plate assay was from 2.5 (fentanyl) to 15.5 (morphine) times, respectively. The ED 50 was used in a fixed ratio for each of the six pairs of opioid combinations, which, resulted in a synergistic antinociception except for methadone/tramadol and fentanyl/ tramadol which were additive, in the hot plate. The opioid antagonists naltrexone, naltrindole and nor-binaltorphimine, suggests that the synergism of morphine combinations are due to the activation of MOR subtypes with partially contribution of DOR and KOR, however fentanyl and methadone combinations are partially due to the activation of MOR and DOR subtypes and KOR lack of participation. The antinociceptive effects of tramadol combinations, are partially due to the activation of MOR, DOR and KOR opioid subtypes. Conclusion: These results suggets that effectiveness and magnitude of the interactions between opioids are dependent on pain stimulus intensity.

DEPARTAMENTO DE CIRUGÍA

AESTHETIC PLAST SURG. 2014 JUN;38(3):575-83.

THE BODY-QOL(®): MEASURING PATIENT REPORTED OUTCOMES IN BODY CONTOURING SURGERY PATIENTS.

Danilla S, Dominguez C, Cuevas P, Calderón ME, Rios MA, Andrades P, Benitez S, Erazo C, Shulz R, Al-Himdani S, Sepúlveda S.

BACKGROUND: This study aimed to design a new patient-reported outcome (PRO) instrument to measure patient satisfaction after body-contouring procedures such as liposculpture, abdominoplasty, body-lift, thigh-lift, and arm-lift. METHODS: Phase 1a involved an extensive literature review, 16 in-depth patient interviews, and expert focus groups with 5 plastic surgeons to develop a conceptual framework for the outcomes deemed important for body image and preliminary PRO instruments. In phase 1b, the preliminary instrument was tested with a second independent sample of 29 patients with whom simple interviews were additionally performed. In the second sample, scale reliability was calculated. RESULTS: In phase 1a, the domains identified for the conceptual framework included clothing and body image, sexual and affective life, self-image and self-esteem, social relationships, and physical symptoms. In phase 1b, the scale internal consistency was 91.5 %. CONCLUSIONS: When psychometric evaluation is completed, the Body-Shape-Related Quality of Life instrument and its subscales will provide a reliable tool for plastic surgeons, researchers, and patients to use in measuring the impact and effectiveness of body-contouring procedures from the patient's perspective. LEVEL OF EVIDENCE IV: This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266 . This journal requires that authors assign a level of evidence to each submission to which Evidence-Based Medicine rankings are applicable. This excludes Review Articles, Book Reviews, and manuscripts that concern Basic Science, Animal Studies, Cadaver Studies, and Experimental Studies. For a full description of these Evidence-B.

DIS COLON RECTUM. 2014 NOV;57(11):1324-8.

APEX TECHNIQUE IN THE TREATMENT OF OBSTRUCTED DEFECATION SYNDROME ASSOCIATED WITH RECTAL INTUSSUSCEPTION AND FULL RECTAL MUCOSA PROLAPSE.

Regadas FS, Abedrapo M, Cruz JV, Murad Regadas SM, Regadas Filho FS.

BACKGROUND: The aim of the current study was to demonstrate the use of a modified stapling technique, called the apex technique, to treat rectal intussusception and full rectal mucosal prolapse. It was conducted as a retrospective study at 3 centers (2 in Brazil and 1 in Chile). TECHNIQUE: The apex technique is performed by using a HEM/EEA-33 stapler. A pursestring suture is placed at the apex of the prolapse, on the 4 quadrants, independent of the distance to the dentate line. A second pursestring is then placed to define the band of rectal mucosa to be symmetrically resected. MAIN OUTCOME MEASURES: Outcome measures included width of the resected full-thickness rectal wall; the intensity of postoperative pain on a visual analog scale from 1 to 10; full mucosal prolapse and rectal intussusception assessed by physical examination, cinedefecography, or echodefecography; and change in the constipation scale. RESULTS: Forty-five patients (30 women/15 men; mean age, 59.5 years) with rectal intussusception and full mucosal prolapse were included. The median operative time was 17 (range, 15-30) minutes. Bleeding after stapler fire requiring manual suture occurred in 3 patients (6.7%); 25 (55.6%) patients reported having no postoperative pain. Hospital stay was 24 hours. The mean width of the resected rectal wall was 5.9 (range, 5.0-7.5) cm. Stricture at the staple line was seen in 4 patients, of whom 1 required dilation under anesthesia. The median follow-up time was 120 (range, 90-120) days. A small residual prolapse was identified in 6 (13.3%) patients. Imaging demonstrated complete disappearance of rectal intussusception in all patients, and the mean postoperative constipation score decreased from 13 (range, 8-15) to 5 (range, 3-7). CONCLUSIONS: The apex technique appears to be a safe, quickly performed, and low-cost method for the treatment of rectal intussusception. In this series, imaging examinations showed the disappearance of rectal intussusception, and a significant decrease in constipation score suggested improvement in functional outcomes.

WORLD J GASTROENTEROL. 2014 JUN 7;20(21):6534-40. DOI: 10.3748/WJG.V20.I21.6534.

CHANGES IN IRON TRANSPORTER DIVALENT METAL TRANSPORTER 1 IN PROXIMAL JEJUNUM AFTER GASTRIC BYPASS.

Marambio A, Watkins G, Castro F, Riffo A, Zúñiga R, Jans J, Villanueva ME, Díaz G.

AIM: To describe the variation that divalent metal transporter 1 (DMT1) shows in patients after Roux-en-Y gastric bypass (RYGB) surgery. METHODS: Prospective and analytical study of DMT1 level at the brush border of proximal jejunum in patients having undergone RYGB surgery. The mucosa of proximal jejunum forming the gastrojejunal anastomosis was biopsied during surgery and after 6 mo later with an endoscopic biopsy. All the patients received precise instructions regarding feeding and nutritional supplementation. Both samples were processed at the same time by immunohistochemistry and western blot. Samples were analysed by a pathologist. For statistical analysis, the $\chi(2)$ and Wilcoxon tests were used. RESULTS: Sixteen patients were recruited, 13 of whom completed the study. Twelve were women. Average age and body mass index (BMI) were 44.1 and 40.4, respectively. Both body weight and BMI decreased significantly during the study period, with an average percent excess weight loss (%EWL) of 60% ± 13.3% and an average percent excess BMI loss (%EBMIL) of 79.6% ± 21.6%. Only two patients presented with mild anaemia 6 mo after surgery, but their ferritin levels stayed within normal ranges. Staining for DMT1 showed a significant increase in the cytoplasm of enterocytes located at the tips of the villi ($\chi(2) = 6.03$; $P = 0.049$). Nevertheless, the total quantity of DMT1 decreased significantly ($Z = 2.04$; $P = 0.04$). Associated with these results, we observed a significant increase in goblet cells in the villi 6 mo postoperatively ($Z = -2.47$; $P = 0.013$). CONCLUSION: Six months after RYGB surgery, patients exhibit an increase in DMT1 expression in the enterocytes of the tips of the villi at the proximal jejunum.

MELANOMA RES. 2014 APR;24(2):108-19.

CAVEOLIN-1 IS A RISK FACTOR FOR POSTSURGERY METASTASIS IN PRECLINICAL MELANOMA MODELS.

Lobos-Gonzalez L, Aguilar-Guzmán L, Fernandez JG, Muñoz N, Hossain M, Bieneck S, Silva V, Burzio V, Sviderskaya EV, Bennett DC, Leyton L, Quest AF.

Melanomas are highly lethal skin tumours that are frequently treated by surgical resection. However, the efficacy of such procedures is often limited by tumour recurrence and metastasis. Caveolin-1 (CAV1) has been attributed roles as a tumour suppressor, although in late-stage tumours, its presence is associated with enhanced metastasis. The expression of this protein in human melanoma development and particularly how the presence of CAV1 affects metastasis after surgery has not been defined. CAV1 expression in human melanocytes and melanomas increases with disease progression and is highest in metastatic melanomas. The effect of increased CAV1 expression can then be evaluated using B16F10 murine melanoma cells injected into syngenic immunocompetent C57BL/6 mice or human A375 melanoma cells injected into immunodeficient B6Rag1-/- mice. Augmented CAV1 expression

suppresses tumour formation upon a subcutaneous injection, but enhances lung metastasis of cells injected into the tail vein in both models. A procedure was initially developed using B16F10 melanoma cells in C57BL/6 mice to mimic better the situation in patients undergoing surgery. Subcutaneous tumours of a defined size were removed surgically and local tumour recurrence and lung metastasis were evaluated after another 14 days. In this postsurgery setting, CAV1 presence in B16F10 melanomas favoured metastasis to the lung, although tumour suppression at the initial site was still evident. Similar results were obtained when evaluating A375 cells in B6Rag1-/- mice. These results implicate CAV1 expression in melanomas as a marker of poor prognosis for patients undergoing surgery as CAV1 expression promotes experimental lung metastasis in two different preclinical models.

EUR SURG. 2014;46:32-37.

SINGLE-INCISION LAPAROSCOPIC SLEEVE GASTRECTOMY: INITIAL EXPERIENCE IN 20 PATIENTS AND 2-YEAR FOLLOW-UP.

Maluenda F, León J, Csendes A, Burdiles P, Giordano J, Molina M.

BACKGROUND: The transumbilical route began being clinically feasible with or without unique access devices. SETTING: The setting for this study was a private practice at Clínica Las Condes, Santiago, Chile. OBJECTIVE: The objective was to describe our experience performing a laparoscopic sleeve gastrectomy (LSG) via transumbilical route using a single-port access device in addition to standard laparoscopic instruments. METHOD: A prospective nonrandomized protocol was applied to patients fulfilling the following inclusion criteria: to have been medically indicated for an LSG, to have a body mass index (BMI) of less than or equal to 40 kg/m2, and the distance between the xiphoid appendix and umbilicus should be less than 22 cm. All patients were female with a median (p50) age of 34.5 (ranging from 21 to 57) years, a median weight of 92 (ranging from 82.5 to 113) kg, and a median BMI of 35.1 (ranging from 30.5 to 40) kg/m2. The device insertion technique, the gastrectomy, and postoperative management are described. RESULTS: LSG via transumbilical route was successfully carried out in 19 of the 20 patients in whom the procedure was performed; one patient had to be converted to a conventional laparoscopic procedure. Mean operating time was 127 (ranging from 90 to 170) min. On the second postoperative day, all patients were assessed through an upper gastrointestinal barium-contrasted radiological series. There was neither morbidity nor mortality in this group. Excess weight loss at 25 months after surgery was 114%. CONCLUSIONS: Single-port LSG can be successfully performed in selected obese patients with a BMI of less than 40 kg/m2 using traditional laparoscopic instruments. The technique allows performing a safe and effective vertical gastrectomy.

OBES SURG. 2014 JUN;24(6):877-84.

CHANGES IN BONE MINERAL DENSITY AFTER SLEEVE GASTRECTOMY OR GASTRIC BYPASS: RELATIONSHIPS WITH VARIATIONS IN VITAMIN D, GHRELIN, AND ADIPONECTIN LEVELS.

Carrasco F, Basfi-Fer K, Rojas P, Valencia A, Csendes A, Codoceo J, Inostroza J, Ruz M.

BACKGROUND: A major long-term concern after gastric bypass (GBP) is the risk of osteoporosis; however, little is known about this complication in patients undergoing sleeve gastrectomy (SG). OBJECTIVE: To evaluate changes in bone mineral density (BMD) after GBP and SG, and its relationship with changes in vitamin D, parathyroid hormone (PTH), ghrelin, and adiponectin. METHODS: Twenty-three women undergoing GBP (BMI 42.0 ± 4.2 kg/m2; 37.3 ± 8.1 years) and 20 undergoing SG (BMI 37.3 ± 3.2 kg/m2; 34.2 ± 10.2 years) were studied before and 6 and 12 months after surgery. BMD was measured by dual-energy X-ray absorptiometry. Plasma PTH, 25-hydroxyvitamin D (25-OHD), ghrelin, and adiponectin concentrations were determined. Food as well as calcium and vitamin D supplement intake was recorded. RESULTS: Excess weight loss (mean ± SE), adjusted by baseline excess weight, was 79.1±3.8% and 74.9 ± 4.1% 1 year after GBP and SG, respectively (p = 0.481). Significant reduction in BMD for total body (TB), lumbar spine (LS), and femoral neck (FN) was observed after GBP. In the SG group, reduction in BMD was significant only for TB. Adjusted by baseline BMD, the difference between change in BMD for GBP vs. SG was not significant for TB, LS, or FN. Percent reduction in ghrelin concentration was a main factor related to total BMD loss (GBP group) and LS BMD loss (GBP and SG groups). CONCLUSIONS: One year after gastric bypass, bone mineral density was significantly affected, mainly at the femoral neck. Decreases in bone mineral density were more dramatic among patients who had greater baseline BMD and greater reduction in ghrelin concentrations.

ANTICANCER RES. 2014 JUL;34(7):3523-30.

ROLE OF CYTOKINE GENE POLYMORPHISMS IN GASTRIC CANCER RISK IN CHILE.

Gonzalez-Hormazabal P, Musleh M, Bustamante M, Stambuk J, Escandar S, Valladares H, Lanzarini E, Chiong H, Rojas J, Castro VG, Rubio-Reyes C, Jara L, Berger Z.

AIM: To assess the role of pro- and anti-inflammatory polymorphisms in gastric cancer susceptibility. PATIENTS AND METHODS: We genotyped 12 polymorphisms in eight cytokine genes (Interleukin-1β -IL1B-, IL8, IL17A, IL17F, IL32, tumor necrosis factor-α

-TNF-, IL1RN, IL10) in a case-control study of 147 patients with gastric cancer and 172 controls. RESULTS: Single polymorphism analysis revealed an association between the IL10 -592C>A single nucleotide polymorphism and cases with moderately- or well-differentiated tumors [AA vs. GG, odds ratio (OR)=3.01; 95% confidence interval (CI)=1.08-8.50]. We further analyzed gene-gene interactions using a combined attribute network implemented in multifactor dimensionality reduction software. The analysis revealed an interaction between IL8 -251A>T and IL32 rs28372698 SNPs among cases with moderately- or well-differentiated tumors. Homozygosity for both IL8 -251T and IL32 T alleles increases the odds for developing gastric cancer up to 2.63-fold (OR=2.63; 95% CI=1.15-6.03). This association was higher compared to the homozygosity for the IL8-251 T allele alone (OR=1.11; 95% CI=0.51-2.43) or the IL32 T allele alone (OR=1.21; 95% CI=0.54-2.72). CONCLUSION: These findings suggest that IL10 -592C>A increases the odds for developing gastric cancer. An interaction between IL8 -251A>T and IL32 rs28372698 SNPs is also proposed.

CIR ESP. 2014 MAY;92(5):316-23.

OBESITY SURGERY MORTALITY RISK SCORE FOR THE PREDICTION OF COMPLICATIONS AFTER LAPAROSCOPIC BARIATRIC SURGERY.

Lorente L, Ramón JM, Vidal P, Goday A, Parri A, Lanzarini E, Pera M, Grande L.

INTRODUCTION: Morbimortality after bariatric surgery varies according to patient characteristics and associated comorbidities. The aim of this study was to evaluate the usefulness of the Obesity sugery mortality risk score scale (OS-MRS) to predict the risk of postoperative complications after bariatric surgery. METHODS: A retrospective study was performed of a prospective series of patients undergoing bariatric surgery in which the OS-MRS scale was applied preoperatively. Postoperative complications were classified as proposed by Dindo-Clavien. We analyzed the relationship between the categories of OS-MRS scale: A) low risk, B) intermediate risk, and C) high risk and the presence of complications. RESULTS: Between May 2008 and June 2012, 198 patients were included (85 [42.9%] after gastric bypass and 113 [57.1%] after sleeve gastrectomy). Using the OS-MRS scale, 124 patients were classified as class A (62.6%), 70 as class B (35.4%) and 4 as class C (2%). The overall morbidity rate was 12.6% (25 patients). A significant association between OS-MRS scale and rate of complications (7.3, 20 and 50%, respectively, P=.004) was demonstrated. The gastric bypass was associated with a higher complication rate than sleeve gastrectomy (P=.007). In multivariate analysis, OS-MRS scale and surgical technique were the only significant predictive factors. CONCLUSIONS: The OS-MRS scale is a useful tool to predict the risk of complications and can be used as a guide when choosing the type of bariatric surgery.

DEPARTAMENTO DE DERMATOLOGÍA

J EUR ACAD DERMATOL VENEREOL. 2014 SEP 8. [EPUB AHEAD OF PRINT]

ULTRASOUND AS PREDICTOR OF HISTOLOGIC SUBTYPES LINKED TO RECURRENCE IN BASAL CELL CARCINOMA OF THE SKIN.

Wortsman X, Vergara P, Castro A, Saavedra D, Bobadilla F, Sazunic I, Zemelman V, Wortsman J.

BACKGROUND: Basal cell carcinoma (BCC) recurrences, especially in the facial region, represent a complex cosmetic problem. To date the possibility of predicting recurrence is supported solely by the histologic subtype. OBJECTIVE: To evaluate the relationship between BCC histologic subtypes linked to high and low risk of recurrence and the presence of hyperechoic spots on sonography. METHODS: Retrospective analysis of the pre-surgical ultrasound examinations of primary BCC tumours with visualization and counting of intra-tumoural hyperechoic spots. The data were then correlated with the corresponding histologic subtype. RESULTS: Thirty one patients with histologically proven BCC were included in the study. Hyperechoic spots were detected in all cases and there was a positive, statistically significant association between hyperechoic spots count and high recurrence risk histologic subtypes. Higher hyperechoic spots count was found in the recurrence-prone micronodular, sclerosing variant and morpheiform BCC subtypes. Low risk and high risk of recurrence showed a significant difference on the mean hyperechoic spots count of 5.5 (range: 3-25) and 8 (4-81). A cut-off point ≥7 hyperechoic spots presented a sensitivity of 79% and specificity of 53% for predicting the high risk of recurrence subtypes. CONCLUSION: The presence and count of hyperechoic spots within BCC lesions may help predicting the high risk of recurrence histologic subtypes.

DEPARTAMENTO DE NEUROLOGÍA Y NEUROCIRUGÍA

CURR ALZHEIMER RES. 2014;11(9):892-8.

INCREASED SUSCEPTIBILITY TO OXIDATIVE DEATH OF LYMPHOCYTES FROM ALZHEIMER PATIENTS CORRELATES WITH DEMENTIA SEVERITY.

Ponce DP, Salech F, SanMartin CD, Silva M, Xiong C, Roe CM, Henriquez M, Quest AF, Behrens MI.

We previously reported on enhanced susceptibility to death of lymphocytes from Alzheimer's disease (AD) patients when exposed to hydrogen peroxide (H2O2)-induced oxidative stress and an increased resistance to death in those of patients with a history of skin cancer. This is consistent with our hypothesis proposing that the cellular machinery controlling cell death is deregulated in opposite directions in Alzheimer's disease (AD) and cancer, to explain the inverse association observed in epidemiological studies. Here we investigated whether the observed increased susceptibility correlates with the degree of dementia severity. Peripheral lymphocytes from 23 AD patients, classified using the Clinical Dementia Rating (CDR) into severe dementia (CDR 3, n=10) and mild-to-moderate dementia (CDR 1- 2, n=13), and 15 healthy controls (HC) (CDR 0), were exposed to H2O2 for 20 hours. Lymphocyte death was determined by flow cytometry and propidium iodide staining. The greatest susceptibility to H2O2-induced death was observed for lymphocytes from severe dementia patients, whereas those with mild-to-moderate dementia exhibited intermediate values, compared to healthy controls. A significant increase in the apoptosis/necrosis ratio was found in AD patients. Poly (ADP-ribosyl) polymerase-1 (PARP-1) inhibition significantly protected from H2O2-induced death of lymphocytes, whereby a lower degree of protection was observed in severe AD patients. Moreover, inhibition of PARP-1 abolished the differences in apoptosis/necrosis ratios observed between the three groups of patients. These results support the notion that AD is a systemic disorder, whereby enhanced susceptibility to H2O2-induced death in peripheral lymphocytes correlates with dementia severity and enhanced death in AD patients is attributable to a PARP-dependent increase in the apoptosis/necrosis ratio.

BIOMATERIALS. 2014 JAN;35(1):489-99.

DIFFERENTIAL NANOTOXICOLOGICAL AND NEUROINFLAMMATORY LIABILITIES OF NON-VIRAL VECTORS FOR RNA INTERFERENCE IN THE CENTRAL NERVOUS SYSTEM.

Godinho BM, McCarthy DJ, Torres-Fuentes C, Beltrán CJ, McCarthy J, Quinlan A, Ogier JR, Darcy R, O'Driscoll CM, Cryan JF.

Progression of RNA interference-based gene silencing technologies for the treatment of disorders of the central nervous system (CNS) depends on the availability of efficient non-toxic nanocarriers. Despite advances in the field of nanotechnology undesired and non-specific interactions with different brain-cell types occur and are poorly investigated. To this end, we studied the cytotoxic and neuroinflammatory effects of widely-used transfection reagents and modified amphiphilic β-cyclodextrins (CDs). All non-viral vectors formed positively charged nanoparticles with distinctive physicochemical properties. Differential and significant cytotoxic effects were observed among commercially available cationic vectors, whereas CDs induced limited disruptions of cellular membrane integrity and mitochondrial dehydrogenase activity. Interestingly, murine derived BV2 microglia cells and a rat striatal in vitro model of Huntington's disease (ST14A-HTT120Q) were more susceptible to toxicity than human U87 astroglioma cells. BV2 microglia presented significant increases in cytokine, toll-like receptor 2 and cyclooxygenase-2 gene expression after transfection with selected commercial vectors but not with CD.siRNA nanoparticles. Non-viral siRNA nanoparticles formulated with G6 polyamidoamine (PAMAM) also significantly increased cytokine gene expression in the brain following injections into the mouse striatum. Together our data identify modified CDs as nanosystems that enable siRNA delivery to the brain with low levels of cytotoxicity and immunological activation.

J ALZHEIMERS DIS. 2014;42(2):357-67.

NUTRACEUTICALS: A NOVEL CONCEPT IN PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE AND RELATED DISORDERS.

Farías GA, Guzmán-Martínez L, Delgado C, Maccioni RB.

Alzheimer's disease is a growing health problem worldwide. The pharmaceutical industry has not recently developed any new drugs that have had a significant impact on the natural history of the disease, so considerable attention has been given to nutraceuticals and nutritional bioactive compounds that can be obtained directly from diet or supplementation. These compounds may be able to modify physiopathological processes responsible for neurodegeneration and/or to have pro-cognitive properties. Here, we review current knowledge on the role of diet modifications, lipid and carbohydrates consumption, vitamin supplementation, and the possible effects of antioxidant and nutraceutical compounds with neuroprotective activity, in the prevention and treatment of Alzheimer's disease and related disorders.

MOL CANCER. 2014 SEP 9;13:209.

SURVIVIN EXPRESSION PROMOTES VEGF-INDUCED TUMOR ANGIOGENESIS VIA PI3K/AKT ENHANCED B-CATENIN/TCF-LEF DEPENDENT TRANSCRIPTION.

Fernández JG, Rodríguez DA, Valenzuela M, Calderon C, Urzúa U, Munroe D, Rosas C, Lemus D, Díaz N, Wright MC, Leyton L, Tapia JC, Quest AF.

Early in cancer development, tumour cells express vascular endothelial growth factor (VEGF), a secreted molecule that is important in all stages of angiogenesis, an essential process that provides nutrients and oxygen to the nascent tumor and thereby enhances tumor-cell survival and facilitates growth. Survivin, another protein involved in angiogenesis, is strongly expressed in most human cancers, where it promotes tumor survival by reducing apoptosis as well as favoring endothelial cell proliferation and migration. The mechanisms by which cancer cells induce VEGF expression and angiogenesis upon survivin up-regulation remain to be fully established. Since the PI3K/Akt signalling and β-catenin-Tcf/Lef dependent transcription have been implicated in the expression of many cancer-related genes, including survivin and VEGF, we evaluated whether survivin may favor VEGF expression, release from tumor cells and induction of angiogenesis in a PI3K/Akt-β-catenin-Tcf/Lef-dependent manner. Here, we provide evidence linking survivin expression in tumor cells to increased β-catenin protein levels, β-catenin-Tcf/Lef transcriptional activity and expression of several target genes of this pathway, including survivin and VEGF, which accumulates in the culture medium. Alternatively, survivin downregulation reduced β-catenin protein levels and β-catenin-Tcf/Lef transcriptional activity. Also, using inhibitors of PI3K and the expression of dominant negative Akt, we show that survivin acts upstream in an amplification loop to promote VEGF expression. Moreover, survivin knock-down in B16F10 murine melanoma cells diminished the number of blood vessels and reduced VEGF expression in tumors formed in C57BL/6 mice. Finally, in the chick chorioallantoid membrane assay, survivin expression in tumor cells enhanced VEGF liberation and blood vessel formation. Importantly, the presence of neutralizing anti-VEGF antibodies precluded survivin-enhanced angiogenesis in this assay. These findings provide evidence for the existance of a posititve feedback loop connecting survivin expression in tumor cells to PI3K/Akt enhanced β-catenin-Tcf/Lef-dependent transcription followed by secretion of VEGF and angiogenesis.

INT J GERIATR PSYCHIATRY. 2014 JUL;29(7):730-40.

TEST YOUR MEMORY-SPANISH VERSION (TYM-S): A VALIDATION STUDY OF A SELF-ADMINISTERED COGNITIVE SCREENING TEST.

Muñoz-Neira C, Henríquez Chaparro F, Delgado C, Brown J, Slachevsky A.

OBJECTIVES: To develop the Test Your Memory (TYM)-Spanish version (TYM-S), a self-administered cognitive screening test, in a Chilean older sample and to estimate its psychometric properties and diagnostic accuracy. METHODS: The TYM was translated into Spanish and adapted for a Chilean population to develop the TYM-S. Measures of global cognitive impairment and executive dysfunction were administered to 30 controls, 30 dementia patients, and 14 subjects with mild cognitive impairment (MCI). All participants' proxies were interviewed with assessments of dementia severity, functionality in daily living activities, and cognitive change. Convergent validity and internal consistency reliability of the TYM-S were estimated. Cut-off points, sensitivity, and specificity were determined to test its diagnostic capacity for dementia or MCI. RESULTS: Regarding convergent validity, the TYM-S was significantly correlated ($p < 0.001$) with global cognitive impairment (Mini-Mental State Examination: $r = 0.902$; Addenbrooke's Cognitive Examination-Revised-Chilean version: $r = 0.922$; Montreal Cognitive Assessment: $r = 0.923$), executive dysfunction (Frontal Assessment Battery: $r = 0.862$), dementia severity (Clinical Dementia Rating: $r = -0.757$), functional capacity (Technology-Activities of Daily Living Questionnaire: $r = -0.864$; Pfeffer Functional Activities Questionnaire: $r = -0.748$; Instrumental Activities of Daily Living: $r = 0.769$), and cognitive change (Alzheimer's Disease 8-Chilean version: $r = -0.700$) measures. Regarding reliability, Cronbach's α was 0.776. Optimum cut-off scores of 39 and 44 distinguished dementia cases from controls (93.1% sensitivity, 82.2% specificity) and MCI cases from controls (85.7% sensitivity, 69% specificity), respectively. The extent of assistance required in the TYM-S and cognitive impairment was correlated. CONCLUSIONS: The TYM-S is a valid and reliable instrument to assess cognitive impairment, showing good psychometric properties and diagnostic capacity to identify cases of dementia in a Spanish-speaking older cohort. Although its need for assistance may be limiting, its ability to quickly assess several cognitive domains supports widespread clinical use.

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DYNAMIN-2 IN NERVOUS SYSTEM DISORDERS

Arlek M. González-Jamett, Valentina Haro-Acuña, Fanny Momboisse, Pablo Caviedes, Jorge A. Bevilacqua and Ana M. Cárdenas

Dynamin-2 is a pleiotropic GTPase whose best-known function is related to membrane scission during vesicle budding from the plasma or Golgi membranes. In the nervous system, dynamin-2 participates in synaptic vesicle recycling, post-synaptic receptor internalization, neurosecretion, and neuronal process extension. Some of these functions are shared with the other two dynamin

isoforms. However, the involvement of dynamin-2 in neurological illnesses points to a critical function of this isoform in the nervous system. In this regard, mutations in the dynamin-2 gene results in two congenital neuromuscular disorders. One of them, Charcot-Marie-Tooth disease, affects myelination and peripheral nerve conduction, whereas the other, Centronuclear Myopathy, is characterized by a progressive and generalized atrophy of skeletal muscles, yet it is also associated with abnormalities in the nervous system. Furthermore, single nucleotide polymorphisms located in the dynamin-2 gene have been associated with sporadic Alzheimer's disease. In the present review, we discuss the pathogenic mechanisms implicated in these neurological disorders.

AM J MED GENET A. 2014 SEP;164A(9):2365-9.

ACTIVATING PIK3CA SOMATIC MUTATION IN CONGENITAL UNILATERAL ISOLATED MUSCLE OVERGROWTH OF THE UPPER EXTREMITY.

Castiglioni C, Bertini E, Orellana P, Villarroel C, Las Heras F, Hinzpeter D, Paolinelli P, Bevilacqua JA, Alvarez K.

Congenital unilateral overgrowth of the upper extremity affecting only the muscle tissue is rare. We describe on the clinical, histopathological, and neuroimaging findings in a 6-year-old girl with a congenital, non-progressive muscle enlargement of the entire left upper limb with an ipsilateral hand deformity. No cutaneous stigmata or additional features were detected. Sanger sequencing for the AKT1, PIK3CA, and PTEN genes identified an activating c.3140A>G, p.H1047R mutation in the PIK3CA gene from the affected muscle DNA. We demonstrate that isolated congenital muscular upper limb overgrowth with aberrant hand muscles is another condition related genetically to the PIK3CA-related overgrowth spectrum.

DEPARTAMENTO DE OBSTETRICIA Y GINECOLOGÍA

FASEB J. 2014 NOV;28(11):4835-46.

EICOSANOMIC PROFILING REVEALS DOMINANCE OF THE EPOXYGENASE PATHWAY IN HUMAN AMNIOTIC FLUID AT TERM IN SPONTANEOUS LABOR.

Maddipati KR, Romero R, Chaiworapongsa T, Zhou SL, Xu Z, Tarca AL, Kusanovic JP, Munoz H, Honn KV.

Lipid mediators play an important role in reproductive biology, especially, in parturition. Enhanced biosynthesis of eicosanoids, such as prostaglandin E2 (PGE2) and PGF2α, precedes the onset of labor as a result of increased expression of inducible cyclooxygenase 2 (COX-2) in placental tissues. Metabolism of arachidonic acid results in bioactive lipid mediators beyond prostaglandins that could significantly influence myometrial activity. Therefore, an unbiased lipidomic approach was used to profile the arachidonic acid metabolome of amniotic fluid. In this study, liquid chromatography-mass spectrometry was used for the first time to quantitate these metabolites in human amniotic fluid by comparing patients at midtrimester, at term but not in labor, and at term and in spontaneous labor. In addition to exposing novel aspects of COX pathway metabolism, this lipidomic study revealed a dramatic increase in epoxygenase- and lipoxygenase-pathway-derived lipid mediators in spontaneous labor with remarkable product selectivity. Despite their recognition as anti-inflammatory lipid mediators and regulators of ion channels, little is known about the epoxygenase pathway in labor. Epoxygenase pathway metabolites are established regulators of vascular homeostasis in cardiovascular and renal physiology. Their presence as the dominant lipid mediators in spontaneous labor at term portends a yet undiscovered physiological function in parturition.

FRONT PHARMACOL. 2014 JUN 24;5:149.

THE PLACENTAL PURSUIT FOR AN ADEQUATE OXIDANT BALANCE BETWEEN THE MOTHER AND THE FETUS.

Herrera EA, Krause B, Ebensperger G, Reyes RV, Casanello P, Parra-Cordero M, Llanos AJ.

The placenta is the exchange organ that regulates metabolic processes between the mother and her developing fetus. The adequate function of this organ is clearly vital for a physiologic gestational process and a healthy baby as final outcome. The umbilico-placental vasculature has the capacity to respond to variations in the materno-fetal milieu. Depending on the intensity and the extensity of the insult, these responses may be immediate-, mediate-, and long-lasting, deriving in potential morphostructural and functional changes later in life. These adjustments usually compensate the initial insults, but occasionally may switch to long-lasting remodeling and dysfunctional processes, arising maladaptation. One of the most challenging conditions in modern perinatology is hypoxia and oxidative stress during development, both disorders occurring in high-altitude and in low-altitude placental insufficiency. Hypoxia and oxidative stress may induce endothelial dysfunction and thus, reduction in the perfusion of the placenta and restriction in the fetal growth and development. This Review will focus on placental responses to hypoxic conditions, usually related with high-

altitude and placental insufficiency, deriving in oxidative stress and vascular disorders, altering fetal and maternal health. Although day-to-day clinical practice, basic and clinical research are clearly providing evidence of the severe impact of oxygen deficiency and oxidative stress establishment during pregnancy, further research on umbilical and placental vascular function under these conditions is badly needed to clarify the myriad of questions still unsettled.

ULTRASOUND OBSTET GYNECOL. 2014 MAR;43(3):291-6.

IS THERE A ROLE FOR CERVICAL ASSESSMENT AND UTERINE ARTERY DOPPLER IN THE FIRST TRIMESTER OF PREGNANCY AS A SCREENING TEST FOR SPONTANEOUS PRETERM DELIVERY?

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

OBJECTIVE: To evaluate the role of cervical length (CL) and uterine artery pulsatility index (UtA-PI) at 11+0 to 13+6 weeks as predictors of spontaneous preterm delivery (sPTD) in a Chilean population. METHODS: This was a prospective study of asymptomatic women with singleton pregnancies attending for a nuchal translucency scan at 11+0 to 13+6 weeks' gestation and who underwent a transvaginal scan for evaluation of CL and UtA-PI. Exclusion criteria were fetal and pregnancy complications (other than sPTD) and iatrogenic delivery at<34 weeks. Measurements of CL and UtA-PI were adjusted for fetal crown-rump length and maternal characteristics and expressed as multiples of the median (MoM) of the unaffected group. Prediction of sPTD using maternal and pregnancy characteristics was studied using logistic regression analysis. RESULTS: A total of 3480 women were recruited into the study and, after application of exclusion criteria, 3310 were included in the analysis. The rate of sPTD at<34 weeks was 0.9% (n=31). A previous PTD had occurred in 7.4% of parous women. Patients with sPTD in the index pregnancy were characterized by a significantly higher prevalence of previous PTD (12.9% vs 3.7%, P<0.05). No significant difference was found in either CL or UtA-PI between pregnancies with and without subsequent sPTD. Logistic regression analysis showed that smoking and previous PTD were significantly associated with sPTD at<34 weeks. The combination of these characteristics provided a detection rate of 26% with a false-positive rate of 8%. CONCLUSIONS: Neither UtA-PI nor CL during the first trimester was shown to be a useful predictor of early sPTD. However, a combined model that includes smoking and previous PTD predicts approximately one-quarter of those women destined to deliver at<34 weeks, with a false-positive rate of 8%.

MED HYPOTHESES. 2015 JAN;84(1):72-7.

A PUTATIVE ROLE FOR TELOCYTES IN PLACENTAL BARRIER IMPAIRMENT DURING PREECLAMPSIA.

Bosco C, Díaz E, Gutiérrez R, González J, Parra-Cordero M, Rodrigo R, Barja P.

Preeclampsia (PE) is a major health problem occurring in pregnant women and the principal cause of maternal morbidity and perinatal mortality. It is characterized by alteration of the extravilli trophoblast cell migration toward the endometrial spiral arteries with a concomitant reduction in maternal blood flow in the placenta. This result in a state of ischemia-hypoxia which triggers an oxidative stress stage with production of reactive oxygen species. A cascade of cellular and molecular events leads then to endothelial dysfunction, transduction pathway signal disruption and induction of apoptosis and necrosis mechanisms and therefore a significant reduction in the amount of nutrients required for normal fetal development. Placental anchoring chorionic and stem villi present a skeleton of myofibroblasts arranged in parallel disposition to its longitudinal axis. The intraplacental blood volume is controlled by the contraction/relaxation of these myofibroblasts, promoting the delivery of nutrients and metabolites to the fetus. Recently, a new mesodermal originated cell type has been described in the villous stroma, the so named "telocytes". These cells are strategically located between the smooth muscle cells of the blood vessel wall and the myofibroblasts, and it is reasonable to hypothesize that they may play a pacemaker role, as in the intestine. This study provide new information supporting the notion that the occurrence of oxidative stress in PE is not only related to endothelial dysfunction and apoptosis of the trophoblast cells, but also involves telocytes and its putative role in the regulation of fetal blood flow and the intra-placental blood volume. Some ideas aimed at dilucidating the relationship between placental failure and the behavior of telocytes in pathological organs in adulthood, are also discussed.

STEROIDS. 2014 NOV;89:11-9.

THE ROLE OF ANDROST-5-ENE-3Β,17Β-DIOL (ANDROSTENEDIOL) IN CELL PROLIFERATION IN ENDOMETRIUM OF WOMEN WITH POLYCYSTIC OVARY SYNDROME.

Plaza-Parrochia F, Bacallao K, Poblete C, Gabler F, Carvajal R, Romero C, Valladares L, Vega M.

Women with polycystic ovary syndrome (PCOS) show high prevalence of endometrial hyperplasia and adenocarcinoma. Endometrial proliferation is increased, evaluated by high levels of Ki67 (cell cycle marker) and low levels of p27 (negative regulator of cell cycle). Nevertheless, endometrial changes in cyclin D1 (positive regulator of cell cycle) in PCOS-women are not described. Androst-5-ene-

3β,17β-diol (androstenediol), steroid with estrogenic activity present in endometria, could be related to increased endometrial cell proliferation. The objective of this study was to determine protein content of cyclin D1 and androstenediol levels in endometria from PCOS and control-women and to evaluate the possible mechanism favoring cell proliferation associated with hormonal characteristics of patients. Therefore, cyclin D1 protein content in PCOS-women and control-endometrial tissue were assessed by western blot and immunohistochemistry. The androstenediol levels were evaluated by ELISA. To further analyze the effect of steroids (androstenediol, 17β-estradiol, testosterone) in cell proliferation, levels of proteins cyclin D1, p27 and Ki67 were evaluated in an in vitro model of stromal endometrial cells T-HESC and St-T1b. An increase in cyclin D1 and androstenediol was observed in tissues from PCOS-women relative to control group ($p<0.05$). In the in vitro model, androstenediol exerted increase in cyclin D1 ($p<0.05$) and a decrease in p27 protein level ($p<0.05$), while Ki67 in St-T1b cells increased under this stimulus ($p<0.05$). Testosterone produces opposite effects in the levels of the above markers ($p<0.05$). Therefore, the hormonal imbalance associated with this syndrome could alter endometrial tissue homeostasis, promoting cell proliferation. Androstenediol is a molecule that could be involved by stimulating proliferation, whereas testosterone elicits a role of cell cycle repressor.

GYNECOL OBSTET INVEST. 2014;78(2):130-5.

ROLE OF THE GLUCOSE TOLERANCE TEST AS A PREDICTOR OF PREECLAMPSIA.

Parra-Cordero M, Sepúlveda-Martínez A, Preisler J, Pastén J, Soto-Chacón E, Valdés E, Rencoret G.

OBJECTIVE: To determine whether oral glucose tolerance tests (OGTT) play a role as predictors of preeclampsia (PET) in pregnant women. METHODS: A retrospective case-control study was conducted in 2,002 singleton pregnancies that had a uterine artery (UtA) Doppler at 22-25 weeks and an OGTT. The UtA Doppler and OGTT were adjusted based on maternal characteristics, and the results were expressed as multiples of the expected normal median and compared between groups. Logistic regression analysis was used to determine whether maternal characteristics, OGTT, and UtA Doppler significantly contribute to the prediction of early- (<34 weeks), intermediate- (34-37 weeks), or late-onset (>37 weeks) PET. The performance of the screening was determined by ROC curves. RESULTS: Women who developed PET were characterized by an older maternal age, an increased body mass index, and an altered UtA Doppler. The group with intermediate-onset PET was the only one associated with higher 2-hour OGTT levels compared to controls. Combined models were developed via logistic regression analysis using maternal characteristics, UtA Doppler, and OGTT to predict PET. These combined models were able to detect around 74, 42, and 21% of women who later developed early-, intermediate-, or late-onset PET, respectively, with only a 5% false-positive rate. CONCLUSIONS: This study shows that the combination of maternal characteristics, second-trimester UtA Doppler, and OGTT is a predictor of the development of PET in healthy pregnant women.

GYNECOL OBSTET INVEST. 2014;77(2):111-6.

ASSESSMENT OF PREGESTATIONAL INSULIN RESISTANCE AS A RISK FACTOR OF PREECLAMPSIA.

Valdés E, Sepúlveda-Martínez A, Manukián B, Parra-Cordero M.

AIM: To assess the impact that pregestational insulin resistance (PIR) has as a risk factor for preeclampsia (PE). METHODS: Nested case-control study that included patients with PIR and a control group that was randomly selected from pregnancies admitted to the Fetal Medicine Unit between January 2005 and May 2011. Clinical and hemodynamic variables were analyzed by a multiple logistic regression analysis. RESULTS: Of the 13,124 patients admitted during the study period, 119 had a diagnosis of PIR (0.9%). Patients with PIR were older and had a higher body mass index (BMI). PIR was also related to a significantly higher frequency of chronic hypertension (CrHT; 10.1 vs. 2.2%, $p < 0.05$) and hypothyroidism (5.0 vs. 1.6%, $p < 0.05$) than in the control group. Moreover, women with PIR were more likely to develop PE (8.4 vs. 4.2%, $p < 0.05$) and gestational diabetes mellitus (9.2 vs. 2.9%) than the control group. Multivariate analysis showed that maternal age, CrHT and altered uterine artery Doppler sonography during the first and second trimesters were good predictors of PE and that PIR was not. CONCLUSION: Although PIR correlates with PE, conditions related to the latter (CrHT, higher maternal age and increased BMI) may be predominant as risk factors for PE.

J OVARIAN RES. 2014 AUG 10;7:82.

ROLE OF NERVE GROWTH FACTOR AND ITS TRKA RECEPTOR IN NORMAL OVARIAN AND EPITHELIAL OVARIAN CANCER ANGIOGENESIS.

Vera C, Tapia V, Vega M, Romero C.

In normal ovarian function a controlled angiogenesis is essential. Several growth factors are involved in this process, such as the vascular endothelial growth factor (VEGF) and nerve growth factor (NGF). The angiogenesis process in the normal ovary is a tightly controlled process that occurs in each ovarian cycle. Also, angiogenesis is critical for ovarian cancer development

and it is responsible for tumor spread, metastasis and its peritoneal dissemination. Ovarian cancer is the fifth leading cause of cancer death in women and it is distinguished as the most lethal gynecologic cancer. In recent years angiogenesis has been given considerable attention in order to identify targets for developing effective anti-tumor therapies. Several molecules have been reported to promote angiogenesis, such as platelet-derived growth factor (PDGF) and its receptors, the angiopoietin/Tie ligand/receptor system and fibroblast growth factor (FGF). Primarily, VEGF has been identified to play key roles in driving angiogenesis. The above-mentioned molecules are candidate drug targets. Used in combination with other treatments, anti-angiogenic therapies have managed to reduce disease progression. The present review is focused in NGF and its high affinity receptor tyrosine kinase A (TRKA). The expression of VEGF, proliferation and the angiogenesis process in ovarian cancer is importantly induced by NGF, among other molecules.

MOL BIOL REP. 2014 JUN;41(6):3715-22.

ASSOCIATION OF GENETIC VARIANTS AT TOX3, 2Q35 AND 8Q24 WITH THE RISK OF FAMILIAL AND EARLY-ONSET BREAST CANCER IN A SOUTH-AMERICAN POPULATION.

Elematore I, Gonzalez-Hormazabal P, Reyes JM, Blanco R, Bravo T, Peralta O, Gomez F, Waugh E, Margarit S, Ibañez G, Romero C, Pakomio J, Roizen G, Di Capua GA, Jara L.

Recent Genome-Wide Association Studies have identified several single nucleotide polymorphisms (SNPs) associated with breast cancer (BC) among women of Asian, European, and African-American ancestry. Nevertheless, the contribution of these variants in the South American population is unknown. Furthermore, there is little information about the effect of these risk alleles in women with early BC diagnosis. In the present study, we evaluated the association between rs3803662 (TOX3, also known as TNRC9), rs13387042 (2q35), and rs13281615 (8q24) with BC risk in 344 Chilean BRCA1/2-negative BC cases and in 801 controls. Two SNPs, rs3803662 and rs13387042, were significantly associated with increased BC risk in familial BC and in non-familial early-onset BC. The risk of BC increased in a dose-dependent manner with the number of risk alleles (P-trend < 0.0001 and 0.0091, respectively). The odds ratios for BC in familial BC and in early-onset non-familial BC were 3.76 (95%CI 1.02-13.84, P = 0.046) and 8.0 (95%CI 2.20-29.04, P = 0.002), respectively, for the maximum versus minimum number of risk alleles. These results indicate an additive effect of the TOX3 rs3803662 and 2q35 rs13387042 alleles for BC risk. We also evaluated the interaction between rs3803662 and rs13387042 SNPs. We observed an additive interaction only in non-familial early-onset BC cases (AP = 0.72 (0.28-1.16), P = 0.001). No significant association was observed for rs13281615 (8q24) with BC risk in women from the Chilean population. The strongly increased risk associated with the combination of low-penetrance risk alleles supports the polygenic inheritance model of BC.

DEPARTAMENTO DE OFTALMOLOGÍA

MOL VIS. 2014 MAR 14;20:334-40.

PAN-AMERICAN MDNA HAPLOGROUPS IN CHILEAN PATIENTS WITH LEBER'S HEREDITARY OPTIC NEUROPATHY.

Romero P, Fernández V, Slabaugh M, Seleme N, Reyes N, Gallardo P, Herrera L, Peña L, Pezo P, Moraga M.

PURPOSE: The clinical impact of mDNA mutations on the development of Leber hereditary optic neuropathy (LHON) may be modulated by mitochondrial haplogroups, which vary across populations. The aim of this research was to determine the clinical spectrum and molecular characteristics, including the haplogroup, of 15 South American families with LHON. METHODS: This study was a prospective, observational study conducted between March 2006 and August 2012. All patients were referred to the Clinical Hospital of the University of Chile, where the clinical study was conducted. Molecular studies were conducted at the Biomedical Sciences Institute (ICBM) of the University of Chile. Fifteen index cases were identified with molecular analysis after initial neuroophthalmic examination at different centers throughout Chile. Clinical features of patients with LHON and maternal relatives of the 15 families (75 individuals: 26 affected and 49 healthy carriers) were evaluated. The primary mDNA mutations (m.3460G>A, m.11778G>A, or m.14484T>C) were determined with restriction fragment length polymorphism analysis in all individuals. Mitochondrial haplogroups were determined with direct sequencing of two hypervariable regions (HV1 and HV2) and compared with reference sequences. RESULTS: The m.11778G>A mutation was found in 59 subjects (78.7%), the m.14484T>C mutation was found in 12 subjects (16.0%), and the m.3460G>A mutation was found in four (5.3%) subjects. The average age of onset of symptoms in affected subjects was 22.2 years old (range 3 to 53 years); 21 (80.7%) were male, and five (19.3%) were female. Twelve families (80%) had Amerindian haplogroups: One family had the A2 haplogroup, four families had the B2i2 haplogroup, six families had the C1b haplogroup, and one family had the D1g haplogroup. CONCLUSIONS: In this limited sample

size, the Amerindian haplogroup A2 was associated with delayed onset of disease in this population. Patients with haplogroup C retained better vision than the patients with other haplogroups in this population. Disease in subjects with haplogroup D appeared to be underrepresented compared to the population at large.

DEPARTAMENTO DE PSIQUIATRÍA Y SALUD MENTAL

BMC PSYCHIATRY. 2014 AUG 3;14:220.

RELATIONSHIP OF CORTISOL LEVELS AND GENETIC POLYMORPHISMS TO ANTIDEPRESSANT RESPONSE TO PLACEBO AND FLUOXETINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A PROSPECTIVE STUDY.

Ventura-Juncá R, Symon A, López P, Fiedler JL, Rojas G, Heskia C, Lara P, Marín F, Guajardo V, Araya AV, Sasso J, Herrera L.

BACKGROUND: Increased cortisol levels and genetic polymorphisms have been related to both major depressive disorder and antidepressant treatment outcome. The aim of this study is to evaluate the relationship between circadian salivary cortisol levels, cortisol suppression by dexamethasone and genetic polymorphisms in some HPA axis-related genes to the response to placebo and fluoxetine in depressed patients. METHODS: The diagnosis and severity of depression were performed using the Mini International Neuropsychiatric Interview (M.I.N.I.) and Hamilton depression scale (HAM-D17), respectively. Euthyroid patients were treated with placebo (one week) followed by fluoxetine (20 mg) (two months). Severity of depression was re-evaluated after placebo, three weeks and two months of fluoxetine treatments. Placebo response was defined as HAM-D17 score reductions of at least 25% and to < 15. Early response and response were reductions of at least 50% after three weeks and two months, and remission with ≤ 7 after two months. Plasma TSH, free-T4, circadian salivary cortisol levels and cortisol suppression by dexamethasone were evaluated. Seven genetic polymorphisms located in the Corticotrophin-releasing-hormone-receptor-1 (rs242939, rs242941, rs1876828), Corticotrophin-releasing-hormone-receptor-2 (rs2270007), Glucocorticoid-receptor (rs41423247), FK506-binding-protein-5 (rs1360780), and Arginine-vasopressin (rs3729965) genes were determined. Association analyses between response to placebo/fluoxetine and polymorphism were performed by chi-square or Fisher exact test. Cortisol levels were compared by t-test, ANOVA and the general linear model for repeated measures. RESULTS: 208 depressed patients were recruited, 187 of whom were euthyroid. Placebo responders, fluoxetine responders and remitters exhibited significantly lower circadian cortisol levels than those who did not respond (p-values of 0.014, 0.008 and 0.021 respectively). Patients who abandoned treatment before the third week also exhibited a trend to low cortisol levels (p = 0.057). The polymorphisms rs242939 (CRHR1) and rs2270007 (CRHR2) were not in Hardy-Weinberg equilibrium. Only the rs242939 polymorphism (CRHR1) exhibited association with early response (three weeks) to fluoxetine (p-value = 0.043). No other association between outcomes and polymorphisms was observed. CONCLUSIONS: These results support the clinical relevance of low salivary cortisol levels as a predictor of antidepressant response, either to placebo or to fluoxetine. Only one polymorphism in the CRHR1 gene was associated with the early response. Other factors may be involved in antidepressant response, although further studies are needed to identify them.

INT J SOC PSYCHIATRY. 2014 FEB;60(1):75-82.

SOCIAL CHARACTERISTICS OF PSYCHOLOGICAL DISTRESS IN DISADVANTAGED AREAS OF BERLIN.

Mundt A, Kliewe T, Yayla S, Ignatyev Y, Busch MA, Heimann H, Heinz A, Rapp MA, Schouler-Ocak M, Ströhle A, Aichberger MC.

PURPOSE: Living in disadvantaged urban areas is associated with poor mental health. The purpose of this study was to assess which social characteristics were associated with psychological distress within a disadvantaged, multi-ethnic neighbourhood of Berlin. METHODS: The study was conducted in an area of Berlin with the highest rates of unemployment and highest density of migrants. A total of 143 participants aged 18-57 years were included from a random sample. The social characteristics educational level, employment status, marital status, living alone, per-capita income and background of migration were collected. Psychological distress was assessed using the General Health Questionnaire GHQ-28; scores ≥ 5 indicated psychological distress corresponding to psychiatric caseness. RESULTS: Psychological distress was found in 40.6% (n = 58) of the sample. Psychological distress was associated with younger age (OR = 0.95, 95% CI = 0.92-0.98, p = .004), female gender (OR = 3.51, 95% CI = 1.55-7.92, p = .003) and living alone (OR = 3.88, 95% CI = 1.58-9.52, p = .003), but not with background of migration, low educational level or with unemployment. CONCLUSIONS: Young age and female gender may predispose for psychological distress in disadvantaged areas. Living alone could be a social indicator of poor mental health within disadvantaged urban areas. The directionality of the association is unclear. BACKGROUND: of migration, low income and educational level do not seem to be associated with poor mental health within those areas.

JAMA PSYCHIATRY. 2014 DEC 3.

PSYCHIATRIC HOSPITAL BEDS AND PRISON POPULATIONS IN SOUTH AMERICA SINCE 1990: DOES THE PENROSE HYPOTHESIS APPLY?

Mundt AP, Chow WS, Arduino M, Barrionuevo H, Fritsch R, Girala N, Minoletti A, Mitkiewicz F, Rivera G, Tavares M, Priebe S.

Importance: In 1939, English mathematician, geneticist, and psychiatrist Lionel Sharples Penrose hypothesized that the numbers of psychiatric hospital beds and the sizes of prison populations were inversely related; 75 years later, the question arises as to whether the hypothesis applies to recent developments in South America. Objective: To explore the possible association of changes in the numbers of psychiatric hospital beds with changes in the sizes of prison populations in South America since 1990.Design, Setting, and Participants: We searched primary sources for the numbers of psychiatric hospital beds in South American countries since 1990 (the year that the Latin American countries signed the Caracas Declaration) and compared these changes against the sizes of prison populations. The associations between the numbers of psychiatric beds and the sizes of prison populations were tested using fixed-effects regression of panel data. Economic variables were considered as covariates. Sufficiently reliable and complete data were obtained from 6 countries: Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay. Main Outcomes and Measures: The numbers of psychiatric beds and the sizes of prison populations. Results: Since 1990, the numbers of psychiatric beds decreased in all 6 countries (ranging from -2.0% to -71.9%), while the sizes of prison populations increased substantially (ranging from 16.1% to 273.0%). Panel data regression analysis across the 6 countries showed a significant inverse relationship between numbers of psychiatric beds and sizes of prison populations. On average, the removal of 1 bed was associated with 5.18 more prisoners (95% CI, 3.10-7.26; P = .001), which was reduced to 2.78 prisoners (95% CI, 2.59-2.97; P < .001) when economic growth was considered as a covariate. The association between the numbers of psychiatric beds and the sizes of prison populations remained practically unchanged when income inequality was considered as a covariate (-4.28 [95% CI, -5.21 to -3.36]; P < .001). Conclusions and Relevance: Since 1990, the numbers of psychiatric beds have substantially decreased in South America, while the sizes of the prison populations have increased against a background of strong economic growth. The changes appear to be associated because the numbers of beds decreased more extensively when and where the sizes of prison populations increased. These findings are consistent with and specify the assumption of an association between the numbers of psychiatric beds and the sizes of prison populations. More research is needed to understand the drivers of the capacities of psychiatric hospitals and prisons and to explore reasons for their association.

CLIN ENDOCRINOL (OXF). 2014 MAY;80(5):677-84.

HIGH SODIUM INTAKE IS ASSOCIATED WITH INCREASED GLUCOCORTICOID PRODUCTION, INSULIN RESISTANCE AND METABOLIC SYNDROME.

Baudrand R, Campino C, Carvajal CA, Olivieri O, Guidi G, Faccini G, Vöhringer PA, Cerda J, Owen G, Kalergis AM, Fardella CE.

OBJECTIVE: High sodium (HS) diet is associated with hypertension (HT) and insulin resistance (IR). We evaluated whether HS diet was associated with a dysregulation of cortisol production and metabolic syndrome (MetS). PATIENTS AND MEASUREMENTS: We recruited 370 adults (18-85 years, BMI 29·3 ± 4·4 kg/m(2) , 70% women, 72% HT, 61% MetS). HS diet (urinary sodium >150 mEq/day) was observed in 70% of subjects. We measured plasma hormones, lipid profile, urinary free cortisol (UFC) and cortisol tetrahydrometabolites (THM). RESULTS: Urinary sodium was correlated with UFC (r = +0·45, P < 0·001), cortisol THM (r = +0·41, P < 0·001) and inversely with adiponectin, HDL and aldosterone, after adjusting by age, gender and BMI. Subjects with high, compared with adequate sodium intake (50-149 mEq/day) had higher UFC (P < 0·001), THM (P < 0·001), HOMA-IR (P = 0·04), HT (81% vs 50%, P < 0·001), MetS (69% vs 41%, P < 0·001) and lower adiponectin (P = 0·003). A multivariate predictive model adjusted by confounders showed a high discriminative capacity for MetS (ROC curve 0·878) using four clinical variables: HS intake [OR = 5·6 (CI 2·3-15·3)], HOMA-IR [OR 1·7 (1·3-2·2)] cortisol THM [OR 1·2 (1·1-1·4)] and adiponectin [OR = 0·9 (0·8-0·9)], the latter had a protective effect. CONCLUSIONS: High sodium diet was associated with increased urinary cortisol and its metabolites. Also, HS diet was associated with HT, insulin resistance, dyslipidaemia and hypoadiponectinaemia, even when adjusting by confounding variables. Further, we observed that high salt intake, IR and higher cortisol metabolites, alone or combined in a clinical simple model, accurately predicted MetS status, suggesting an additive mechanism in obesity-related metabolic disorders.

J AFFECT DISORD. 2014 OCT;167:136-9.

INTERNATIONAL PRESCRIBING PATTERNS FOR MOOD ILLNESS: THE INTERNATIONAL MOOD NETWORK (IMN).

Mauer S, Alahmari R, Vöhringer PA, Vergne DE, Lövdahl H, Correa E, Patkar A, Pae C, Strejilevich S, Dalley S, Ghaemi SN.

OBJECTIVE: To show the feasibility of creating an international network that will build a common database for mood disorders research, and to present initial data on prescribing patterns worldwide. METHODS: An international research database was

organized with clinicians and researchers actively treating mood disorders. Participating sites were asked to provide data on 10-50 subjects initially. This work was conducted under the auspices of a committee with representatives from North and South America, Europe, and Asia. Data was pooled from multiple sites using a centralized online system and then analyzed. Each site received IRB approval for its participation in the IMN and the Tufts Medical Center IRB provided approval for the entire project. LIMITATIONS: More than half of the population came from one country (United States) and there is the possibility of cultural bias. RESULTS: Among the 186 subjects enrolled in the IMN, a majority of subjects were prescribed mood stabilizers including lithium (64%), lamotrigine (37%), valproate (31%), and carbamazepine (3%). 79% had a diagnosis of bipolar disorder type I, II or NOS and 21% had a diagnosis of MDD. 81% of subjects used antidepressants at some point. 25% experienced antidepressant-induced mania and 26% had antidepressant-related rapid cycling. Mood stabilizers were prescribed more in Europe (86%), neuroleptics in South America (70%), and antidepressants in Asia (58%). CONCLUSIONS: The results confirm the diversity and feasibility of an international mood disorders database. Important regional differences in psychotropic drug treatment of mood illnesses were observed, with more mood stabilizer use in Europe and South America, and more antidepressant use in non-European populations.

J AFFECT DISORD. 2014 AUG;164:14-8.

KOUKOPOULOS DIAGNOSTIC CRITERIA FOR MIXED DEPRESSION: A VALIDATION STUDY.

Sani G, Vöhringer PA, Napoletano F, Holtzman NS, Dalley S, Girardi P, Ghaemi SN, Koukopoulos A.

BACKGROUND: Mixed depression (MxD) is one subtype of depressive experiences within the depressive spectrum. MxD definition is debated among experts. Koukopoulos proposed diagnostic criteria focused primarily on psychic agitation, marked irritability, and intense mood lability as markers of a mixed depressive episode. The present study validates Koukopoulos criteria as diagnostic for MxD. METHODS: A sample of 435 patients from the International Mood Network (IMN), multi-center, international network of sites, and the Centro LucioBini of Rome was analyzed. Koukopoulos criteria were assessed in all patients. RESULTS: The most prevalent MxD criteria were “absence of psychomotor retardation” (84%), “mood lability or marked reactivity” (78%), and “psychic agitation or inner tension” (75%). Multivariable predictors of a MxD (+) diagnosis were: higher current CGI (OR=1.23, 95% CI 1.23, 2.84), lower rates of previous bipolar type I diagnosis (OR=0.54, 95% CI -3.28, -0.13), mixed symptoms on the index episode (OR=10.02, 95% CI 2.32, 24.12), rapid cycling course (OR=2.6 95% CI 1.45, 3.56), past substance abuse (OR=3.02, 95% CI 2.01, 5.67) and lower education status (OR=0.44, 95% CI -3.23, -0.98). This model showed a sensitivity of 76.4%, specificity of 86.3%, negative predictive value of 75%, and positive predictive value of 86%. LIMITATIONS: An external validation of these criteria in an independent sample is warranted. CONCLUSION: A broad definition of mixed depression was internally validated with multiple diagnostic validators and was sensitively and specifically predicted. Contrary to DSM-5, Koukopoulos broad criteria include agitation, irritability and mood lability as core features.

PSYCHOTHER PSYCHOSOM. 2014;83(4):213-21.

MIXED DEPRESSION: CLINICAL FEATURES AND PREDICTORS OF ITS ONSET ASSOCIATED WITH ANTIDEPRESSANT USE.

Sani G, Napoletano F, Vöhringer PA, Sullivan M, Simonetti A, Koukopoulos A, Danese E, Girardi P, Ghaemi N.

BACKGROUND: Mixed depression (MxD) is narrowly defined in the DSM-IV and somewhat broader in the DSM-5, although both exclude psychomotor agitation as a diagnostic criterion. This article proposes a clinical description for defining MxD, which emphasizes psychomotor excitation. METHODS: Two hundred and nineteen consecutive outpatients were diagnosed with an MxD episode using criteria proposed by Koukopoulos et al. [Acta Psychiatr Scand 2007;115(suppl 433):50-57]; we here report their clinical features and antidepressant-related effects. RESULTS: The most frequent MxD symptoms were: psychic agitation or inner tension (97%), absence of retardation (82%), dramatic description of suffering or weeping spells (53%), talkativeness (49%), and racing or crowded thoughts (48%). MxD was associated with antidepressants in 50.7% of patients, with similar frequency for tricyclic antidepressants (45%) versus selective serotonin reuptake inhibitors (38.5%). Positive predictors of antidepressant-associated MxD were bipolar disorder type II diagnosis, higher index depression severity, and higher age at index episode. Antipsychotic or no treatment was protective against antidepressant-associated MxD. CONCLUSIONS: MxD, defined as depression with excitatory symptoms, can be clinically identified, is common, occurs in both unipolar depression and bipolar disorder, and is frequently associated with antidepressant use. If replicated, this view of MxD could be considered a valid alternative to the DSM-5 criteria for depression with mixed features.

NEUROPSYCHIATR DIS TREAT. 2014 AUG 19;10:1509-22.

DIAGNOSTIC AND THERAPEUTIC UTILITY OF NEUROIMAGING IN DEPRESSION: AN OVERVIEW.

Wise T, Cleare AJ, Herane A, Young AH, Arnone D.

A growing number of studies have used neuroimaging to further our understanding of how brain structure and function are altered in major depression. More recently, these techniques have begun to show promise for the diagnosis and treatment of depression, both as aids to conventional methods and as methods in their own right. In this review, we describe recent neuroimaging findings in the field that might aid diagnosis and improve treatment accuracy. Overall, major depression is associated with numerous structural and functional differences in neural systems involved in emotion processing and mood regulation. Furthermore, several studies have shown that the structure and function of these systems is changed by pharmacological and psychological treatments of the condition and that these changes in candidate brain regions might predict clinical response. More recently, "machine learning" methods have used neuroimaging data to categorize individual patients according to their diagnostic status and predict treatment response. Despite being mostly limited to group-level comparisons at present, with the introduction of new methods and more naturalistic studies, neuroimaging has the potential to become part of the clinical armamentarium and may improve diagnostic accuracy and inform treatment choice at the patient level.

TRIALS. 2014 AUG 5;15:309.

COMPUTER-ASSISTED COGNITIVE-BEHAVIORAL THERAPY FOR ADOLESCENT DEPRESSION IN PRIMARY CARE CLINICS IN SANTIAGO, CHILE (YPSA-M): STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL.

Martínez V, Martínez P, Vöhringer PA, Araya R, Rojas G.

BACKGROUND: Depression is a common and disabling condition. In Chile, assistance is guaranteed by law through a national program for depression in primary care services, and there is evidence of effective treatment for depressed women. However, there is a shortage of evidence-based treatments for depression in adolescents. The incorporation of technology to expand therapeutic options is becoming more common. This proposal aims to compare the efficacy of therapy that enhances traditional face-to-face cognitive-behavioral therapy (CBT) with a computer-based program versus usual care to treat depression in adolescents in primary care clinics in Santiago, Chile. METHODS AND DESIGN: This is a two-arm, single-blind, randomized controlled trial with a target enrollment of 216 depressed adolescents between 15 and 19 years of age, attending four primary care clinics in Santiago, Chile. In the active arm, depressed adolescents will receive eight sessions of computer-assisted CBT, led by trained psychologists on a weekly basis. In the control arm, depressed adolescents will receive treatment as usual from the primary care centers. Mean depression scores and indicators of dysfunctional thoughts, problem-solving strategies, and health-related quality of life will be measured at baseline and four and six months after randomization. DISCUSSION: As far as we know, this is the first randomized controlled trial of a computer-assisted CBT intervention for depressed adolescents in a Latin American country.

OAIC

HUM VACCIN IMMUNOTHER. 2014 NOV 2;10(11):3261-9.

TUMOR CELL LYSATES AS IMMUNOGENIC SOURCES FOR CANCER VACCINE DESIGN.

González FE, Gleisner A, Falcón-Beas F, Osorio F, López MN, Salazar-Onfray F.

Autologous dendritic cells (DCs) loaded with tumor-associated antigens (TAAs) are a promising immunological tool for cancer therapy. These stimulate the antitumor response and immunological memory generation. Nevertheless, many patients remain refractory to DC approaches. Antigen (Ag) delivery to DCs is relevant to vaccine success, and antigen peptides, tumor-associated proteins, tumor cells, autologous tumor lysates, and tumor-derived mRNA have been tested as Ag sources. Recently, DCs loaded with allogeneic tumor cell lysates were used to induce a potent immunological response. This strategy provides a reproducible pool of almost all potential Ags suitable for patient use, independent of MHC haplotypes or autologous tumor tissue availability. However, optimizing autologous tumor cell lysate preparation is crucial to enhancing efficacy. This review considers the role of cancer cell-derived lysates as a relevant source of antigens and as an activating factor for ex vivo therapeutic DCs capable of responding to neoplastic cells. These promising therapies are associated with the prolonged survival of advanced cancer patients.

IMMUNOLOGY. 2014 JUL;142(3):396-405.

MELANOMA CELL LYSATE INDUCES CCR7 EXPRESSION AND IN VIVO MIGRATION TO DRAINING LYMPH NODES OF THERAPEUTIC HUMAN DENDRITIC CELLS.

González FE, Ortiz C, Reyes M, Dutzan N, Patel V, Pereda C, Gleisner MA, López MN, Gutkind JS, Salazar-Onfray F.

We have previously reported a novel method for the production of tumour-antigen-presenting cells (referred to as TAPCells) that are currently being used in cancer therapy, using an allogeneic melanoma-derived cell lysate (referred to as TRIMEL) as an antigen provider and activation factor. It was recently demonstrated that TAPCell-based immunotherapy induces T-cell-mediated immune responses resulting in improved long-term survival of stage IV melanoma patients. Clinically, dendritic cell (DC) migration from injected sites to lymph nodes is an important requirement for an effective anti-tumour immunization. This mobilization of DCs is mainly driven by the C-C chemokine receptor type 7 (CCR7), which is up-regulated on mature DCs. Using flow cytometry and immunohistochemistry, we investigated if TRIMEL was capable of inducing the expression of the CCR7 on TAPCells and enhancing their migration in vitro, as well as their in vivo relocation to lymph nodes in an ectopic xenograft animal model. Our results confirmed that TRIMEL induces a phenotypic maturation and increases the expression of surface CCR7 on melanoma patient-derived DCs, and also on the monocytic/macrophage cell line THP-1. Moreover, in vitro assays showed that TRIMEL-stimulated DCs and THP-1 cells were capable of migrating specifically in the presence of the CCR7 ligand CCL19. Finally, we demonstrated that TAPCells could migrate in vivo from the injection site into the draining lymph nodes. This work contributes to an increased understanding of the biology of DCs produced ex vivo allowing the design of new strategies for effective DC-based vaccines for treating aggressive melanomas.

J IMMUNOL. 2014 FEB 1;192(3):1313-9.

GAP JUNCTION INTERCELLULAR COMMUNICATIONS REGULATE NK CELL ACTIVATION AND MODULATE NK CYTOTOXIC CAPACITY.

Tittarelli A, Mendoza-Naranjo A, Farías M, Guerrero I, Ihara F, Wennerberg E, Riquelme S, Gleisner A, Kalergis A, Lundqvist A, López MN, Chambers BJ, Salazar-Onfray F.

Gap junctions (GJs) mediate intercellular communication between adjacent cells. Previously, we showed that connexin 43 (Cx43), the main GJ protein in the immune system, mediates Ag transfer between human dendritic cells (DCs) and is recruited to the immunological synapse during T cell priming. This crosstalk contributed to T cell activation, intracellular Ca(2+) responses, and cytokine release. However, the role of GJs in NK cell activation by DCs and NK cell-mediated cytotoxicity against tumor cells remains unknown. In this study, we found polarization of Cx43 at the NK/DC and NK/tumor cell-contact sites, accompanied by the formation of functional GJs between NK/DCs and NK/tumor cells, respectively. Cx43-GJ-mediated intercellular communication (GJIC) between human NK and DCs was bidirectional. Blockage of Cx43-GJIC inhibited NK cell activation, though it affected neither the phenotype nor the function of DCs. Cx43 knockdown or inhibition using mimetic peptides greatly reduced CD69 and CD25 expression and IFN-β release by DC-stimulated NK cells. Moreover, blocking Cx43 strongly inhibited the NK cell-mediated tumor cell lysis associated with inhibition of granzyme B activity and Ca(2+) influx. Our data identify a novel and active role for Cx43-GJIC in human NK cell activation and antitumor effector functions that may be important for the design of new immune therapeutic strategies.

CENTRO DE IMAGENOLOGÍA

J ULTRASOUND MED. 2014 JAN;33(1):93-102.

SONOGRAPHY OF ACNE VULGARIS.

Wortsman X, Claveria P, Valenzuela F, Molina MT, Wortsman J.

OBJECTIVES: The purpose of this study was to assess the sonographic morphology of the clinical and subclinical pathology of facial acne vulgaris. METHODS: We studied patients with facial acne vulgaris diagnosed by certified dermatologists, and using a standardized protocol for sonographic examinations, we sequentially described the sonographic pathomorphologic characteristics. Lesions of particular interest to the referring clinician were also analyzed separately. Additionally, acne involvement was staged clinically and sonographically (SOS-Acne) using morphologic definitions of the relevant lesions and predefined scoring systems for gradation of the severity of acne lesions. RESULTS: A total of 245 acne lesions in 20 consecutive patients were studied. Sonographic abnormalities consisted of pseudocysts, folliculitis, fistulas, and calcinosis. Most conditions were subclinical and mostly due to lesion extensions deep into the dermis and hypodermis (52% of pseudocysts and 68% of fistulas). The statistical concordance between acne severity scores assigned by two separate clinicians was strong (β = 0.8020), but the corresponding sonographic scores generally showed more severe and clinically occult involvement. CONCLUSIONS: Facial acne vulgaris often involves deeper tissues, beyond the reach of the spatially restricted clinical examination; these subclinical conditions can be detected and defined with sonography. Additionally, acne vulgaris is amenable to sonographic scoring.

UNIDAD DE PACIENTES CRÍTICOS

ANN INTENSIVE CARE. 2014 OCT 11;4:30.

WHEN TO STOP SEPTIC SHOCK RESUSCITATION: CLUES FROM A DYNAMIC PERFUSION MONITORING.

Hernandez G, Luengo C, Bruhn A, Kattan E, Friedman G, Ospina-Tascon GA, Fuentealba A, Castro R, Regueira T, Romero C, Ince C, Bakker J.

BACKGROUND: The decision of when to stop septic shock resuscitation is a critical but yet a relatively unexplored aspect of care. This is especially relevant since the risks of over-resuscitation with fluid overload or inotropes have been highlighted in recent years. A recent guideline has proposed normalization of central venous oxygen saturation and/or lactate as therapeutic end-points, assuming that these variables are equivalent or interchangeable. However, since the physiological determinants of both are totally different, it is legitimate to challenge the rationale of this proposal. We designed this study to gain more insights into the most appropriate resuscitation goal from a dynamic point of view. Our objective was to compare the normalization rates of these and other potential perfusion-related targets in a cohort of septic shock survivors. METHODS: We designed a prospective, observational clinical study. One hundred and four septic shock patients with hyperlactatemia were included and followed until hospital discharge. The 84 hospital-survivors were kept for final analysis. A multimodal perfusion assessment was performed at baseline, 2, 6, and 24 h of ICU treatment. RESULTS: Some variables such as central venous oxygen saturation, central venous-arterial pCO2 gradient, and capillary refill time were already normal in more than 70% of survivors at 6 h. Lactate presented a much slower normalization rate decreasing significantly at 6 h compared to that of baseline (4.0 [3.0 to 4.9] vs. 2.7 [2.2 to 3.9] mmol/L; $p < 0.01$) but with only 52% of patients achieving normality at 24 h. Sublingual microcirculatory variables exhibited the slowest recovery rate with persistent derangements still present in almost 80% of patients at 24 h. CONCLUSIONS: Perfusion-related variables exhibit very different normalization rates in septic shock survivors, most of them exhibiting a biphasic response with an initial rapid improvement, followed by a much slower trend thereafter. This fact should be taken into account to determine the most appropriate criteria to stop resuscitation opportunely and avoid the risk of over-resuscitation.

AM J EMERG MED. 2014 OCT;32(10):1275-7.

CENTRAL VENOUS SATURATION IN SEPTIC SHOCK: CO-OXIMETRY VS GASOMETRY.

Romero CM, Luengo C, Tobar E, Fábrega L, Vial MJ, Cornejo R, Gálvez R, Llanos O.

OBJECTIVES: Central venous oxygen saturation calculated by gasometry (Gaso-Scvo2) is more available than central venous oxygen saturation measured by co-oximetry (Co-oxy-Scvo2) in environments with less resources and underdeveloped countries. Therefore, we aimed to determine the agreement between Co-oxy-Scvo2 and Gaso-Scvo2 and between central venous oxygen tension measured by gasometry (Gaso-Pcvo2) and Co-oxy-Scvo2, respectively. DESIGN AND SETTINGS: This is a prospective study in a university hospital's intensive care unit. PATIENTS: Sixteen patients were studied during the first 48 hours after diagnosis of septic shock. All patients were intubated, connected to mechanical ventilation, and resuscitated according to the standards of care. MEASUREMENTS AND RESULTS: One hundred eleven pairs of central venous blood measurements were analyzed both by conventional gasometry and co-oximetry. Bland and Altman analysis between Co-oxy-Scvo2 and Gaso-Scvo2 showed lack of agreement (1.7 [-10.7, +14.2]). A Gaso-Scvo2 less than 70% had a positive predictive value of 63% in relation to Co-oxy-Scvo2, and its negative predictive value was 90% with 20% false-positives and 5% false-negatives. The area under the receiver operator characteristic curve of Gaso-Pcvo2 to discriminate a Co-oxy-Scvo2 greater than or equal to 70% was 0.87 (confidence interval, 0.80-0.93), and the best cut-off point was a Gaso-Pcvo2 more than 40 mm Hg, (sensitivity, 75%; specificity, 93%). CONCLUSIONS: The reliability of Gaso-Scvo2 determination during the resuscitation phase of septic shock is not acceptable. There is a good agreement between a Gaso-Pcvo2 more than 40 mm Hg and a Co-oxy-Scvo2 greater than or equal to 70%. Our results suggest that given these limitations, Gaso-Scvo2 results should be interpreted with caution, helped by Gaso-Pcvo2 measurements and in context with other perfusion parameters.

REV BRAS TER INTENSIVA. 2014 APR-JUN;26(2):193-9.

HIGH-VOLUME HEMOFILTRATION AND PRONE VENTILATION IN SUBARACHNOID HEMORRHAGE COMPLICATED BY SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME AND REFRACTORY SEPTIC SHOCK.

Cornejo R, Romero C, Ugalde D, Bustos P, Diaz G, Galvez R, Llanos O, Tobar E.

We report the successful treatment of two patients with aneurismal subarachnoid hemorrhage complicated by severe respiratory failure and refractory septic shock using simultaneous prone position ventilation and high-volume hemofiltration. These rescue therapies allowed the patients to overcome the critical situation without associated complications and with no detrimental effects on

the intracranial and cerebral perfusion pressures. Prone position ventilation is now an accepted therapy for severe acute respiratory distress syndrome, and high-volume hemofiltration is a non-conventional hemodynamic support that has several potential mechanisms for improving septic shock. In this manuscript, we briefly review these therapies and the related evidence. When other conventional treatments are insufficient for providing safe limits of oxygenation and perfusion as part of basic neuroprotective care in subarachnoid hemorrhage patients, these rescue therapies should be considered on a case-by-case basis by an experienced critical care team.

ANN ONCOL. 2014 SEP;25(9):1829-35.

INTENSIVE CARE IN PATIENTS WITH LUNG CANCER: A MULTINATIONAL STUDY.

Soares M, Toffart AC, Timsit JF, Burghi G, Irrazábal 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, Tejera D, Salluh JI, Azoulay E; Lung Cancer in Critical Care (LUCCA) Study Investigators.

BACKGROUND: Detailed information about lung cancer patients requiring admission to intensive care units (ICUs) is mostly restricted to single-center studies. Our aim was to evaluate the clinical characteristics and outcomes of lung cancer patients admitted to ICUs. PATIENTS AND METHODS: Prospective multicenter study in 449 patients with lung cancer (small cell, n = 55; non-small cell, n = 394) admitted to 22 ICUs in six countries in Europe and South America during 2011. Multivariate Cox proportional hazards frailty models were built to identify characteristics associated with 30-day and 6-month mortality. RESULTS: Most of the patients (71%) had newly diagnosed cancer. Cancer-related complications occurred in 56% of patients; the most common was tumoral airway involvement (26%). Ventilatory support was required in 53% of patients. Overall hospital, 30-day, and 6-month mortality rates were 39%, 41%, and 55%, respectively. After adjustment for type of admission and early treatment-limitation decisions, determinants of mortality were organ dysfunction severity, poor performance status (PS), recurrent/progressive cancer, and cancer-related complications. Mortality rates were far lower in the patient subset with nonrecurrent/progressive cancer and a good PS, even those with sepsis, multiple organ dysfunctions, and need for ventilatory support. Mortality was also lower in high-volume centers. Poor PS predicted failure to receive the initially planned cancer treatment after hospital discharge. CONCLUSIONS: ICU admission was associated with meaningful survival in lung cancer patients with good PS and non-recurrent/progressive disease. Conversely, mortality rates were very high in patients not fit for anticancer treatment and poor PS. In this subgroup, palliative care may be the best option.

SERVICIO DE ANATOMÍA PATOLÓGICA

ANN RHEUM DIS. 2014 OCT;73(10):1873-9.

SERUM LEVELS OF NOVEL NOGGIN AND SCLEROSTIN-IMMUNE COMPLEXES ARE ELEVATED IN ANKYLOSING SPONDYLITIS.

Tsui FW, Tsui HW, Las Heras F, Pritzker KP, Inman RD.

BACKGROUND: Unravelling the basis of joint inflammation and ankylosis represents a major challenge in ankylosing spondylitis (AS) research. As noggin (NOG) and sclerostin (SOST) have recently been associated with the disease process in mouse and human studies, respectively, we explored the immune responses to these two molecules in AS. METHODS: Immune complexes (IC) composed of IgG autoantibodies to NOG and SOST were detected by immunoprecipitation and Western blot analyses. Epitope-specific IgG were measured using peptide-binding ELISA. Serum samples were obtained from healthy controls and patients with AS, mechanical back pain (MBP) and inflammatory bowel disease (IBD) with or without concomitant AS. RESULTS: NOG and SOST-IgG IC were present in NOG-treated and untreated ank/ank (progressive ankylosis), but not in wild-type mice. Higher than normal levels of NOG and SOST-IgG IC are present in AS sera ($p<0.001$). We showed a SOST peptide (SOST-S146, with homology to a bacterial glycotransferase peptide) binds to a NOG peptide (NOG-N54), which contains a N-glycosylation site. AS patients have higher levels of IgG recognising the NOG-N54 and SOST-S146 peptides compared to the levels in normal controls, IBD and MBP patients (one way analysis of variance $p<0.0001$). CONCLUSIONS: This is the first report showing IgG autoantibodies to NOG and SOST in normal individuals, and higher levels of NOG and/or SOST-IgG IC probably contribute to neo-ossification in AS patients. These novel findings hold the promise of earlier diagnosis, better management of AS with comorbidities and new therapeutic approaches to modulate ankylosis in AS.

INT J ONCOL. 2014 MAR;44(3):647-54.

INCREASED SNAIL EXPRESSION AND LOW SYNDECAN LEVELS ARE ASSOCIATED WITH HIGH GLEASON GRADE IN PROSTATE CANCER.

Poblete CE, Fulla J, Gallardo M, Muñoz V, Castellón EA, Gallegos I, Contreras HR.

Prostate cancer (PC) is a leading male oncologic malignancy wideworld. During malignant transformation, normal epithelial cells undergo genetic and morphological changes known as epithelial-mesenchymal transition (EMT). Several regulatory genes and

specific marker proteins are involved in PC EMT. Recently, syndecans have been associated with malignancy grade and Gleason score in PC. Considering that SNAIL is mainly a gene repressor increased in PC and that syndecan promoters have putative binding sites for this repressor, we propose that SNAIL might regulate syndecan expression during PC EMT. The aim of this study was to analyze immunochemically the expression of SNAIL, syndecans 1 and 2 and other EMT markers in a tissue microarray (TMA) of PC samples and PC cell lines. The TMAs included PC samples of different Gleason grade and benign prostatic hyperplasia (BPH) samples, as non-malignant controls. PC3 and LNCaP cell lines were used as models of PC representing different tumorigenic capacities. Semi-quantitative immunohistochemistry was performed on TMAs and fluorescence immunocytochemistry and western blot analysis were conducted on cell cultures. Results show that SNAIL exhibits increased expression in high Gleason specimens compared to low histological grade and BPH samples. Accordingly, PC3 cells show higher SNAIL expression levels compared to LNCaP cells. Conversely, syndecan 1, similarly to E-cadherin (a known marker of EMT), shows a decreased expression in high Gleason grades samples and PC3 cells. Interestingly, syndecan 2 shows no changes associated to histological grade. It is concluded that increased SNAIL levels in advanced PC are associated with low expression of syndecan 1. The mechanism by which SNAIL regulates the expression of syndecan 1 remains to be investigated

SERVICIO DE OTORRINOLARINGOLOGÍA

AJNR AM J NEURORADIOL. 2014 SEP;35(9):1820-4.

USE OF NON-ECHO-PLANAR DIFFUSION-WEIGHTED MR IMAGING FOR THE DETECTION OF CHOLESTEATOMAS IN HIGH-RISK TYMPANIC RETRACTION POCKETS.

Alvo A, Garrido C, Salas Á, Miranda G, Stott CE, Delano PH.

BACKGROUND AND PURPOSE: Non-echo-planar DWI MR imaging (including the HASTE sequence) has been shown to be highly sensitive and specific for large cholesteatomas. The purpose of this study was to determine the diagnostic accuracy of HASTE DWI for the detection of incipient cholesteatoma in high-risk retraction pockets. MATERIALS AND METHODS: This was a prospective study of 16 patients who underwent MR imaging with HASTE DWI before surgery. Surgeons were not informed of the results, and intraoperative findings were compared against the radiologic diagnosis. Sensitivity, specificity, and positive and negative predictive values were calculated. RESULTS: Among the 16 retraction pockets, 10 cholesteatomas were diagnosed intraoperatively (62.5%). HASTE showed 90% sensitivity, 100% specificity, 100% positive predictive value, and 85.7% negative predictive value in this group of patients. We found only 1 false-negative finding in an infected cholesteatoma. CONCLUSIONS: We demonstrate a high correlation between HASTE and surgical findings, suggesting that this technique could be useful for the early detection of primary acquired cholesteatomas arising from retraction pockets and could help to avoid unnecessary surgery.

ACTA OTORRINOLARINGOL ESP. 2014 MAR-APR;65(2):109-13.

UNUSUAL SINONASAL FOREIGN BODY: PRESENTATION OF THREE CASES.

Nazar R, Cabrera N, Martelo G, Machiavello C, Naser A.

Sinonasal foreign bodies are rare clinical entities. Their presence in the sinuses can originate complications, so their removal is always indicated. We present 3 cases of sinonasal foreign body, indicating their symptoms, imaging findings and surgical removal. Each patient was assessed with computerized tomography of the sinuses, rigid endoscopy, and then surgical removal. We confirmed the presence of the foreign bodies in all 3 cases and then performed a successful surgical removal by transnasal endoscopy. Sinonasal foreign bodies are infrequent entities that require surgical removal to prevent complications, with transnasal endoscopic surgery being the most commonly used surgical approach.

ACTA OTORRINOLARINGOL ESP. 2014 MAR-APR;65(2):114-9.

DECANNULATION AND ASSESSMENT OF DEGLUTITION IN THE TRACHEOSTOMIZED PATIENT IN NON-NEUROCRITICAL INTENSIVE CARE.

Alvo A, Olavarría C.

With intensive care patients, decannulation and deglutition disorders are frequent reasons for otorhinolaryngological assessment. The objective of a tracheostomy is to maintain a patent airway. It does not necessarily prevent episodes of aspiration and may even favour them. When the cause that led to the tracheostomy resolves, a decannulation may be proposed. Deglutition is a complex act involving the coordinated interaction of several structures of the aerodigestive tract. Fibre-optic endoscopy and videofluoroscopy are 2 useful, complementary tools for the evaluation of patients with swallowing disorders. In managing these patients, a thorough knowledge of laryngeal and swallowing physiology, as well as of the different therapeutic alternatives, is required. Although it is

not uncommon for swallowing disorders to coexist in tracheostomy patients, decannulation evaluation is not synonymous with deglutition assessment. A patient could be a candidate for decannulation and have a swallowing disorder, or a tracheostomy patient could swallow adequately. Knowing and understanding these concepts will lead to more efficient management and help to clarify communication between the intensive care physician and the otorhinolaryngologist. Ideally, a multidisciplinary team should be formed to evaluate and manage these patients.

J VOICE. 2015 JAN;29(1):130.E21-8.

LARYNGOSCOPIC AND SPECTRAL ANALYSIS OF LARYNGEAL AND PHARYNGEAL CONFIGURATION IN NON-CLASSICAL SINGING STYLES.

Guzman M, Lanas A, Olavarria C, Azocar MJ, Muñoz D, Madrid S, Monsalve S, Martinez F, Vargas S, Cortez P, Mayerhoff RM.

PURPOSE: The present study aimed to assess three different singing styles (pop, rock, and jazz) with laryngoscopic, acoustic, and perceptual analysis in healthy singers at different loudness levels. Special emphasis was given to the degree of anterior-posterior (A-P) laryngeal compression, medial laryngeal compression, vertical laryngeal position (VLP), and pharyngeal compression. STUDY DESIGN: Prospective study. METHODS: Twelve female trained singers with at least 5 years of voice training and absence of any voice pathology were included. Flexible and rigid laryngeal endoscopic examinations were performed. Voice recording was also carried out. Four blinded judges were asked to assess laryngoscopic and auditory perceptual variables using a visual analog scale. RESULTS: All laryngoscopic parameters showed significant differences for all singing styles. Rock showed the greatest degree for all of them. Overall A-P laryngeal compression scores demonstrated significantly higher values than overall medial compression and VLP. High loudness level produced the highest degree of A-P compression, medial compression, pharyngeal compression, and the lowest VLP for all singing styles. Additionally, rock demonstrated the highest values for alpha ratio (less steep spectral slope), L1-L0 ratio (more glottal adduction), and Leq (more vocal intensity). Statistically significant differences between the three loudness levels were also found for these acoustic parameters. CONCLUSIONS: Rock singing seems to be the style with the highest degree of both laryngeal and pharyngeal activity in healthy singers. Although, supraglottic activity during singing could be labeled as hyperfunctional vocal behavior, it may not necessarily be harmful, but a strategy to avoid vocal fold damage.

SERVICIO TRAUMATOLOGÍA

EUR J ORTHOP SURG TRAUMATOL. 2014 JUL;24 SUPPL 1:S93-101.

DOES KYPHOTIC DEFORMITY CORRELATE WITH FUNCTIONAL OUTCOMES IN FRACTURES AT THE THORACOLUMBAR JUNCTION TREATED BY 360° INSTRUMENTED FUSION?

Schulz R, Melcher RP, Garib MC, Schulz H, Weissman K, Harms J.

Sagittal balance and its relationship with back pain and functional outcomes has become an important factor in the management of thoracolumbar fractures. The kyphosis threshold at the thoracolumbar junction (TLJ) that produces a significant functional impairment remains unclear. Ninety-four patients who were treated surgically for TLJ fractures were evaluated after a follow-up period of 2-10 years. Functional evaluation based on the Oswestry and Hannover Scores (HS) was performed. Additionally, such patients underwent clinical and radiological evaluation. A significant inversely proportional correlation between the HS and the degrees of local kyphosis ("K-Angle") ($p = 0.0172$) was found. A significant directly proportional correlation between Oswestry Score and "K-Angle" ($p = 0.0142$) was found. Significantly poorer scores with both measurement tools (Hannover and Oswestry Scores) were found in patients with a kyphosis higher than 12°.

SPORTS HEALTH. 2014 MAR;6(2):119-21.

EFFECT OF ACTIVE VERSUS PASSIVE RECOVERY ON PERFORMANCE DURING INTRAMEET SWIMMING COMPETITION.

Hinzpeter J, Zamorano A, Cuzmar D, Lopez M, Burboa J.

BACKGROUND: During competition, high-performance swimmers are subject to repeated physical demands that affect their final performance. Measurement of lactate concentration in blood seeks to indirectly gauge physiologic responses to the increase in physical exercise. Swimmers face multiple maximal-exertion events during competition. Strenuous physical exercise leads to fatigue and, thus, a decrease in sports performance. HYPOTHESIS: Regeneration exercises in swimming increase the clearance of blood lactate and therefore improve athletic performance within a single day of competition. STUDY DESIGN: Crossover study. LEVEL OF EVIDENCE: Level 1. METHODS: Of 25 swimmers, 21 were included, with a mean age of 17 years. They performed exercises that increased blood lactate on 2 days. The protocol was a warm-up, followed by a 100-m freestyle workout at full speed.

Swimming exercises followed that were increasingly demanding, during which serial lactatemia measurements were taken. On the first day, regeneration exercises were performed; on the second day, the swimmers rested. Next, lactatemia was measured, and a timed 100-m freestyle workout was performed at maximum speed. RESULTS: The stress exercises increased the mean lactate concentration by 4.6 mmol/L, which corresponds to 78% of the initial basal level. The postregeneration lactatemia level was lower than that after resting (mean, 2.76 vs 6.51 mmol/L). The time to swim 100 m after regeneration was 68.11 seconds, while that after rest was 69.31 seconds. CONCLUSION: Blood lactate levels rose by up to 78% after the intensity of the training sessions was progressively increased. Regeneration exercises increased the rate in which blood lactate dissipated, in comparison with passive recuperation. The rate of lactate dissipation for regeneration exercises was 68%. This factor may have improved the physical performance of swimmers. CLINICAL RELEVANCE: Regeneration exercises improved the performance of swimmers in maximal-exertion competition in a single day. The blood lactate level correlated with physical exercise load.

FOOT ANKLE SURG. 2014 JUN;20(2):115-9.

ARE LOCKING PLATES BETTER THAN NON-LOCKING PLATES FOR TREATING DISTAL TIBIAL FRACTURES?

Bastias C1, Henríquez H1, Pellegrini M2, Rammelt S3, Cuchacovich N1, Lagos L4, Carcuro G1.

BACKGROUND: Locking and non-locking plates has been used for distal tibia fracture osteosynthesis. Sufficient evidence to favor one implant over the other is lacking in the current literature. Our aim is to compare them in terms of fracture healing, alignment, functional outcome, complications. METHODS: Sixty-eight patients operated on using a percutaneous plate were retrospectively reviewed. They were divided into two groups: in group 1 (28 patients) a 4.5mm narrow conventional dynamic compression plate (DCP) was used. In group 2 (40 patients) a titanium locked compression plate (LCP) was used. RESULTS: Mean time to union was 16.2 and 15.4 weeks for group 1 and 2, respectively (p=0.618). 11 patients (39.3%) in group 1 and 4 patients (10%) in group 2 showed malalignment (p=0.016). AOFAS scores at follow up were 89 and 88 in groups 1 and 2, respectively. Implant removal was necessary in 9 cases (32.1%) and 4 cases (10%) in group 1 and group 2, respectively (p=0.042). Three patients (10.7%) in group 1 and three patients (7.5%) in group 2 had an infection. CONCLUSIONS: Both plating systems have similar results in terms of time to union, infection, and AOFAS scores. The LCP seems superior with respect to alignment and the need for implant removal.

SERVICIO UROLOGÍA

J MENS HEALTH 2014; VOLUMEN 11, N° 2

QUALITY OF LIFE EVALUATION IN PATIENTS WITH PROSTATE CANCER TREATED WITH RADICAL PROSTATECTOMY: PROSPECTIVE STUDY AND RESULTS OF EIGHTEEN MONTHS OF FOLLOW-UP

Juan Fulla, Rodolfo Rosenfeld, Catherine Sanchez, Felipe Oyanedel, Rodrigo Valenzuela, Jose M. Campero, Raúl Valdevenito, Heinz Nicolai, Christian Ramos

Background: Prostate cancer is a serious problem throughout the Western hemisphere. Because a number of effective treatment options for localized cancer are now available, it is important to consider quality of life when selecting a treatment. This study evaluated quality of life in patients with localized prostate cancer before and after treatment with radical prostatectomy. Methods: This was a prospective open cohort study. Fifty-five patients treated for localized prostate cancer on the Urology Service of two health care facilities were screene d for inclusion. Quality of life parameters were evaluated using the UCLA Prostate Cancer Index questionnaire prior to treatment and 3, 6, 9, 12, and 18 months after surgery. Scores were compared using the Mann Whitney U test, with the level of statistical significance set at $p<0.05$. Multivariate analysis was used to identify factors predictive of recovery to at least 70% of baseline function. Results: Fifty-five patients were enrolled and followed for at least 12 months. Mean age was 65.3 years (range 44–78, SD 7.8). At the 3-month evaluation, there was a significant decline in urinary (80 vs. 59;$p<0.001$) and sexual (53 vs. 24;$p<0.001$) function as compared with baseline. Bowel function did not suffer a significant decline during the evaluation period. Both urinary (59 vs. 69.1;$p=0.03$) and sexual (24 vs. 33.8;$p=0.02$) function recovered significantly by 18 months as compared with 3 months. Multivariate analysis indicated that age, prostate-specific antigen level, lack of postoperative radiation, and preservation of the neurovascular bundles were protective factors against loss of more than 30% of baseline sexual and urinary function. Conclusions: Urinary and sexual function both suffered a significant decline in patients who underwent radical prostatectomy; however, these functions tended to recover over time. Age, prostate-specific antigen level, and preservation of the neurovascular bundles were protective factors associated with early recovery of many functions.

INT BRAZ J UROL. 2014 SEP-OCT;40(5):666-75.

DIFFERENCES IN URODYNAMIC VOIDING VARIABLES RECORDED BY CONVENTIONAL CYSTOMETRY AND AMBULATORY MONITORING IN SYMPTOMATIC WOMEN.

Valdevenito JP, Leonard A, Griffiths CJ, Pickard R, Harding C.

OBJECTIVES: To determine whether there are differences in pressure and flow measurements between conventional cystometry (CONV) and ambulatory urodynamic monitoring (AMB) in women with overactive bladder syndrome and urinary incontinence. MATERIALS AND METHODS: Retrospective study which included female subjects who underwent both CONV (with saline filling medium) and AMB, separated by less than 24 months, not using medication active on the lower urinary tract and without history of prior pelvic surgery. Both tests were carried out in compliance with the International Continence Society standards. The paired Student's t test was used to compare continuous variables. Bland-Altman statistics were used to assess the agreement of each variable between both studies. RESULTS: Thirty women with a median (range) age of 50 (14 - 73) years met the inclusion criteria. AMB was carried out at a mean (SD) of 11 (6) months after CONV. Measurements of pves and pabd at the end of filling, and Qmax were significantly higher from AMB recordings. There were no differences in pdet at the end of filling, pdetQmax or pdetmax during voiding, nor significant difference in Vvoid. CONCLUSIONS: We provide previously undocumented comparative voiding data between CONV and AMB for patients who most commonly require both investigations. Our findings show higher values of Qmax but similar values of pdetQmax measured by AMB which may partly reflect an overall lower catheter caliber, physiological filling but perhaps also more 'normal' voiding conditions.

ACTAS UROL ESP. 2014 NOV 27. PII: S0210-4806(14)00339-8.

COMPARISON BETWEEN RETROGRADE INTRARENAL SURGERY AND EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY IN THE TREATMENT OF LOWER POLE KIDNEY STONES UP TO 15MM. PROSPECTIVE, RANDOMIZED STUDY.

Vilches RM, Aliaga A, Reyes D, Sepulveda F, Mercado A, Moya F, Ledezma R, Hidalgo JP, Olmedo T, Marchant F.

INTRODUCTION: Extracorporeal Shock Wave Lithotripsy (ESWL) is currently the recommended treatment for intra-renal calculi smaller than 2cm. However the low Stone Free Rate (SFR) in lower pole calculi gives rise to new techniques, such us retrograde intrarenal surgery (RIRS), for improve the surgery outcomes. OBJECTIVE: To compare the efficacy of a treatment with ESWL with RIRS, in terms of SFR after surgery, in patients with kidney stones up to 15mm in the lower pole. MATERIAL AND METHODS: A prospective study was carried out in order to assess the results of ESWL and RIRS in patients with lower pole stones less than 15mm. Among a total of 55 patients, 31 were underwent to ESWL (Group 1) and the remaining 24 to RIRS (Group 2). Clinical data recorded, including general characteristics of each patient, were: calculi size, side, operative time, complications according to Clavien scale, SFR and the presence of residual fragments at 2 months post-treatment assessed by a CT scan. STATA 11 was used to perform the statistical analysis. RESULTS: There were no differences for general descriptors among groups with the exception of a significantly longer operative time for RIRS. The rates of SFR and residual fragments lesser than 3mm. were lower in the RIRS group than in ESWL ones. RIRS also showed a lower rate of clinically significant fragments (0% vs 42.3%. P<.05). In the subgroup of patients with stones between 10/15mm RIRS showed higher SFR (75% vs. 41.2%) and a lower rate of stones>3mm (0% vs. 58.8%), being statistically significant (P<.05). Clavien III or higher complications were not reported in any of the groups. CONCLUSIONS: In the treatment of lower pole stone RIRS has the same results than ESWL in terms of SFR. Regarding absence of a clinically significant residual fragment, RIRS was superior to ESWL. A bigger sample size is required in order to confirm this results.

ACTAS UROL ESP. 2014 SEP 1. PII: S0210-4806(14)00309-X.

URODYNAMIC STUDY IN WOMEN WITH PURE STRESS URINARY INCONTINENCE.

Valdevenito JP, Aguila F, Naser M, Manríquez V, Wenzel Díaz JP.

OBJECTIVE: To describe the results of urodynamic study in women with pure stress urinary incontinence symptoms, including the characteristics of the overactive detrusor. No other clinical assessments were taken into account. MATERIAL AND METHODS: A retrospective study in women with urinary incontinence consecutively evaluated by urodynamic study. From a total of 710 women, only 108 (15%) with pure stress urinary incontinence symptoms were selected. Women with prior urinary incontinence surgery, pelvic organ prolapse (stage≥iii), pelvic radiotherapy, using medication active on the lower urinary tract and neurological diseases were excluded. Infusion rate was 70ml/min. Detrusor overactivity was induced only by cough. A standardized cough stress test with progressive cough intensity was carried out. RESULTS: Reference urodynamic values for stress incontinent women are described. Urodynamic stress incontinence was observed in 79 women (73.1%), detrusor overactivity in 4 (3.7%) and mixed urodynamic diagnosis in 15 (13.8%). Test was inconclusive in 10 patients (9.2%). Two women had detrusor overactivity incontinence (1.9%).

One patient had detrusor overactivity induced by cough without urodynamic stress incontinence (0.9%). There was an association between detrusor overactivity and nocturia≥2 (P=.002; odds ratio: 3.74; 95% confidence interval: 1.22-11.39). One woman had a bladder outlet obstruction (0.9%). CONCLUSIONS: In women with pure stress urinary incontinence, without knowing the outcome of other clinical assessments, urodynamic study can provide useful information to define the proper therapy.

INT BRAZ J UROL. 2014 MAR-APR;40(2):154-9.

IS ACTIVE SURVEILLANCE A SAFE ALTERNATIVE IN THE MANAGEMENT OF LOCALIZED PROSTATE CANCER? PATHOLOGICAL FEATURES OF RADICAL PROSTATECTOMY SPECIMENS IN POTENTIAL CANDIDATES FOR ACTIVE SURVEILLANCE.

Norman Z, Militza P, Andres F, Daniela F, Alejandro Catherine S, Juan F.

INTRODUCTION AND OBJECTIVE: Active surveillance (AS) has become an accepted alternative for patients with low risk prostate cancer. The purpose of AS is to defer definitive therapy in these patients to avoid treatment-related complications. Our aim was to determine the pathological features of the surgical specimen from potential AS candidates that underwent radical prostatectomy (RP). MATERIALS AND METHODS: We retrospectively reviewed a group of patients submitted to RP who met criteria for AS: Gleason score (GS) ≤ 3+3 = 6, PSA ≤ 10ng/mL, T1c - T2a,< 1/3 of positive cores, < 50% of involvement in any core and PSA density < 0.15. We determined the concordance between GS in biopsy and RP specimen (RPS). Other pathological features of the RPS were also analyzed, including surgical margins, extracapsular extension, seminal vesicles and lymph node involvement. RESULTS: We identified 167 patients subjected to RP that met the criteria for AS. Fifty two patients (31.1%) had a GS > 6 in the RPS (GS 7 n = 49; GS 8 n = 3). Extracapsular extension, seminal vesicle and lymph node involvement was found in 6.1%, 3.1% and 1.2% of the specimens, respectively. CONCLUSION: In this study a significant proportion of potential candidates for AS showed features of aggressive and/or high-risk tumors in the RPS. Therefore, before considering a patient for an AS protocol, a proper and strict selection must be performed, and informed consent is crucial for these patients.

UROL ONCOL. 2014 APR;32(3):280-90.

IMPACT OF CYP1A1, GSTM1, AND GSTT1 POLYMORPHISMS IN OVERALL AND SPECIFIC PROSTATE CANCER SURVIVAL.

Acevedo CA, Quiñones LA, Catalán J, Cáceres DD, Fullá JA, Roco AM.

OBJECTIVE: Prognostic biomarkers that distinguish between patients with good or poor outcome can be used to guide decisions of whom to treat and how aggressively. In this sense, several groups have proposed genetic polymorphisms as potential susceptibility and prognostic biomarkers; however, their validity has not been proven. Thus, the main goal of the present work was to investigate the potential role of single and combined CYP1A1, GSTM1, and GSTT1 genotypes as modifiers of cancer survival in Chilean patients with prostate cancer. METHODS AND MATERIALS: A total of 260 histologically confirmed patients were recruited from a voluntary screening, and genomic DNA was obtained from their blood samples for genotyping analyses to detect the CYP1A1*2A polymorphism and GSTM1 and GSTT1 deletions. The progression of illness and mortality were estimated with a median follow-up of 8.82 years. Adjusted estimated genotype risks were evaluated by hazard ratio and 95% CI using the Cox proportional model. In addition, the Kaplan-Meier survival method and log-rank test were used to evaluate patient survival with regard to genotype. RESULTS: The 9-year overall and specific survival rates were 67.6% and 36.6% in the GSTT1null group, 67.6% and 58.7% in the GSTM1non-null group, 69.0% and 51.6% in the *1A/*2A group, 63.9% and 61.5% in the *2A/*2A group vs. 76.2% and 62.3% in the GSTT1non-null group, 82.3% and 50% in the GSTM1null group, and 83.7% and 56.3% in the *1A/*1A group, respectively. The hazard ratios and the Kaplan-Meier curve results demonstrate that the GSTM1non-null, GSTT1null, and CYP1A1*2A genotypes are significantly associated with mortality. Our study has two main limitations: a relatively small sample size and a low global mortality percentage (25.4%); thus, we need to continue the follow-up to confirm these findings. CONCLUSIONS: Our results suggest that the GSTM1non-null, GSTT1null, and CYP1A1*2A genotypes may be good prognosis markers, particularly in patients with high-risk tumors.

ARCH ESP UROL. 2009 JUN;62(5):392-5.

[EMPHYSEMATOUS CYSTITIS: CASE REPORT].

Pérez Fentes D, Blanco Parra M, Lema Grille J, Toucedo Caamaño V, Novás Castro S, Lamas Cedrón P, Villar Núñez M.

OBJECTIVE: To report one case of emphysematous cystitis and to review its diagnosis and treatment in the related literature. METHOD: We report the case of a type II diabetic 91-year-old woman with jaundice, hematuria, vomits, abdominal pain and poor glycemia control. Diagnosis was obtained by plain abdominal X-ray and ultrasonography, and confirmed by CT. E.coli was isolated in urinary culture. RESULTS: Antibiotic intravenous therapy with piperacillin-tazo-bactam, urinary bladder catheterization and strict

glycemia control. The patient was discharged from hospital on day 5, with 14 additional days of orally administered amoxicillin-clavulanic and bladder catheterization. Complete clinical, radiologic and microbiologic resolution was achieved. CONCLUSIONS: Emphysematous cystitis is a rare entity, most common in diabetic women, which results from infection of the urinary bladder with gas-producing pathogens, mainly E.coli. Clinical presentation is variable. Emphysematous cystitis can be diagnosed radiologically, mainly with CT scan. The management consists of broad-spectrum antibiotics, strict glycemic control and bladder drainage. Emphysematous cystitis usually has a benign course, but complications may arise in up to 10-20% of cases, requiring surgical treatment.

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GASTROENTEROLOGÍA

BIOMATERIALS. 2014 JAN;35(1):489-99.

DIFFERENTIAL NANOTOXICOLOGICAL AND NEUROINFLAMMATORY LIABILITIES OF NON-VIRAL VECTORS FOR RNA INTERFERENCE IN THE CENTRAL NERVOUS SYSTEM.

Godinho BM, McCarthy DJ, Torres-Fuentes C, Beltrán CJ, McCarthy J, Quinlan A, Ogier JR, Darcy R, O'Driscoll CM, Cryan JF.

Progression of RNA interference-based gene silencing technologies for the treatment of disorders of the central nervous system (CNS) depends on the availability of efficient non-toxic nanocarriers. Despite advances in the field of nanotechnology undesired and non-specific interactions with different brain-cell types occur and are poorly investigated. To this end, we studied the cytotoxic and neuroinflammatory effects of widely-used transfection reagents and modified amphiphilic β-cyclodextrins (CDs). All non-viral vectors formed positively charged nanoparticles with distinctive physicochemical properties. Differential and significant cytotoxic effects were observed among commercially available cationic vectors, whereas CDs induced limited disruptions of cellular membrane integrity and mitochondrial dehydrogenase activity. Interestingly, murine derived BV2 microglia cells and a rat striatal in vitro model of Huntington's disease (ST14A-HTT120Q) were more susceptible to toxicity than human U87 astroglioma cells. BV2 microglia presented significant increases in cytokine, toll-like receptor 2 and cyclooxygenase-2 gene expression after transfection with selected commercial vectors but not with CD.siRNA nanoparticles. Non-viral siRNA nanoparticles formulated with G6 polyamidoamine (PAMAM) also significantly increased cytokine gene expression in the brain following injections into the mouse striatum. Together our data identify modified CDs as nanosystems that enable siRNA delivery to the brain with low levels of cytotoxicity and immunological activation.

ALIMENT PHARMACOL THER. 2015 JAN;41(1):116-25.

DISTINCT PHENOTYPE OF HEPATOTOXICITY ASSOCIATED WITH ILLICIT USE OF ANABOLIC ANDROGENIC STEROIDS.

Robles-Diaz M1, Gonzalez-Jimenez A, Medina-Caliz I, Stephens C, García-Cortes M, García-Muñoz B, Ortega-Alonso A, Blanco-Reina E, Gonzalez-Grande R, Jimenez-Perez M, Rendón P, Navarro JM, Gines P, Prieto M, Garcia-Eliz M, Bessone F, Brahm JR, Paraná R, Lucena MI, Andrade RJ; Spanish DILI Registry; SLatinDILI Network.

BACKGROUND: We have observed an increase in hepatotoxicity (DILI) reporting related to the use of anabolic androgenic steroids (AAS) for bodybuilding. AIM: To characterise phenotype presentation, outcome and severity of AAS DILI. METHODS: Data on 25 cases of AAS DILI reported to the Spanish (20) and Latin-American (5) DILI Registries were collated and compared with previously published cases. RESULTS: AAS DILI increased from representing less than 1% of the total cases in the Spanish DILI Registry in the period 2001-2009 to 8% in 2010-2013. Young men (mean age 32 years), requiring hospitalisation, hepatocellular injury and jaundice were predominating features among the AAS cases. AAS DILI caused significantly higher bilirubin values independent of type of damage when compared to other drug classes (P = 0.001). Furthermore, the cholestatic AAS cases presented significantly higher mean peak bilirubin (P = 0.029) and serum creatinine values (P = 0.0002), compared to the hepatocellular cases. In a logistic regression model, the interaction between peak bilirubin values and cholestatic damage was associated with the development of AAS-induced acute kidney impairment (AKI) [OR 1.26 (95% CI: 1.035-1.526); P = 0.021], with 21.5 ×ULN being the best bilirubin cut-off point for predicting AKI risk (AUCROC 0.92). No fatalities occurred. CONCLUSIONS: Illicit recreational AAS use is a growing cause of reported DILI that can lead to severe hepatic and renal injury. AAS DILI is associated with a distinct phenotype, characterised by considerable bilirubin elevations independent of type of damage. Although hepatocellular injury predominates, acute kidney injury develops in cholestatic cases with pronounced jaundice.

ANN HEPATOL. 2014 MAR-APR;13(2):231-9.
GENOME ANNOUNC. 2014 OCT 23;2(5).

FULL-GENOME SEQUENCE OF A HEPATITIS B VIRUS GENOTYPE F1B CLONE FROM A CHRONICALLY INFECTED CHILEAN PATIENT.

Hernández S, Venegas M, Brahm J, Villanueva RA.

The hepatitis B virus (HBV) is a DNA virus belonging to the Hepadnaviridae family. Viral isolates have been classified into 10 genotypes, named from A to J, and several subtypes. We report the full-genome sequence from a single molecular clone of HBV genotype F1b, amplified from a chronically infected Chilean patient.

INT J MED MICROBIOL. 2014 MAY;304(3-4):384-92.

ESCHERICHIA COLI ISOLATES FROM INFLAMMATORY BOWEL DISEASES PATIENTS SURVIVE IN MACROPHAGES AND ACTIVATE NLRP3 INFLAMMASOME.

De la Fuente M, Franchi L, Araya D, Díaz-Jiménez D, Olivares M, Álvarez-Lobos M, Golenbock D, González MJ, López-Kostner F, Quera R, Núñez G, Vidal R, Hermoso MA.

Crohn's disease (CD) is a multifactorial pathology associated with the presence of adherent-invasive Escherichia coli (AIEC) and NLRP3 polymorphic variants. The presence of intracellular E. coli in other intestinal pathologies (OIP) and the role of NLRP3-inflammasome in the immune response activated by these bacteria have not been investigated. In this study, we sought to characterize intracellular strains isolated from patients with CD, ulcerative colitis (UC) and OIP, and analyze NLRP3-inflammasome role in the immune response and bactericidal activity induced in macrophages exposed to invasive bacteria. For this, intracellular E. coli isolation from ileal biopsies, using gentamicin-protection assay, revealed a prevalence and CFU/biopsy of E. coli higher in biopsies from CD, UC and OIP patients than in controls. To characterize bacterial isolates, pulsed-field gel electrophoresis (PFGE) patterns, virulence genes, serogroup and phylogenetic group were analyzed. We found out that bacteria isolated from a given patient were closely related and shared virulence factors; however, strains from different patients were genetically heterogeneous. AIEC characteristics in isolated strains, such as invasive and replicative properties, were assessed in epithelial cells and macrophages, respectively. Some strains from CD and UC demonstrated AIEC properties, but not strains from OIP. Furthermore, the role of NLRP3 in pro-inflammatory cytokines production and bacterial elimination was determined in macrophages. E. coli strains induced IL-1β through NLRP3-dependent mechanism; however, their elimination by macrophages was independent of NLRP3. Invasiveness of intracellular E. coli strains into the intestinal mucosa and IL-1β production may contribute to CD and UC pathogenesis.

ANTIVIR THER. 2014 OCT 16.

GENOTYPE F OF HEPATITIS B: RESPONSE TO INTERFERON.

Venegas M, Poniachik J, Fuster F, Hurtado C, Villanueva RA, Brahm J.

BACKGROUND: The relevance of diverse HBV genotypes for the therapy outcome to IFN of chronic hepatitis B has become recently highlighted. Data available for genotype F is poor. The aim of this work was analyzing the response of HBV genotype F to treatment with IFN. Additionally, response was analyzed according to the role of single nucleotide polymorphisms (SNP) near to IL28B gene. METHODS: A total of 29 HBeAg positive patients with chronic infection were included with a median age 47 years (18-68), 27 males. One patient was treated with standard IFNα for 16 weeks, 6 patients received PegIFNα2a 180 μg weekly for 24 weeks and 22 patients for 48 weeks. Response to treatment was defined as loss of HBeAg, anti-HBe seroconversion, and decline of HBV DNA level to below 3 Log of baseline (IU/mL) at the sixth months of following-up. The SNPs rs12979860, rs12980275, and rs8099917 were studied by PCR-RFLP. RESULTS: The overall response was obtained in 18 patients (62%), including one patient who was treated with standard interferon. Additionally, a total of 9 patients (31%) cleared HBsAg, with appearance of anti-HBs. The viral load was undetectable in all of these patients. The same variants associated with IFN response in HCV infections were also more frequently found in the HBV patients compared to non-responders. CONCLUSIONS: Our study indicates that treatment with IFN is a good therapy in patients with HBV genotype F.

ANN HEPATOL. 2014 MAR-APR;13(2):231-9.

PROFILE OF IDIOSYNCRATIC DRUG INDUCED LIVER INJURY IN LATIN AMERICA: AN ANALYSIS OF PUBLISHED REPORTS.

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, Dávalos M, Méndez-Sánchez N, Arrese M, Schinoni M, Lucena MI, Andrade RJ.

INTRODUCTION: Drug-induced liver injury (DILI) remains a major problem for drug development and represents a challenging

diagnosis for clinicians. The absence of specific biomarkers for diagnosing DILI precludes the availability of reliable data on the epidemiology of the disease. In this study we aimed to describe the features of idiosyncratic hepatotoxicity reports in Latin American countries. MATERIAL AND METHODS: A literature search was performed using the online version of MEDLINE, EMBASE, Scopus, Google Scholar and specific data bases from Latin America (LA) (Scielo, Lilacs) to identify any case report or case series of published DILI from 1996 to 2012. From 1996 to 2012, a total of 176 patients with DILI were published in LA, involving 53 suspicious drugs. The median age in the adult population of these patients was 55 years (17-82) with prevalence of women (67%). Among main therapeutic classes, the rank order was led by non-steroidal anti-inflammatory (61 cases) and systemic antibacterial drugs (37 cases). Nimesulide was the individual drug responsible for the highest number of cases (53), followed by cyproterone acetate (18), nitrofurantoin (17), antituberculous drugs (13) and flutamide (12). Thirty two percent of published cases evolved to acute liver failure (ALF), and half of the subjects required liver transplantation or eventually died. CONCLUSIONS: This study represents the first structured attempt to assess the spectrum of DILI profile in LA. The establishment of a Latin American registry to collect prospective DILI cases using a standardized protocol will advance our knowledge about idiosyncratic DILI in this region.

J INTERFERON CYTOKINE RES. 2014 FEB;34(2):106-10.

LAMBDA INTERFERON SERUM LEVELS IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION ACCORDING TO THEIR RESPONSE TO THERAPY WITH PEGYLATED INTERFERON AND RIBAVIRIN.

Torres C, Brahm J, Venegas M.

Lambda interferon IL-28A/B and IL-29 serum levels have been associated with the course of hepatitis C virus (HCV) infection. However, there is not information about these cytokine in patients with antiviral therapy. We investigated IL-28A/B and IL-29 serum levels in 45 samples from patients chronically infected with HCV genotype 1, and undergoing therapy with PEG-IFN/RBV, at baseline and after 12 weeks of therapy, comparing those that developed a sustained virologic response (SVR) with null responders (NR). IL-28B polymorphisms (rs12979860, rs12980275, and rs8099917) were also considered. We found that, IL-28A/B and IL-29 levels were not significantly different between SVR and NR patients at baseline or after 12 weeks of therapy. TT rs8099917 genotype carriers had significantly higher IL29 levels at baseline (60.5 vs 19.5 pg/mL; p=0.045) and after 12 weeks of therapy (35 vs 16.5 pg/mL; p=0.023) than non-TT carriers. In conclusion, there were no differences in IL-28A/B or IL-29 levels according to response to therapy, suggesting that these cytokines do not play an important role in viral elimination during treatment, at least not during the first 12 weeks of therapy. Genotypes associated with high IL-28B levels may be related to a mechanism of protection against infection but are not involved in the response to antiviral therapy.

WORLD J GASTROENTEROL. 2014 SEP 14;20(34):12182-201.

MANAGEMENT OF NONALCOHOLIC FATTY LIVER DISEASE: AN EVIDENCE-BASED CLINICAL PRACTICE REVIEW.

Arab JP, Candia R, Zapata R, Muñoz C, Arancibia JP, Poniachik J, Soza A, Fuster F, Brahm J, Sanhueza E, Contreras J, Cuellar MC, Arrese M, Riquelme A.

AIM: To build a consensus among Chilean specialists on the appropriate management of patients with nonalcoholic fatty liver disease (NAFLD) in clinical practice. METHODS: NAFLD has now reached epidemic proportions worldwide. The optimal treatment for NAFLD has not been established due to a lack of evidence-based recommendations. An expert panel of members of the Chilean Gastroenterological Society and the Chilean Hepatology Association conducted a structured analysis of the current literature on NAFLD therapy. The quality of the evidence and the level of recommendations supporting each statement were assessed according to the recommendations of the United States Preventive Services Task Force. A modified three-round Delphi technique was used to reach a consensus among the experts. RESULTS: A group of thirteen experts was established. The survey included 17 open-ended questions that were distributed among the experts, who assessed the articles associated with each question. The levels of agreement achieved by the panel were 93.8% in the first round and 100% in the second and third rounds. The final recommendations support the indication of lifestyle changes, including diet and exercise, for all patients with NAFLD. Proven pharmacological therapies include only vitamin E and pioglitazone, which can be used in nondiabetic patients with biopsy-proven nonalcoholic steatohepatitis (the progressive form of NAFLD), although the long-term safety and efficacy of these therapies have not yet been established. CONCLUSION: Current NAFLD management is rapidly evolving, and new pathophysiology-based therapies are expected to be introduced in the near future. All NAFLD patients should be evaluated using a three-focused approach that considers the risks of liver disease, diabetes and cardiovascular events.

GENÉTICA

EUR J MED GENET. 2014 SEP;57(9):536-42.

RAINE SYNDROME: AN OVERVIEW.

Faundes V, Castillo-Taucher S, Gonzalez-Hormazabal P, Chandler K, Crosby A, Chioza B.

Raine syndrome (RS) is a bone dysplasia characterised by generalised osteosclerosis with periosteal bone formation, characteristic face, and brain abnormalities [MIM # 259775]. Its prevalence is estimated to be < 1/1,000,000. Although it was originally thought always to be lethal, there have now been six reports of patients surviving into childhood and this phenotype is still being defined. The skeletal dysplasia predominantly affects craniofacial development explaining the severe proptosis, underdeveloped midface, depressed nasal bridge and short nose. The main radiological manifestation is a diffuse, marked osteosclerosis of the base of skull and long bones. Raine syndrome is caused by biallelic mutations in FAM20C, located on chromosome 7p22.3. This gene encodes a Golgi casein kinase, which phosphorylates serine residues of extracellular proteins involved in biomineralisation. Facial appearance and radiological findings allow the clinical diagnosis, and molecular testing of FAM20C can confirm this. Desmosterolosis and congenital cytomegalovirus infection may resemble Raine syndrome. If Raine syndrome is suspected prenatally the newborn should be admitted at a neonatal intensive care unit as significant respiratory distress is often present immediately after birth. We present here a review of the pertinent literature in clinical manifestations, molecular background, diagnosis and management.

INMUNOLOGÍA

PLOS ONE. 2014 JAN 22;9(1):E85930.

TOLEROGENIC DENDRITIC CELLS DERIVED FROM DONORS WITH NATURAL RUBBER LATEX ALLERGY MODULATE ALLERGEN-SPECIFIC T-CELL RESPONSES AND IGE PRODUCTION.

Escobar A, Aguirre A, Guzmán MA, González R, Catalán D, Acuña-Castillo C, Larrondo M, López M, Pesce B, Rolland J, O'Hehir R, Aguillón JC.

Natural rubber latex (NRL; Hevea brasiliensis) allergy is an IgE-mediated reaction to latex proteins. When latex glove exposure is the main sensitizing agent, Hev b 5 is one of the major allergens. Dendritic cells (DC), the main antigen presenting cells, modulated with pharmacological agents can restore tolerance in several experimental models, including allergy. In the current study, we aimed to generate DC with tolerogenic properties from NRL-allergic patients and evaluate their ability to modulate allergen-specific T and B cell responses. Here we show that dexamethasone-treated DC (dxDC) differentiated into a subset of DC, characterized by low expression of MHC class II, CD40, CD80, CD86 and CD83 molecules. Compared with LPS-matured DC, dxDC secreted lower IL-12 and higher IL-10 after CD40L activation, and induced lower alloantigenic T cell proliferation. We also show that dxDC pulsed with the dominant Hev b 5 T-cell epitope peptide, Hev b 5(46-65), inhibited both proliferation of Hev b 5-specific T-cell lines and the production of Hev b 5-specific IgE. Additionally, dxDC induced a subpopulation of IL-10-producing regulatory T cells that suppressed proliferation of Hev b 5-primed T cells. In conclusion, dxDC generated from NRL-allergic patients can modulate allergen-specific T-cell responses and IgE production, supporting their potential use in allergen-specific immunotherapy.

AIDS BEHAV. 2014 DEC;18(12):2274-84.

DEVELOPMENT OF THE SCALE OF PERCEIVED SOCIAL SUPPORT IN HIV (PSS-HIV).

Cortes A, Hunt N, McHale S.

Social support (SS) plays a key role for HIV/AIDS prevention and disease management. Numerous general and disease-specific SS instruments have been developed and perception of support has been increasingly considered, though no scales have been specifically developed to measure perceived social support (PSS) in HIV/AIDS. To help fill this gap a 12-item scale was developed. The study comprised 406 (HIV(+) and HIV(-)) participants from Chile and the UK. A principal component factor analysis yielded three factors explaining 77.0 % of the total variance: Belonging, Esteem and Self-development with Cronbach α of 0.759, 0.882 and 0.927 respectively and 0.893 on the full scale. The PSS-HIV is brief, easy-to-apply, available in English and Spanish and evaluates the perception of supportive social interactions. Further research is needed to corroborate its capacity to detect psycho-socio-immune interactions, its connection with Maslow's hierarchy of need theory and to evaluate its properties for different health states.

J CLIN VIROL. 2014 JUL;60(3):290-4.

PREVALENCE OF R5 AND X4 HIV VARIANTS IN ANTIRETROVIRAL TREATMENT EXPERIENCED PATIENTS WITH VIROLOGIC FAILURE.

Ferrer P, Tello M, Montecinos L, Tordecilla R, Rodríguez C, Beltrán C, Guzmán MA, Ferrés M, Pérez CM, Afani A.

BACKGROUND: Antiretroviral therapy (ART) inhibits virus replication. Nevertheless, ART has the disadvantage of generate selective resistance and adverse events. Coreceptor antagonists are a family of antiretroviral drugs that are used with the prior knowledge of patients HIV tropism. OBJECTIVES: The purpose of this work was to estimate the prevalence of R5 and X4 variants among Chilean patients under antiretroviral therapy and virological failure and investigate variables such as plasma viral load (pVL) and CD4 cell count in the population studied. STUDY DESIGN: HIV RNA or proviral DNA was extracted from 454 consecutives patients and tropism testing was performed using a genotypic method performed with Geno2pheno setting a cutoff value for FPR 5.75%. RESULTS: Among 454 individuals analyzed, 299 (66%) harbouring exclusively R5 variants. They not displayed a better clinical profile than individuals harbouring X4 strains (22%). For R5 patients the median of pVL and CD4 cell count were 268,000copies/mL, and 223cells/μL respectively. For X4 samples the values were 368,000copies/mL and 214cells/μL [P>0.05]). Only, 53 patients (12%) could not be analyzed and were categorized as non-reportable. CONCLUSIONS: The genotypic method confirmed that R5 strains were more prevalent despite the fact that patients were treatment-experienced for several years. The genotypic strategy proved to be a faster and cost-effective option as compared to phenotypic assays. According to our results, two of every three patients under antiretroviral therapy and with virologic failure harbour R5 strains, and may be candidates for use of a CCR5 antagonist.

EUR RESPIR J. 2014 AUG;44(2):304-23.

INTEGRATED CARE PATHWAYS FOR AIRWAY DISEASES (AIRWAYS-ICPS).

European Innovation Partnership on Active and Healthy Ageing, Action Plan B3; Mechanisms of the Development of Allergy, WP et al.

The objective of Integrated Care Pathways for Airway Diseases (AIRWAYS-ICPs) is to launch a collaboration to develop multi-sectoral care pathways for chronic respiratory diseases in European countries and regions. AIRWAYS-ICPs has strategic relevance to the European Union Health Strategy and will add value to existing public health knowledge by: 1) proposing a common framework of care pathways for chronic respiratory diseases, which will facilitate comparability and trans-national initiatives; 2) informing cost-effective policy development, strengthening in particular those on smoking and environmental exposure; 3) aiding risk stratification in chronic disease patients, using a common strategy; 4) having a significant impact on the health of citizens in the short term (reduction of morbidity, improvement of education in children and of work in adults) and in the long-term (healthy ageing); 5) proposing a common simulation tool to assist physicians; and 6) ultimately reducing the healthcare burden (emergency visits, avoidable hospitalisations, disability and costs) while improving quality of life. In the longer term, the incidence of disease may be reduced by innovative prevention strategies. AIRWAYSICPs was initiated by Area 5 of the Action Plan B3 of the European Innovation Partnership on Active and Healthy Ageing. All stakeholders are involved (health and social care, patients, and policy makers).

HUM VACCIN IMMUNOTHER. 2014;10(11):3261-9.

TUMOR CELL LYSATES AS IMMUNOGENIC SOURCES FOR CANCER VACCINE DESIGN.

González FE, Gleisner A, Falcón-Beas F, Osorio F, López MN, Salazar-Onfray F.

Autologous dendritic cells (DCs) loaded with tumor-associated antigens (TAAs) are a promising immunological tool for cancer therapy. These stimulate the antitumor response and immunological memory generation. Nevertheless, many patients remain refractory to DC approaches. Antigen (Ag) delivery to DCs is relevant to vaccine success, and antigen peptides, tumor-associated proteins, tumor cells, autologous tumor lysates, and tumor-derived mRNA have been tested as Ag sources. Recently, DCs loaded with allogeneic tumor cell lysates were used to induce a potent immunological response. This strategy provides a reproducible pool of almost all potential Ags suitable for patient use, independent of MHC haplotypes or autologous tumor tissue availability. However, optimizing autologous tumor cell lysate preparation is crucial to enhancing efficacy. This review considers the role of cancer cell-derived lysates as a relevant source of antigens and as an activating factor for ex vivo therapeutic DCs capable of responding to neoplastic cells. These promising therapies are associated with the prolonged survival of advanced cancer patients.

MEDICINA NUCLEAR

ARTERIOSCLER THROMB VASC BIOL. 2014 NOV;34(11):2439-48.

ATORVASTATIN REDUCES THE PROADHESIVE AND PROTHROMBOTIC ENDOTHELIAL CELL PHENOTYPE INDUCED BY COCAINE AND PLASMA FROM COCAINE CONSUMERS IN VITRO.

Sáez CG, Pereira-Flores K, Ebensperger R, Panes O, Massardo T, Hidalgo P, Mezzano D, Pereira J.

OBJECTIVE: Cocaine consumption is a risk factor for vascular ischemic complications. Although endothelial dysfunction and accelerated atherosclerosis have been observed in cocaine consumers, the mechanisms underlying their pathogenesis are not fully understood. This study aimed at identifying the effects of atorvastatin in relation to a proadhesive and prothrombotic phenotype induced by cocaine and plasma from chronic cocaine users on endothelial cells. APPROACH AND RESULTS: Human umbilical vein endothelial cells were exposed to either cocaine or platelet-free plasma (PFP) from chronic cocaine consumers in the presence or absence of 10 μmol/L of atorvastatin. Atorvastatin significantly reduced the enhanced platelet adhesion that was induced by cocaine and PFP from chronic cocaine consumers, as well as the release of the von Willebrand factor. Atorvastatin also avoided striking alterations on cell monolayer structure triggered by both stimuli and enhanced NO reduction because of cocaine stimulation through disrupting interactions between endothelial nitric oxide synthase (eNOS) and caveolin-1, thus increasing eNOS bioavailability. Cocaine-increased tissue factor-dependent procoagulant activity and reactive oxygen species generation were not counteracted by atorvastatin. Although monocyte chemoattractant protein-1 levels were not significantly higher than controls either under cocaine or PFP stimulation, atorvastatin completely avoided monocyte chemoattractant protein-1 release in both conditions. Platelets stimulated with cocaine or PFP did not express P-selectin, glycoprotein IIb/IIIa, or CD40L and failed to adhere to resting human umbilical vein endothelial cell. CONCLUSIONS: Cocaine and patient plasma equally induced a proadhesive and prothrombotic phenotype in endothelial cells, except for von Willebrand Factor release, which was only induced by PFP from chronic cocaine consumers. Atorvastatin improved endothelial cell function by reducing cocaine-induced and PFP from chronic cocaine consumer-induced effects on platelet adhesion, cell architecture, and NO production.

NEFROLOGÍA

J PHOTOCHEM PHOTOBIOL B. 2014 NOV;140:8-13.

VITAMIN B12 DEFICIENCY IS ASSOCIATED WITH GEOGRAPHICAL LATITUDE AND SOLAR RADIATION IN THE OLDER POPULATION.

Cabrera S, Benavente D, Alvo M, de Pablo P, Ferro CJ.

BACKGROUND: Vitamin B12 and folic acid deficiency are common in the older and are associated with several conditions including anaemia, cardiovascular disease, cognitive impairment and cancer. Evidence from in vitro studies suggests that solar radiation can degrade both vitamins in the skin. Chile is the longest country in the world running perfectly North-South making it an ideal place to study potential associations of latitude and solar radiation on vitamin B12 and folic acid deficiency. OBJECTIVES: The objective was to examine the association between vitamin B12 and folic acid deficiencies and latitude. METHODS: Plasma samples were collected from Chileans aged 65+ years (n=1013) living across the whole country and assayed for vitamin B12 and folic acid concentrations as part of the Chilean Health Survey 2009-2010, which is a national representative sample study. RESULTS: Overall, the prevalence of vitamin B12 deficiency was 11.3%, with the prevalence in the North of the country being significantly greater than in the Central and South zones (19.1%,10.5%, and 5.7%, respectively; P<0.001). The prevalence of folic acid deficiency in the whole cohort was 0.7% with no difference between the 3 geographical zones. Using logistic regression analyses, vitamin B12 deficiency was significantly associated with geographical latitude (OR 0.910 [95% confidence intervals 0.890-0.940], P<0.001) and solar radiation (OR 1.203 [95% confidence intervals 1.119-1.294], P<<0.001). These associations persisted after adjustments for confounders (OR 0.930, P<0.001 and 1.198, P=0.002, respectively). CONCLUSIONS: In the Chilean population of 65+, the prevalence of vitamin B12 deficiency is associated with living closer to the Equator and solar radiation. Although degradation by solar radiation might explain this observation, further work is required to establish the potential mechanisms. In countries that routinely fortify food with folic acid, efforts to identify vitamin B12 deficiency might be more cost-efficiently targeted in areas closest to the Equator.

NEUMOLOGÍA

EUR RESPIR J. 2014 SEP 26. PII: ERJ00845-2014.

PEDOMETERS TO ENHANCE PHYSICAL ACTIVITY IN COPD: A RANDOMISED CONTROLLED TRIAL.

Mendoza L, Horta P, Espinoza J, Aguilera M, Balmaceda N, Castro A, Ruiz M, Díaz O, Hopkinson NS.

Physical inactivity is a cardinal feature of chronic obstructive pulmonary disease (COPD), and is associated with increased morbidity and mortality. Pedometers, which have been used in healthy populations, might also increase physical activity in patients with COPD. COPD patients taking part in a 3-month individualised programme to promote an increase in their daily physical activity were randomised to either a standard programme of physical activity encouragement alone, or a pedometer-based programme. Assessments were performed by investigators blinded to treatment allocation. Change in average 1-week daily step count, 6-min walking distance (6MWD), modified Medical Research Council scale, St George's respiratory questionnaire (SGRQ) and COPD assessment test (CAT) were compared between groups. 102 patients were recruited, of whom 97 completed the programme (pedometer group: n = 50; control group: n = 47); 60.8% were male with a mean±sd age of 68.7±8.5 years, and forced expiratory volume in 1 s (FEV1) 66.1±19.4% and FEV1/forced vital capacity 55.2±9.5%. Both groups had comparable characteristics at baseline. The pedometer group had significantly greater improvements in: physical activity 3080±3254 steps·day-1 versus 138.3±1950 steps·day-1 ($p<0.001$); SGRQ -8.8±12.2 versus -3.8±10.9 ($p = 0.01$); CAT score -3.5±5.5 versus -0.6±6.6 ($p = 0.001$); and 6MWD 12.4±34.6 versus -0.7±24.4 m ($p = 0.02$) than patients receiving activity encouragement only. A simple physical activity enhancement programme using pedometers can effectively improve physical activity level and quality of life in COPD patients.

REUMATOLOGÍA

CLIN RHEUMATOL. 2014 DEC;33(12):1815-21.

DISTINCT GENETIC PROFILE IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF PSORIATIC ARTHRITIS PATIENTS TREATED WITH METHOTREXATE AND TNF-INHIBITORS.

Cuchacovich R, Perez-Alamino R, Zea AH, Espinoza LR.

Psoriatic arthritis (PsA) is a systemic inflammatory condition associated with psoriasis. Despite considerable heterogeneity in clinical presentation, genetic studies and animal models support the notion that PsA is a distinct disease. We aimed to characterize the PsA genotype by gene expression profile and to research the effect in gene modulation of methotrexate (MTX) and TNF-inhibitors (TNF-I) in PsA-treated patients. Nine PsA patients, according to CASPAR criteria, and three healthy controls were recruited from an outpatient rheumatology clinic. Three out of nine PsA patients were naïve to treatment, three received TNF-I, and the remaining three were on MTX-monotherapy. Blood samples were collected and analyzed by human genome U95 Array-Affymetrix (GeneChip® instrument system). Identification of statistically significant differences between differentially expressed genes was determined by Mann-Whitney and t test ($p < 0.05$). The microarray profile identified a predominance of differentially expressed genes with an increased expression in baseline PsA patients: 115/12,000 genes were up-regulated and 13/12,000 down-regulated, as compared to healthy controls. The great majority were involved in inflammatory cells and pathways. In the biologic-treated patients, a higher number of down-regulated genes were expressed vs. the MTX patients, 161 vs. 33, respectively. This study shows that in PsA patients, TNF-I and MTX are able to modulate the gene expression in a synergistic and additive manner.

CLIN RHEUMATOL. 2014 DEC;33(12):1707-14.

CLINICAL PARAMETERS AND BIOMARKERS FOR ANTI-TNF TREATMENT PROGNOSIS IN RHEUMATOID ARTHRITIS PATIENTS.

Cuchacovich M, Bueno D, Carvajal R, Bravo N, Aguillón JC, Catalán D, Soto L.

Tumor necrosis factor (TNF) plays a pivotal role in the pathogenesis of rheumatoid arthritis (RA). This finding has led to the development of TNF blockers for RA treatment. However, response to these therapies is heterogeneous with success in only two thirds of patient. Some clinical aspects useful in the attempt to predict the response to TNF inhibitors is the promptness and the magnitude of the response at the first weeks and a low basal disease activity, while comorbidities, tobacco, glucocorticoids treatment, and high basal radiological score correlate with a poorer response. The role of TNF promoter polymorphisms in clinical response to anti-TNF therapies is controversial. A correlation between the presence of high baseline titers of rheumatoid factor (RF) and decreased response to anti-TNF treatment has been reported. Most studies show decreased RF titers during anti-TNF treatment mainly in patients who responded to treatment. There is no consensus about the usefulness of basal anti-citrullinated protein antibodies (ACPA) levels, and a decrease in ACPA titers as predictor of clinical response to anti-TNF therapy. Despite some

promising markers identified to fulfill this role, currently the predictive value of single markers seems not strong enough to predict treatment response in an individual RA patient.

J CLIN RHEUMATOL. 2014 JAN;20(1):42-4.

ACUTE HERPES SIMPLEX VIRUS 1 PNEUMONITIS IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS.

Sabugo F, Espinoza-Araya R, Meneses MF, Cuchacovich M.

A woman with severe and longstanding systemic lupus erythematosus presented with a 1-week history of fever up to 38°C and pain in her right flank. Computed tomography scan of the chest revealed interstitial infiltrates and multiple nodules. Bronchoalveolar lavage did not show any inflammatory cells. Gram stain and cultures for aerobic and anaerobic bacteria, fungi, and Nocardia; acid-fast staining; polymerase chain reaction for tuberculosis, cytomegalovirus, herpesvirus 6, and parvovirus B19; and IF staining for pneumocystic and Legionella antigen were all negative. Transbronchial biopsy was nondiagnostic. Open lung biopsy with polymerase chain reaction and immunohistochemistry analyses revealed herpes simplex virus 1 infection. Acyclovir therapy was initiated and was followed by significant improvement. Herpes simplex virus 1 infection (although unusual) should be considered in patients with systemic lupus erythematosus with an atypical clinical presentation.

ACTA OPHTHALMOL. 2015 JAN 7.

EARLIER IMMUNOMODULATORY TREATMENT IS ASSOCIATED WITH BETTER VISUAL OUTCOMES IN A SUBSET OF PATIENTS WITH VOGT-KOYANAGI-HARADA DISEASE.

Urzua CA, Velasquez V, Sabat P, Berger O, Ramirez S, Goecke A, Vásquez DH, Gatica H, Guerrero J.

PURPOSE: To evaluate clinical outcomes of first-line immunomodulatory therapy (IMT) and prednisone alone or late IMT in Vogt-Koyanagi-Harada disease. METHODS: Retrospective cohort study of 152 patients with Vogt-Koyanagi-Harada disease evaluated in a referral uveitis clinic in Chile from 1985 to 2011. Medical records of these patients were reviewed. Demographic data, clinical evaluation, type of treatment, functional outcomes, glucocorticoid (GC) dose and complications were recorded. Multivariate logistic regression was used to identify prognostic factors of poor response to GC. RESULTS: There were no significant differences between first-line IMT group and prednisone alone/late IMT group in terms of visual acuity (VA) improvement, complications and GC sparing effect. There was a trend for a higher frequency of systemic adverse effects leading to discontinuation of treatment in patients receiving IMT than in those receiving prednisone (14.6% and 6.5%, respectively). The subgroup of patients with poor response to GC who showed functional improvement had a significantly earlier time to IMT initiation than the patients who had no improvement. We identified following prognostic factors of poor response to GC: VA ≤20/200, fundus depigmentation, chronic disease and tinnitus at diagnosis. Patients with a prognostic factor (excluding tinnitus) and VA improvement had an earlier IMT initiation than those who had worse functional outcome. CONCLUSION: There were no differences in outcomes between first-line IMT and prednisone alone/late IMT in the entire VKH group. However, in a subset of patients, there was a significant better functional outcome with earlier IMT initiation.