Resúmenes de publicaciones ISI 2022

El material que se presenta a continuación proviene de los datos recolectados por nuestra Revista.

SERVICIO ANATOMÍA PATOLÓGICA

LIFE (BASEL). 2022 JAN 28;12(2):194. DOI: 10.3390/LIFE12020194.

EMERGENCE OF SARS-COV-2 VARIANTS IN THE WORLD: HOW COULD THIS HAPPEN?

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The COVID-19 pandemic has had a significant global impact, with more than 280,000,000 people infected and 5,400,000 deaths. The use of personal protective equipment and the anti-SARS-CoV-2 vaccination campaigns have reduced infection and death rates worldwide. However, a recent increase in infection rates has been observed associated with the appearance of SARS-CoV-2 variants, including the more recently described lineage B.1.617.2 (Delta variant) and lineage B.1.1.529/BA.1 (Omicron variant). These new variants put the effectiveness of international vaccination at risk, with the appearance of new outbreaks of COVID-19 throughout the world. This emergence of new variants has been due to multiple predisposing factors, including molecular characteristics of the virus, geographic and environmental conditions, and the impact of social determinants of health that favor the genetic diversification of SARS-CoV-2. We present a literature review on the most recent information available on the emergence of new variants of SARS-CoV-2 in the world. We analyzed the biological, geographical, and sociocultural factors that favor the development of these variants. Finally, we evaluate the surveillance strategies for the early detection of new variants and prevent their distribution outside these regions.

SKIN RES TECHNOL. 2022 JAN;28(1):176-179. DOI: 10.1111/SRT.13099.

ULTRASONOGRAPHY OF CUTANEOUS NODULAR PSEUDOLYMPHOMA AT 18 AND 71 MHZ

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

FRONT ONCOL. 2022 MAR 22;12:835626. DOI: 10.3389/FONC.2022.835626. ECOLLECTION 2022.

THE TRANSCRIPTOMIC PORTRAIT OF LOCALLY ADVANCED BREAST CANCER AND ITS PROGNOSTIC VALUE IN A MULTI-COUNTRY COHORT OF LATIN AMERICAN PATIENTS

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Purposes: Most molecular-based published studies on breast cancer do not adequately represent the unique and diverse genetic admixture of the Latin American population. Searching for similarities and differences in molecular pathways associated with these tumors and evaluating its impact on prognosis may help to select better therapeutic approaches. Patients and methods: We collected clinical, pathological, and transcriptomic data of a multi-country Latin American cohort of 1,071 stage II-III breast cancer patients of the Molecular Profile of Breast Cancer Study (MPBCS) cohort. The 5-year prognostic ability of intrinsic (transcriptomic-based) PAM50

and immunohistochemical classifications, both at the cancer-specific (OSC) and disease-free survival (DFS) stages, was compared. Pathway analyses (GSEA, GSVA and MetaCore) were performed to explore differences among intrinsic subtypes. Results: PAM50 classification of the MPBCS cohort defined 42·6% of tumors as LumA, 21·3% as LumB, 13·3% as HER2E and 16·6% as Basal. Both OSC and DFS for LumA tumors were significantly better than for other subtypes, while Basal tumors had the worst prognosis. While the prognostic power of traditional subtypes calculated with hormone receptors (HR), HER2 and Ki67 determinations showed an acceptable performance, PAM50-derived risk of recurrence best discriminated low, intermediate and high-risk groups. Transcriptomic pathway analysis showed high proliferation (i.e. cell cycle control and DNA damage repair) associated with LumB, HER2E and Basal tumors, and a strong dependency on the estrogen pathway for LumA. Terms related to both innate and adaptive immune responses were seen predominantly upregulated in Basal tumors, and, to a lesser extent, in HER2E, with respect to LumA and B tumors. Conclusions: This is the first study that assesses molecular features at the transcriptomic level in a multicountry Latin American breast cancer patient cohort. Hormone-related and proliferation pathways that predominate in PAM50 and other breast cancer molecular classifications are also the main tumor-driving mechanisms in this cohort and have prognostic power. The immune-related features seen in the most aggressive subtypes may pave the way for therapeutic approaches not yet disseminated in Latin America.

J NUTR BIOCHEM. 2022 FEB;100:108886. DOI: 10.1016/J.JNUTBIO.2021.108886.

PROTECTION AGAINST INDOMETHACIN-INDUCED LOSS OF INTESTINAL EPITHELIAL BARRIER FUNCTION BY A QUERCETIN OXIDATION METABOLITE PRESENT IN ONION PEEL: IN VITRO AND IN VIVO STUDIES

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Oxidative stress is directly implicated in the loss of intestinal epithelial barrier function (IEBF) induced by non-steroidal anti-inflammatory drugs (NSAIDs). Previous studies by our research team demonstrated that 2-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxy-3(2H)-benzofuranone (BZF), a quercetin oxidation metabolite that naturally occurs in onion peels, exhibits an antioxidant potency notably higher than quercetin. Thus, we assessed the potential of BZF and a BZF-rich onion peel aqueous extract (OAE) to protect against the loss of IEBF in Caco-2 cell monolayers and in rats exposed to indomethacin. In vitro, pure BZF and OAE standardized in BZF (100 nM), protected against the drop in transepithelial electrical resistance by 70 - 73%. Likewise, it prevented the increase in fluorescein-isothiocyanate labelled dextran (FITC-dextran) paracellular transport by 74% and oxidative stress by 84 - 86%. In vivo, BZF, given orally at a dose 80 µg/Kg bw as OAE, totally abolished a 30-fold increase in FITC-dextran serum concentration induced by indomethacin. This effect was dose-dependent and largely conserved (85%) when OAE was given 180-min prior to indomethacin. The IEBF-protective effect of OAE was accompanied by a full prevention of the NF-κB activation, and the increases in interleukine-8 secretion and myeloperoxidase activity induced by indomethacin. The protection was also associated with a 21-fold increase in Nrf2, and a 7-fold and 9-fold increase in heme oxygenase-1 and NAD(P)H-quinone oxidoreductase 1, respectively. The IEBF-protecting effect of OAE involves, most likely, its dual capacity to activate Nrf2 while inhibiting NF-κB activation. The extremely low doses of BZF needed to promote such actions warrants extending its IEBF-protective effects to other NSAIDs.

GENE. 2022 APR 20;819:146246. DOI: 10.1016/J.GENE.2022.146246.

INCREASE IN ADAR1P110 ACTIVATES THE CANONICAL WNT SIGNALING PATHWAY ASSOCIATED WITH AGGRESSIVE PHENOTYPE IN TRIPLE NEGATIVE BREAST CANCER CELLS

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Triple-negative breast cancer (TNBC) represents a challenge in the search for new therapeutic targets. TNBCs are aggressive and generate resistance to chemotherapy. Tumors of TNBC patients with poor prognosis present a high level of adenosine deaminase acting on RNA1 (ADAR1). We explore the connection of ADAR1 with the canonical Wnt signaling pathway and the effect of modulation of its expression in TNBC. Expression data from cell line sequencing (DepMap) and TCGA samples were downloaded and analyzed. We lentivirally generated an MDA-MB-231 breast cancer cell line that overexpress (OE) ADAR1p110 or an ADAR knockdown. Abundance of different proteins related to Wnt/β-catenin pathway and activity of nuclear β-catenin were analyzed by Western blot and luciferase TOP/FOP reporter assay, respectively. Cell invasion was analyzed by matrigel assay. In mice, we study the behavior of tumors generated from ADAR1p110 (OE) cells and tumor vascularization immunostaining were analyzed. ADAR1 connects to the canonical Wnt pathway in TNBC. ADAR1p110 overexpression decreased GSK-3β, while increasing active β-catenin. It also increased the activity of nuclear β-catenin and increased its target levels. ADAR1 knockdown has the opposite effect. MDA-MB-231 ADAR1 (OE) cells showed increased capacity of invasion. Subsequently, we observed that tumors derived from ADAR1p110 (OE) cells showed increased invasion towards the epithelium, and increased levels of Survivin and CD-31 expressed in vascular endothelial cells. These results indicate that ADAR1 overexpression alters the expression of some key components of the canonical Wnt pathway, favoring invasion and neovascularization, possibly through activation of the β-catenin, which suggests an unknown role of ADAR1p110 in aggressiveness of TNBC tumors.

MOD PATHOL. 2022 FEB;35(2):249-255. DOI: 10.1038/S41379-021-00912-9.

TESTICULAR GERM-CELL TUMORS WITH SPERMATIC CORD INVOLVEMENT: A RETROSPECTIVE INTERNATIONAL MULTI-INSTITUTIONAL EXPERIENCE

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The 8th Edition of the American Joint Committee on Cancer (AJCC) Staging Manual designates discontinuous involvement of spermatic cord soft tissue by testicular germ cell tumors as a metastatic deposit. We conducted a retrospective international multi-institutional study to validate the current recommendations. Thirty-three (72%) nonseminomatous and 13 (28%) seminomatous testicular germ cell tumors were collected from 15 institutions in America, Europe, and Asia. Testicular tumor size ranged from 1.3 to 18.0 cm (mean: 6.1). Cases were classified as discontinuous involvement of spermatic cord soft tissue (n = 26), continuous cord involvement (n = 17), or cord lymphovascular invasion (n = 3). The mean follow-up was 39 months. Clinical stage for discontinuous involvement of spermatic cord soft-tissue patients was I (local disease) in 2/24 (8%), II (regional disease) in 6/24 (25%), and III (distant disease) in 16/24 (67%) cases; 16 (67%) patients presented with distant metastasis. Clinical stage for continuous cord involvement patients was I in 9/17 (53%), II in 4/17 (23%), and III in 4/17 (23%); 4 (23%) patients presented with distant metastasis. Disease progression was seen in 4 patients with discontinuous involvement of spermatic cord soft tissue and 5 with continuous cord-involvement (p = 0.699). When comparing discontinuous and continuous cord involvement, a significant difference was found in cord margin status (p = 0.044), spermatic cord tumor size (p = 0.016), lymph-node involvement (p = 0.037), distant metastasis (p = 0.010), individual clinical stage (p = 0.003), and nonadvanced vs. advanced disease (p = 0.003) at presentation. In multivariate analysis, after adjusting for age, histology, testicular tumor size, percent of embryonal carcinoma, lymphovascular invasion, and cord margin status, discontinuous involvement of spermatic cord soft tissue was significantly associated (p = 0.011) with advanced clinical stage at presentation. Our findings support the designation of metastatic disease for discontinuous involvement of spermatic cord soft tissue, as introduced by the 8th edition of the AJCC staging.

ORTHOD CRANIOFAC RES. 2022 NOV 1. DOI: 10.1111/OCR.12620.

INHIBITION OF THE 3-HYDROXY-3-METHYL-GLUTARYL-COA REDUCTASE DIMINISHES THE SURVIVAL AND SIZE OF CHONDROCYTES DURING OROFACIAL MORPHOGENESIS IN ZEBRAFISH

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Objectives: The 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) is the enzyme controlling the rate-limiting step in the synthesis of cholesterol, sterols, and isoprenoids in the mevalonate biosynthetic pathway. Impaired function of HMGCR in zebrafish produces craniofacial malformations and orofacial cleft, mainly affecting the post-migratory neural crest cells with little earlier effect. Here we investigate morphogenetic and cellular mechanisms underlying the generation of these malformations. Methods: The morphology of chondrocytes in the lower jaw and the proliferation/apoptosis in the ethmoid plate were analysed in hmgcr1b mutants and in embryos treated with atorvastatin. In the ceratohyal of treated embryos, we measured the number and dimensions of chondrocytes. In the ethmoid plate, we performed proliferation and apoptosis assays to quantify the number of cells undergoing each process in both hmgcr1b mutants and pharmacologically treated embryos. All embryos were imaged using confocal microscopy and processed to obtain maximum intensity z-projection. Results: The shortening of the ceratohyal is produced by a moderate reduction in the number of cells combined with isometric shrinkage of the chondrocytes. At the same time, the shortening of the ethmoid plate is due to a combination of a slightly diminished proliferation with massive abnormal apoptosis at the proliferation front. Conclusion: HMGCR function is necessary for the normal survival and morphology of chondrocytes during condensation and chondrogenesis in the developing palate and jaw. Further studies are required to establish the pathways through which HMGCR acts on apoptosis, proliferation, and cell size during normal craniofacial development.

MICROORGANISMS. 2022 APR 24;10(5):888. DOI: 10.3390/MICROORGANISMS10050888.

CHARACTERIZATION OF HIGH-RISK HPV/EBV CO-PRESENCE IN PRE-MALIGNANT CERVICAL LESIONS AND SQUAMOUS CELL CARCINOMAS

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High-risk human papillomaviruses (HR-HPVs) are the etiological agents of cervical cancer. However, a low proportion of HR-HPV-infected women finally develop this cancer, which suggests the involvement of additional cofactors. Epstein–Barr virus (EBV) has been detected in cervical squamous cell carcinomas (SCCs) as well as in low- (LSIL) and high-grade (HSIL) squamous intraepithelial lesions, although its role is unknown. In this study, we characterized HR-HPV/EBV co-presence and viral gene expression in LSIL (n = 22), HSIL (n = 52), and SCC (n = 19) from Chilean women. Additionally, phenotypic changes were evaluated in cervical cancer cells ectopically expressing BamHI-A Rightward Frame 1 (BARF1). BARF1 is a lytic gene also expressed in EBV-positive epithelial tumors during the EBV latency program. HPV was detected in 6/22 (27.3%) LSIL, 38/52 (73.1%) HSIL, and 15/19 (78.9%) SCC

cases (p < 0.001). On the other hand, EBV was detected in 16/22 (72.7%) LSIL, 27/52 (51.9%) HSIL, and 13/19 (68.4%) SCC cases (p = 0.177). HR-HPV/EBV co-presence was detected in 3/22 (13.6%) LSIL, 17/52 (32.7%) HSIL, and 11/19 (57.9%) SCC cases (p = 0.020). Additionally, BARF1 transcripts were detected in 37/55 (67.3%) of EBV positive cases and in 19/30 (63.3%) of HR-HPV/EBV positive cases. Increased proliferation, migration, and epithelial-mesenchymal transition (EMT) was observed in cervical cancer cells expressing BARF1. Thus, both EBV and BARF1 transcripts are detected in low- and high-grade cervical lesions as well as in cervical carcinomas. In addition, BARF1 can modulate the tumor behavior in cervical cancer cells, suggesting a role in increasing tumor aggressiveness.

CELLS. 2022 APR 30;11(9):1503. DOI: 10.3390/CELLS11091503.

THE AUTOPHAGY PROTEIN PACER POSITIVELY REGULATES THE THERAPEUTIC POTENTIAL OF MESENCHYMAL STEM CELLS IN A MOUSE MODEL OF DSS-INDUCED COLITIS

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Mesenchymal stem cells (MSC) have emerged as a promising tool to treat inflammatory diseases, such as inflammatory bowel disease (IBD), due to their immunoregulatory properties. Frequently, IBD is modeled in mice by using dextran sulfate sodium (DSS)-induced colitis. Recently, the modulation of autophagy in MSC has been suggested as a novel strategy to improve MSC-based immunotherapy. Hence, we investigated a possible role of Pacer, a novel autophagy enhancer, in regulating the immunosuppressive function of MSC in the context of DSS-induced colitis. We found that Pacer is upregulated upon stimulation with the pro-inflammatory cytokine TNFα, the main cytokine released in the inflammatory environment of IBD. By modulating Pacer expression in MSC, we found that Pacer plays an important role in regulating the autophagy pathway in this cell type in response to TNFα stimulation, as well as in regulating the immunosuppressive ability of MSC toward T-cell proliferation. Furthermore, increased expression of Pacer in MSC enhanced their ability to ameliorate the symptoms of DSS-induced colitis in mice. Our results support previous findings that autophagy regulates the therapeutic potential of MSC and suggest that the augmentation of autophagic capacity in MSC by increasing Pacer levels may have therapeutic implications for IBD.

DEPARTAMENTO ANESTESIOLOGÍA Y MEDICINA PERIOPERATORIA

FRONT MED (LAUSANNE). 2022 MAR 16;9:826218. DOI: 10.3389/FMED.2022.826218. ECOLLECTION 2022.

RELATIONSHIP BETWEEN ENDOTHELIAL AND ANGIOGENESIS BIOMARKERS ENVISAGE MORTALITY IN A PROSPECTIVE COHORT OF COVID-19 PATIENTS REQUIRING RESPIRATORY SUPPORT

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Purpose: Endothelial damage and angiogenesis are fundamental elements of neovascularisation and fibrosis observed in patients with coronavirus disease 2019 (COVID-19). Here, we aimed to evaluate whether early endothelial and angiogenic biomarkers detection predicts mortality and major cardiovascular events in patients with COVID-19 requiring respiratory support. Methods: Changes in serum syndecan-1, thrombomodulin, and angiogenic factor concentrations were analysed during the first 24 h and 10 days after COVID-19 hospitalisation in patients with high-flow nasal oxygen or mechanical ventilation. Also, we performed an exploratory evaluation of the endothelial migration process induced by COVID-19 in the patients' serum using an endothelial cell culture model. Results: In 43 patients, mean syndecan-1 concentration was 40.96 ± 106.9 ng/mL with a 33.9% increase (49.96 ± 58.1 ng/mL) at day 10. Both increases were significant compared to healthy controls (Kruskal-Wallis p < 0.0001). We observed an increase in thrombomodulin, Angiopoietin-2, human vascular endothelial growth factor (VEGF), and human hepatocyte growth factor (HGF) concentrations during the first 24 h, with a decrease in human tissue inhibitor of metalloproteinases-2 (TIMP-2) that remained after 10 days. An increase in human Interleukin-8 (IL-8) on the 10th day accompanied by high HGF was also noted. The incidence of myocardial injury and pulmonary thromboembolism was 55.8 and 20%, respectively. The incidence of in-hospital deaths was 16.3%. Biomarkers showed differences in severity of COVID-19. Syndecan-1, human platelet-derived growth factor (PDGF), VEGF, and Ang-2 predicted mortality. A multiple logistic regression model with TIMP-2 and PDGF had positive and negative predictive powers of 80.9 and 70%, respectively, for mortality. None of the biomarkers predicted myocardial injury or pulmonary thromboembolism. A proteome profiler array found changes in concentration in a large number of biomarkers of angiogenesis and chemoattractants. Finally, the serum samples from COVID-19 patients increased cell migration compared to that from healthy individuals. Conclusion: We observed that early endothelial and angiogenic biomarkers predicted mortality in patients with COVID-19. Chemoattractants from patients with COVID-19 increase the migration of endothelial cells. Trials are needed for confirmation, as this poses a therapeutic target for SARS-CoV-2.

J NEUROSURG SCI. 2022 APR;66(2):91-95. DOI: 10.23736/S0390-5616.19.04715-5.

ASSOCIATION BETWEEN PREOPERATIVE SERUM LACTATE CONCENTRATE WITH TUMOR CELL PROLIFERATIVE INDEX IN PRIMARY BRAIN TUMOR

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Background: Elevated preoperative lactate levels have been reported in patients admitted for resection of brain tumors. As histologic type and tumor grade have also been linked to lactate concentration, we hypothesized that preoperative lactate concentration in patients with brain tumors may be associated with tumor proliferation. We describe the relationship between preoperative plasma lactate levels, and the cell proliferation marker Ki-67 in brain tumor surgery. Methods: In this cross-sectional study, records of patients who underwent craniotomy between June 2017 and February 2018 at our Hospital were reviewed to select glioma and meningioma cases in which lactate concentrations in plasma and degree of cell proliferation were registered. Bivariable and linear regression analyses were used to assess the association between lactate concentrations and the Ki-67 Index. Results: Lactate concentrations in plasma and Ki-67 Index were available in 55 patients. Meningioma cases had a mean concentration of 1.2 (0.1) mmol/L compared to diffuse astrocytic and oligodendroglial tumors cases with 1.7 (0.1) mmol/L (P<0.01). Both variables had a low positive correlation in meningiomas (Spearman's r, 0.29; 95% CI, -0.10-0.61; P=0.13) and a high correlation in gliomas (Spearman's r, 0.64; 95% CI, 0.33-0.82; P<0.01). The pooled analysis showed a high correlation index (Spearman's r, 0.61; 95% CI, 0.40-0.76; P<0.01). A linear regression model showed that the Ki-67 Index explained 43% of the variation in lactate (P<0.01). Conclusions: Brain tumors with higher rates of cell proliferation have higher plasma lactate levels. In this scenario, lactate concentrations may not only reflect systemic perfusion.

DEPARTAMENTO CARDIOVASCULAR

FRONT CARDIOVASC MED. 2022 MAY 9;9:848589. DOI: 10.3389/FCVM.2022.848589. ECOLLECTION 2022.

TWO-MINUTE STEP TEST AS A COMPLEMENT TO SIX-MINUTE WALK TEST IN SUBJECTS WITH TREATED CORONARY ARTERY DISEASE

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The 2-Minute Step Test (2MST) has been presented as an alternative to the 6-Minute Walk Test (6MWT) based on the association between the two tests in older adults; however, some authors propose that it should not be a substitute but rather a complement to the latter in the fitness evaluation. Specifically, in coronary disease, despite the potential and clinical utility of 2MST, the relationship of both tests in this population is unknown. This study aimed to determine the relationship between 6MWT and 2MST and to explore the relationship of biodemographic factors for both tests in subjects with treated coronary artery disease. For this, the 6MWT and the 2MST were applied to patients with coronary artery disease treated in 6 hospitals in Chile between May 2019 and February 2020. Additionally, lower limb strength was assessed by a chair-stand test, grip strength was assessed by a dynamometer, and physical measurements were applied. In total, 163 participants underwent both tests (average age = 58.7 ± 9.8 years; 73.6% men; 64.4% revascularized by angioplasty; 28.2% revascularized by surgery, and 7.4% treated by drugs or thrombolysis). Heart rate was higher at the end of the 6MWT, while the perception of effort was greater at the end of the 2MST. There was a weak positive correlation between the 6MWT and the 2MST in subjects with treated coronary disease (r = 0.28, p = 0.0003). While age (r = -0.27), weight (r = 0.25), height (r = 0.49), and strength of both lower limbs (r = 0.41) and grip strength (r = 0.53) correlated weakly or moderately to the covered distance in 6MWT, the number of steps by the 2MST correlated only weakly to height (r = 0.23), lower limb strength (r = 0.34), and grip strength (r = 0.34). Age, weight, height, lower limb strength, and grip strength would explain better the meters walked in the 6MWT than the steps achieved in the 2MST. With these findings, we can conclude that, in patients with treated coronary artery disease, it does not seem advisable to replace 6MWT with 2MST when it is possible to do so. Additionally, the 2MST may provide additional information in the fitness evaluation. However, the usefulness of 2MST in this population needs to be further studied.

FRONT PHYSIOL. 2022 AUG 5;13:948273. DOI: 10.3389/FPHYS.2022.948273. ECOLLECTION 2022.

A HYBRID EXERCISE-BASED CARDIAC REHABILITATION PROGRAM IS AN EFFECTIVE STRATEGY TO IMPROVE MUSCLE STRENGTH AND FUNCTIONAL EXERCISE CAPACITY IN ADULTS AND OLDER PEOPLE WITH CORONARY ARTERY DISEASE

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Coronary heart disease is the most common cause of death worldwide. Standard cardiac rehabilitation (face-to-face sessions) has shown benefits in increasing muscle strength and functional exercise capacity in adults and older people. However, it is unknown whether hybrid cardiac rehabilitation (a first face-to-face phase + a second remote monitoring phase) will have similar benefits in adults versus older subjects. The aim of this study was to compare the effects of a hybrid exercise-based cardiac rehabilitation program on muscle strength and functional exercise capacity in "adult" versus "older" people with coronary artery disease. We hypothesized that a hybrid exercise-based cardiac rehabilitation program would improve muscle strength and functional exercise capacity, but the impact would be smaller

in the older group than the adult individuals. This study is part of a larger project (The Hybrid Cardiac Rehabilitation Trial-HYCARET). We subjected 22 adult (<60 y) females and males (ADULT; n = 5/17 (f/m); 52 ± 5 y; 28.9 ± 3.4 kg·m-2) and 20 older (≥60 y) females and males (OLDER; n = 6/14 (f/m); 66 ± 4 y; 27.4 ± 3.9 kg·m-2) with coronary artery disease to 12 weeks of hybrid exercise-based cardiac rehabilitation program. Prior to and after 12 weeks of a hybrid exercise-based cardiac rehabilitation program, grip strength (handgrip), leg strength (chair stand test), and functional exercise capacity (6-minute walk test, 6MWT) were assessed. The hybrid exercise-based cardiac rehabilitation program resulted in a 9.4 ± 14.6% and a 6.2 ± 12.1% grip strength increase, a 14.4 ± 39.4% and a 28.9 ± 48.1% legs strength increase, and a 14.6 ± 26.4% and a 6.8 ± 14.0% functional exercise capacity improvement in ADULT and OLDER, respectively ($p < 0.05$) with no differences between groups. In conclusion, a hybrid exercise-based cardiac rehabilitation program could increase muscle strength and improve functional exercise capacity in adults and older people with coronary artery disease. More future studies comparing effectiveness among these age groups are needed to strengthen this conclusion.

INT J MOL SCI. 2022 DEC 30;24(1):667. DOI: 10.3390/IJMS24010667.

POLYCYSTIN-1 IS A CRUCIAL REGULATOR OF BIN1 EXPRESSION AND T-TUBULE REMODELING ASSOCIATED WITH THE DEVELOPMENT OF DILATED CARDIOMYOPATHY

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Cardiomyopathy is commonly observed in patients with autosomal dominant polycystic kidney disease (ADPKD), even when they have normal renal function and arterial pressure. The role of cardiomyocyte polycystin-1 (PC1) in cardiovascular pathophysiology remains unknown. PC1 is a potential regulator of BIN1 that maintains T-tubule structure, and alterations in BIN1 expression induce cardiac pathologies. We used a cardiomyocyte-specific PC1-silenced (PC1-KO) mouse model to explore the relevance of cardiomyocyte PC1 in the development of heart failure (HF), considering reduced BIN1 expression induced T-tubule remodeling as a potential mechanism. PC1-KO mice exhibited an impairment of cardiac function, as measured by echocardiography, but no signs of HF until 7-9 months of age. Of the PC1-KO mice, 43% died suddenly at 7 months of age, and 100% died after 9 months with dilated cardiomyopathy. Total BIN1 mRNA, protein levels, and its localization in plasma membrane-enriched fractions decreased in PC1-KO mice. Moreover, the BIN1 + 13 isoform decreased while the BIN1 + 13 + 17 isoform was overexpressed in mice without signs of HF. However, BIN1 + 13 + 17 overexpression was not observed in mice with HF. T-tubule remodeling and BIN1 score measured in plasma samples were associated with decreased PC1-BIN1 expression and HF development. Our results show that decreased PC1 expression in cardiomyocytes induces dilated cardiomyopathy associated with diminished BIN1 expression and T-tubule remodeling. In conclusion, positive modulation of BIN1 expression by PC1 suggests a novel pathway that may be relevant to understanding the pathophysiological mechanisms leading to cardiomyopathy in ADPKD patients.

FUNDAM CLIN PHARMACOL. 2022 JUN;36(3):494-500. DOI: 10.1111/FCP.12754.

RISPERIDONE IN ANALGESIA INDUCED BY PARACETAMOL AND MELOXICAM IN EXPERIMENTAL PAIN

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the best therapeutic options to treat pain. Their use in combination with other drugs may broaden their applicability in analgesia if their ceiling and adverse effects are reduced. The aim of this study was to evaluate the pharmacological interaction of two NSAIDs, paracetamol and meloxicam, with the antipsychotic drug risperidone in mice, in several experimental tests of nociceptive and inflammatory pain. Antinociception was assessed by dose-response curves to paracetamol and meloxicam before and after the i.p. administration of 0.5 mg/kg of risperidone. Results are presented as means ± SEM and differences were calculated by one-way ANOVA followed by Tukey's post-test. Paracetamol and meloxicam produced a dose-related antinociceptive effect with diverse potencies. Risperidone increased the analgesia mediated by paracetamol and meloxicam only in the tonic tests that detected inflammatory pain. This suggests that COX inhibition is only a partial explanation of the increased analgesic potency of paracetamol and meloxicam since the effects of NSAIDs in the CNS are mediated by multiple mechanisms. These results indicate that the combination of risperidone with paracetamol or meloxicam could be a new and effective alternative for the management of inflammatory pain.

CENTRO INVESTIGACIÓN CLÍNICA AVANZADA

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EFICACIA DE UNA ESTRATEGIA ESTANDARIZADA Y SIMPLIFICADA PARA TRATAMIENTO DE LA HIPERTENSIÓN ARTERIAL EN CHILE: LA INICIATIVA HEARTS EN LAS AMÉRICAS

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Objective: To evaluate the effectiveness of a standardized and simplified protocol based on the technical pillars of the HEARTS Initiative for the control of hypertensive patients in the Cardiovascular Health Program at the first level of care in Chile. Methods:

Longitudinal observational study (historical cohort) in two family health centers at the first level of care in Santiago. The control of blood pressure in hypertensive adults using a standardized and simplified protocol was compared to the usual protocol based on national guidelines. Innovations in the standardized protocol included changes in how the health team is coordinated, initiation of pharmacological treatment immediately after confirmed diagnosis, standardized pharmacological treatment with a combination of at least two or three antihypertensive drugs taken daily in a single tablet. Follow-up was conducted after one year to assess the percentage of adherence to treatment and achievement of blood pressure control targets (< 140/90 mmHg). Results: A total of 1490 patients were evaluated: 562 who followed the standardized and simplified protocol, and 928 who were treated with the usual protocol (family health centers: 650; family health centers: 278). After one year, patients in the standardized and simplified protocol group had a higher proportion of adherence to blood pressure control targets (65% versus 37% and 41%, p<0.001) and higher adherence to treatment compared to those following the usual protocol (71% versus 18% and 23%, p<0.001). Conclusions: The results show that the standardized and simplified protocol is more effective than the usual protocol in controlling arterial hypertension in patients undergoing treatment at the first level of care in Chile. Its implementation at the national level could contribute to a decrease in major cardiovascular events.

CELLS. 2022 JUN 7;11(12):1860. DOI: 10.3390/CELLS11121860.

NEURONAL RUBICON REPRESSES EXTRACELLULAR APP/AMYLOID Β DEPOSITION IN ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is the most prevalent age-associated neurodegenerative disease. A decrease in autophagy during aging contributes to brain disorders by accumulating potentially toxic substrates in neurons. Rubicon is a well-established inhibitor of autophagy in all cells. However, Rubicon participates in different pathways depending on cell type, and little information is currently available on neuronal Rubicon's role in the AD context. Here, we investigated the cell-specific expression of Rubicon in postmortem brain samples from AD patients and 5xFAD mice and its impact on amyloid β burden in vivo and neuroblastoma cells. Further, we assessed Rubicon levels in human-induced pluripotent stem cells (hiPSCs), derived from early-to-moderate AD and in postmortem samples from severe AD patients. We found increased Rubicon levels in AD-hiPSCs and postmortem samples and a notable Rubicon localization in neurons. In AD transgenic mice lacking Rubicon, we observed intensified amyloid β burden in the hippocampus and decreased Pacer and p62 levels. In APP-expressing neuroblastoma cells, increased APP/amyloid β secretion in the medium was found when Rubicon was absent, which was not observed in cells depleted of Atg5, essential for autophagy, or Rab27a, required for exosome secretion. Our results propose an uncharacterized role of Rubicon on APP/amyloid β homeostasis, in which neuronal Rubicon is a repressor of APP/amyloid β secretion, defining a new way to target AD and other similar diseases therapeutically.

J NEUROSURG ANESTHESIOL. 2022 JAN 1;34(1):79-83. DOI: 10.1097/ANA.0000000000000733.

ELECTROENCEPHALOGRAPHIC ALPHA AND DELTA OSCILLATION DYNAMICS IN RESPONSE TO INCREASING DOSES OF PROPOFOL

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Background: The electroencephalogram (EEG) may be useful for monitoring anesthetic depth and avoiding overdose. We aimed to characterize EEG-recorded brain oscillations during increasing depth of anesthesia in a real-life surgical scenario. We hypothesized that alpha power and coherency will diminish as propofol dose increases between loss of consciousness (LOC) and an EEG burst suppression (BS) pattern. Methods: This nonrandomized dose-response clinical trial with concurrent control included EEG monitoring in 16 patients receiving slowly increasing doses of propofol. We assessed 3 intraoperative EEG segments (LOC, middle-dose, and BS) with spectral analysis. Results: Alpha band power diminished with each step increase in propofol dose. Average alpha power and average delta power during the BS step (-1.4±3.8 and 6.2±3.1 dB, respectively) were significantly lower than during the LOC step (2.8±2.6; P=0.004 and 10.1±5.2 dB; P=0.03, respectively). Peak alpha power was significantly higher during the LOC (5.4±2.6 dB) compared with middle-dose (2.6±3.6; P=0.04) and BS (0.7±3.2; P=0.0002) steps. In addition, as propofol dose increased, alpha band coherence between the F7 and F8 electrodes decreased, whereas delta band coherence exhibited a biphasic response (initial increase between LOC and middle-dose steps and decrease between middle-dose and BS steps). Conclusion: We report compelling data regarding EEG patterns associated with increases in propofol dose. This information may more accurately define "therapeutic windows" for anesthesia and provide insights into brain dynamics that are sequentially affected by increased anesthetic doses.

FRONT AGING NEUROSCI. 2023 FEB 9;15:1097577. DOI: 10.3389/FNAGI.2023.1097577. ECOLLECTION 2023.

VISUAL-SPATIAL PROCESSING IMPAIRMENT IN THE OCCIPITAL-FRONTAL CONNECTIVITY NETWORK AT EARLY STAGES OF ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD) is the leading cause of dementia worldwide, but its pathophysiological phenomena are not fully elucidated. Many neurophysiological markers have been suggested to identify early cognitive impairments of AD. However, the diagnosis of this disease remains a challenge for specialists. In the present cross-sectional study, our objective was to evaluate the manifestations and mechanisms underlying visual-spatial deficits at the early stages of AD. Methods: We combined behavioral, electroencephalography (EEG), and eye movement recordings during the performance of a spatial navigation task (a virtual version of the Morris Water Maze adapted to humans). Participants (69-88 years old) with amnesic mild cognitive impairment-Clinical Dementia Rating scale (aMCI-CDR 0.5) were selected as probable early AD (eAD) by a neurologist specialized in dementia. All patients included in this study were evaluated at the CDR 0.5 stage but progressed to probable AD during clinical follow-up. An equal number of matching healthy controls (HCs) were evaluated while performing the navigation task. Data were collected at the Department of Neurology of the Clinical Hospital of the Universidad de Chile and the Department of Neuroscience of the Faculty of Universidad de Chile. Results: Participants with aMCI preceding AD (eAD) showed impaired spatial learning and their visual exploration differed from the control group. eAD group did not clearly prefer regions of interest that could guide solving the task, while controls did. The eAD group showed decreased visual occipital evoked potentials associated with eye fixations, recorded at occipital electrodes. They also showed an alteration of the spatial spread of activity to parietal and frontal regions at the end of the task. The control group presented marked occipital activity in the beta band (15-20 Hz) at early visual processing time. The eAD group showed a reduction in beta band functional connectivity in the prefrontal cortices reflecting poor planning of navigation strategies. Discussion: We found that EEG signals combined with visual-spatial navigation analysis, yielded early and specific features that may underlie the basis for understanding the loss of functional connectivity in AD. Still, our results are clinically promising for early diagnosis required to improve quality of life and decrease healthcare costs.

INT J MOL SCI. 2022 AUG 20;23(16):9387. DOI: 10.3390/IJMS23169387.

SENESCENCE MARKERS IN PERIPHERAL BLOOD MONONUCLEAR CELLS IN AMNESTIC MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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Recent studies suggest that cellular senescence plays a role in Alzheimer's Disease (AD) pathogenesis. We hypothesize that cellular senescence markers might be tracked in the peripheral tissues of AD patients. Senescence hallmarks, including altered metabolism, cell-cycle arrest, DNA damage response (DDR) and senescence secretory associated phenotype (SASP), were measured in peripheral blood mononuclear cells (PBMCs) of healthy controls (HC), amnestic mild cognitive impairment (aMCI) and AD patients. Senescence-associated βeta-galactosidase (SA-β-Gal) activity, G0-G1 phase cell-cycle arrest, p16 and p53 were analyzed by flow cytometry, while IL-6 and IL-8 mRNA were analyzed by qPCR, and phosphorylated H2A histone family member X (γH2AX) was analyzed by immunofluorescence. Senescent cells in the brain tissue were determined with lipofuscin staining. An increase in the number of senescent cells was observed in the frontal cortex and hippocampus of advanced AD patients. PBMCs of aMCI patients, but not in AD, showed increased SA-β-Gal compared with HCs. aMCI PBMCs also had increased IL-6 and IL8 mRNA expression and number of cells arrested at G0-G1, which were absent in AD. Instead, AD PBMCs had significantly increased p16 and p53 expression and decreased γH2Ax activity compared with HC. This study reports that several markers of cellular senescence can be measured in PBMCs of aMCI and AD patients.

J ALZHEIMERS DIS. 2022;87(4):1695-1711. DOI: 10.3233/JAD-215660.

CANCER HISTORY IS ASSOCIATED WITH SLOWER SPEED OF COGNITIVE DECLINE IN PATIENTS WITH AMNESTIC COGNITIVE IMPAIRMENT

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Background: Several epidemiological studies report a negative association between Cancer and Alzheimer's disease (AD). Objective: To characterize the trajectories of memory loss in individuals with early amnestic cognitive impairment with and without history of previous cancer. Methods: Cognitive deterioration was assessed using the Montreal Cognitive Assessment (MoCA) or MoCA-Memory Index Score (MoCA-MIS) biannually in subjects with early amnestic cognitive impairment followed-up retrospectively from 2007 to 2021. History of Cancer was obtained from clinical records. Simple linear regressions of MoCA-MIS scores were calculated for each subject and analyzed with K-means cluster analysis to identify subgroups with different cognitive decline trajectories. $\chi 2$ and t tests were used for descriptive categorical and continuous variables and mixed multiple linear regressions to determine cognitive decline

covariates. Results: Analysis of the trajectory of cognitive decline in 141 subjects with early amnestic cognitive impairment identified two subgroups: Fast (n = 60) and Slow (n = 81) progressors. At baseline Fast progressors had better MoCA-MIS (p < 0.001) and functionality (CDR p = 0.02, AD8 p = 0.05), took less anti-dementia medications (p = 0.005), and had higher depression rates (p = 0.02). Interestingly, Fast progressors slowed their speed of memory decline (from 1.6 to 1.1 MoCA-MIS points/year) and global cognitive decline (from 2.0 to 1.4 total MoCA points/year) when Cancer history was present. Conclusion: Two trajectories of amnestic cognitive decline were identified, possibly derived from different neurophysiopathologies or clinical stages. This study suggests that a history of previous Cancer slows down amnestic cognitive decline, specifically in a subgroup of subjects with depression at baseline and accelerated deterioration at follow-up.

DEPARTAMENTO DE CIRUGÍA

CLIN INFECT DIS. 2022 AUG 24;75(1):E594-E602. DOI: 10.1093/CID/CIAC167.

REDUCED IMMUNE RESPONSE TO INACTIVATED SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 VACCINE IN A COHORT OF IMMUNOCOMPROMISED PATIENTS IN CHILE

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Background: Inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been widely implemented in low- and middle-income countries. However, immunogenicity in immunocompromised patients has not been established. Herein, we aimed to evaluate immune response to CoronaVac vaccine in these patients. Methods: This prospective cohort study included 193 participants with 5 different immunocompromising conditions and 67 controls, receiving 2 doses of CoronaVac 8-12 weeks before enrollment. The study was conducted between May and August 2021, at Red de Salud UC-CHRISTUS, Santiago, Chile. Neutralizing antibody (NAb) positivity, total anti-SARS-CoV-2 immunoglobulin G antibody (TAb) concentrations, and T-cell responses were determined. Results: NAb positivity and median neutralizing activity were 83.1% and 51.2% for the control group versus 20.6% and 5.7% (both P < .001) in the solid organ transplant group, 41.5% and 19.2% (both P < .0001) in the autoimmune rheumatic diseases group, 43.3% (P < .001) and 21.4% (P<.01 or P = .001) in the cancer with solid tumors group, 45.5% and 28.7% (both P < .001) in the human immunodeficiency virus (HIV) infection group, 64.3% and 56.6% (both differences not significant) in the hematopoietic stem cell transplant group, respectively. TAb seropositivity was also lower for the solid organ transplant (20.6%; P < .0001), rheumatic diseases (61%; P < .001), and HIV groups (70.9%; P = .003), compared with the control group (92.3%). On the other hand, the number of interferon γ spot-forming T cells specific for SARS-CoV-2 tended to be lower in all immunocompromising conditions but did not differ significantly between groups. Conclusions: Diverse immunocompromising conditions markedly reduce the humoral response to CoronaVac vaccine. These findings suggest that a boosting vaccination strategy should be considered in these vulnerable patients.

SURGERY. 2022 DEC;172(6S):S29-S37. DOI: 10.1016/J.SURG.2022.06.036.

USE OF FLUORESCENCE IMAGING AND INDOCYANINE GREEN FOR SENTINEL NODE MAPPING DURING GASTRIC CANCER SURGERY: RESULTS OF AN INTERCONTINENTAL DELPHI SURVEY

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Background: Understanding the extent of tumor spread to local lymph nodes is critical to managing early-stage gastric cancer. Recently, fluorescence imaging with indocyanine green has been used to identify and characterize sentinel lymph nodes during gastric cancer surgery, but no published guidelines exist. We sought to identify areas of consensus among international experts in the use of fluorescence imaging with indocyanine green for mapping sentinel lymph nodes during gastric-cancer surgery. Methods: In this 2-round, online Delphi survey, 27 international experts voted on 79 statements pertaining to patient preparation and contraindications to fluorescence imaging with indocyanine green during gastric cancer surgery; indications; technical aspects; advantages/disadvantages and limitations; and training and research. Methodological steps were adopted during survey design to minimize bias. Results: Consensus was reached on 61 of 79 statements, including giving single injections of indocyanine green into each of the 4 quadrants peritumorally, administering indocyanine green on the same day as surgery, injecting a total of 1 to 5 mL of 5 mg/mL indocyanine green, injecting endoscopically into submucosa, and repeating indocyanine green injections a second time if sentinel lymph node visualization remains inadequate. Consensus also was reached that fluorescence imaging with indocyanine green is an acceptable single-agent modality for sentinel lymph node identification and that the sentinel lymph node basin method is preferred. However, sentinel lymph node dissection should be limited to T1 gastric cancer and tumors ≤4 cm in diameter, and further research

is necessary to optimize the technique and render fluorescence-guided sentinel lymph nodes dissection acceptable for routine clinical use. laboratConclusion: Although considerable consensus was achieved, further research is necessary before this technology should be used in routine practice.

AESTHETIC PLAST SURG. 2022 DEC 21. DOI: 10.1007/S00266-022-03222-W.

WHAT MAKES A BEAUTIFUL BUTTOCK BEAUTIFUL? A CASE-CONTROL STUDY COMPARING BUTTOCKS MODELS VERSUS NORMAL WOMEN BY MAGNETIC RESONANCE IMAGING, PHOTOGRAPHY AND ANTHROPOMETRY

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Objectives: To describe characteristics of women with aesthetically ideal buttocks and differentiate them from women with normal buttocks. Methods: Case-control study comparing anatomy of women with ideal buttocks (buttocks models) to women with normal buttocks using magnetic resonance images, anthropometric measurements and photography. Results: Comparing to normal women, buttocks models have a narrower waist, narrower iliac crest, wider C point, wider hips and bigger and thicker gluteus maximus muscle (GMM). A bigger GMM adds more projection to the C point, point of maximum projection in the lateral view is 2.7 cm higher than the pubic bone. The amount of subcutaneous fat was equal in models and controls. Conclusions: Our study provides new knowledge regarding the tridimensional aspects of the beauty of the buttocks area. A beautiful buttock is a conjunction of adequate bony shape, muscle development, subcutaneous fat layer, and tight skin. Comparing to normal women, buttocks models have a narrower waist, narrower iliac crest, wider C point, wider hips and bigger and thicker Gluteus Maximus Muscle. Accurate understanding of the aesthetic goals in a given patient can guide surgical technique.

DIS ESOPHAGUS. 2022 DEC 14;35(12):DOAC030. DOI: 10.1093/DOTE/DOAC030.

OBSERVATIONAL MEDICAL TREATMENT OR SURGERY FOR GIANT PARAESOPHAGEAL HIATAL HERNIA IN ELDERLY PATIENTS

Italo Braghetto, Juan Carlos Molina, Owen Korn, Enrique Lanzarini, Maher Musleh, Manuel Figueroa, Jorge Rojas

Giant paraesophageal hernias (GPHH) occur frequently in the elderly and account for about 5-10% of all hiatal hernias. Up to now controversy persists between expected medical treatment and surgical treatment. To assess if an indication for surgical repair of GPHH is possible in elderly patients. A prospective study that includes patients over 70 years of age hospitalized from January 2015 to December 2019 with GPHH. Patients were separated into Group A and Group B. Group A consisted of a cohort of 23 patients in whom observation and medical treatment were performed. Group B consisted of 44 patients submitted to elective laparoscopic hiatal hernia repair. Symptomatic patients were observed in both groups (20/23 in Group A and 38/44 in Group B). Charlson's score >6 and ASA II or III were more frequent in Group A. Patients in Group A presented symptoms many years before their hospitalization in comparison to Group B (21.8+7.8 vs. 6.2+3.5 years, respectively) (P=0.0001). Emergency hospitalization was observed exclusively in Group A. Acute complications were frequently observed and hospital stays were significantly longer in Group A, 14 patients were subjected to medical management and 6 to emergency surgery. In-hospital mortality occurred in 13/20 patients (65%) versus 1/38 patients (2.6%) in Group B (P=0.0001). Laparoscopic paraesophageal hiatal hernia repair can be done safely, effectively, and in a timely manner in elderly patients at specialized surgical teams. Advanced age alone should not be a limiting factor for the repair of paraesophageal hernias.

NUTR CLIN PRACT. 2022 AUG;37(4):743-751. DOI: 10.1002/NCP.10864.

NUTRITIONAL CARE IS A HUMAN RIGHT: TRANSLATING PRINCIPLES TO CLINICAL PRACTICE

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We have previously advocated that nutritional care be raised to the level of a human right, in close relationship to two well-recognized fundamental rights: the right to food and the right to health. This article aims to analyze the implication of nutritional care as a human right for healthcare practitioners. We will focus on the impact of the Human Rights Basic Approach (HRBA) on healthcare professionals (HCPs), namely how they can translate HRBA into routine clinical practice. Ethics and human rights are guiding values for clinical nutrition practitioners. Together they ensure a patient-centered approach, in which the needs and rights of the patients are of the most significant importance. Human rights are based on the powerful idea of equal dignity for all people while expressing a set of core values, including fairness, respect, equality, dignity, and autonomy (FREDA). Through the analysis of FREDA principles, we have provided the elements to understand human rights and how an HRBA can support clinicians in the decision-making process. Clinical practice guidelines in clinical nutrition should incorporate disease-specific ethical issues and the HRBA. The HRBA should contribute to building conditions for HCPs to provide optimal and timely nutritional care. Nutritional care must be exercised by HCPs with due respect for several fundamental ethical values: attentiveness, responsibility competence, responsiveness, and solidarity.

JHEP REP. 2022 FEB 2;4(5):100445. DOI: 10.1016/J.JHEPR.2022.100445. ECOLLECTION 2022 MAY.

R3-AFP SCORE IS A NEW COMPOSITE TOOL TO REFINE PREDICTION OF HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANTATION

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Background & aims: Patients with hepatocellular carcinoma (HCC) are selected for liver transplantation (LT) based on pre-LT imaging ± alpha-foetoprotein (AFP) level, but discrepancies between pre-LT tumour assessment and explant are frequent. Our aim was to design an explant-based recurrence risk reassessment score to refine prediction of recurrence after LT and provide a framework to guide post-LT management. Methods: Adult patients who underwent transplantation between 2000 and 2018 for HCC in 47 centres were included. A prediction model for recurrence was developed using competing-risk regression analysis in a European training cohort (TC; n = 1,359) and tested in a Latin American validation cohort (VC; n=1,085). Results: In the TC, 76.4% of patients with HCC met the Milan criteria, and 89.9% had an AFP score of ≤2 points. The recurrence risk reassessment (R3)-AFP model was designed based on variables independently associated with recurrence in the TC (with associated weights): ≥4 nodules (sub-distribution of hazard ratio [SHR] = 1.88, 1 point), size of largest nodule (3-6 cm: SHR = 1.83, 1 point; >6 cm: SHR = 5.82, 5 points), presence of microvascular invasion (MVI; SHR = 2.69, 2 points), nuclear grade >II (SHR = 1.20, 1 point), and last pre-LT AFP value (101-1,000 ng/ml: SHR = 1.57, 1 point; >1,000 ng/ml: SHR = 2.83, 2 points). Wolber's c-index was 0.76 (95% CI 0.72-0.80), significantly superior to an R3 model without AFP (0.75; 95% CI 0.72-0.79; p = 0.01). Four 5-year recurrence risk categories were identified: very low (score = 0; 5.5%), low (1-2 points; 15.1%), high (3-6 points; 39.1%), and very high (>6 points; 73.9%). The R3-AFP score performed well in the VC (Wolber's c-index of 0.78; 95% CI 0.73-0.83). Conclusions: The R3 score including the last pre-LT AFP value (R3-AFP score) provides a user-friendly, standardised framework to design post-LT surveillance strategies, protocols, or adjuvant therapy trials for HCC not limited to the Milan criteria.

J VIRAL HEPAT. 2023 JAN;30(1):56-63. DOI: 10.1111/JVH.13758.

IMPLEMENTATION OF A RE-LINKAGE TO CARE STRATEGY IN PATIENTS WITH CHRONIC HEPATITIS C WHO WERE LOST TO FOLLOW-UP IN LATIN AMERICA

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To achieve WHO's goal of eliminating hepatitis C virus (HCV), innovative strategies must be designed to diagnose and treat more patients. Therefore, we aimed to describe an implementation strategy to identify patients with HCV who were lost to follow-up (LTFU) and offer them re-linkage to HCV care. We conducted an implementation study utilizing a strategy to contact patients with HCV who were not under regular follow-up in 13 countries from Latin America. Patients with HCV were identified by the international classification of diseases (ICD-9/10) or equivalent. Medicales records were then reviewed to confirm the diagnosis of chronic HCV infection defined by anti-HCV+ and detectable HCV-RNA. Identified patients who were not under follow-up by a liver specialist were contacted by telephone or email, and offered a medical reevaluation. A total of 10,364 patients were classified to have HCV. After reviewing their medical charts, 1349 (13%) had undetectable HCV-RNA or were wrongly coded. Overall, 9015 (86.9%) individuals were identified with chronic HCV infection. A total of 5096 (56.5%) patients were under routine HCV care and 3919 (43.5%) had been LTFU. We were able to contact 1617 (41.3%) of the 3919 patients who were LTFU at the primary medical institution, of which 427 (26.4%) were cured at a different institutions or were dead. Of the remaining patients, 906 (76.1%) were candidates for retrieval. In our cohort, about one out of four patients with chronic HCV who were LTFU were candidates to receive treatment. This strategy has the potential to be effective, accessible and significantly impacts on the HCV care cascade.

LIVER INT. 2022 AUG;42(8):1879-1890. DOI: 10.1111/LIV.15223.

PERFORMANCE OF PRE-TRANSPLANT CRITERIA IN PREDICTION OF HEPATOCELLULAR CARCINOMA PROGRESSION AND WAITLIST DROPOUT

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Background & aim: Liver transplantation (LT) selection models for hepatocellular carcinoma (HCC) have not been proposed to predict waitlist dropout because of tumour progression. The aim of this study was to compare the alpha-foetoprotein (AFP) model and other pre-LT models in their prediction of HCC dropout. Methods: A multicentre cohort study was conducted in 20 Latin American transplant centres, including 994 listed patients for LT with HCC from 2012 to 2018. Longitudinal tumour characteristics, and patterns of progression were recorded at time of listing, after treatments and at last follow-up over the waitlist period. Competing risk regression models were performed, and model's discrimination was compared estimating Harrell's adapted c-statistics. Results: HCC dropout rate was significantly higher in patients beyond (24% [95% CI 16-28]) compared to those within Milan criteria (8% [95% IC 5%-12%]; p < .0001), with a SHR of 3.01 [95% CI 2.03-4.47]), adjusted for waiting list time and bridging therapies (c-index 0.63 [95% CI 0.57; 0.69).

HCC dropout rates were higher in patients with AFP scores >2 (adjusted SHR of 3.17 [CI 2.13-4.71]), c-index of 0.71 (95% CI 0.65-0.77; p = .09 vs Milan). Similar discrimination power for HCC dropout was observed between the AFP score and the Metroticket 2.0 model. In patients within Milan, an AFP score >2 points discriminated two populations with a higher risk of HCC dropout (SHR 1.68 [95% CI 1.08-2.61]). Conclusions: Pre-transplant selection models similarly predicted HCC dropout. However, the AFP model can discriminate a higher risk of dropout among patients within Milan criteria.

SURG ENDOSC. 2022 JAN;36(1):282-291. DOI: 10.1007/S00464-020-08273-1.

LONG-TERM (17 YEARS) SUBJECTIVE AND OBJECTIVE EVALUATION OF THE DURABILITY OF LAPAROSCOPIC HELLER ESOPHAGOMYOTOMY IN PATIENTS WITH ACHALASIA OF THE ESOPHAGUS (90% OF FOLLOW-UP): A REAL CHALLENGE TO POEM

Attila Csendes, Omar Orellana, Manuel Figueroa, Enrique Lanzarini, Benjamin Panza

Introduction: Laparoscopic Heller Myotomy (LHM) with partial anterior or posterior fundoplication is the standard surgical procedure for treating achalasia patients. The results reported are mainly based on symptomatic evaluations and have less than 5 years of follow-up and none more than ten. Objective: To determine the late results of LHM, performing endoscopic, histologic, manometric, and functional studies in addition to clinical evaluations. Materials and methods: Eighty-nine consecutive patients were included in a prospective study from 1993 to 2008. Inclusion criteria corresponded to achalasia patients with Types I to III (radiological evaluation). Exclusion criteria included patients with grade IV, patients with previous procedures (surgical or endoscopic), or giant hiatal hernia. They were submitted to a radiological evaluation, over two endoscopic procedures with biopsy samples, manometric assessments, and 24-h pH monitoring late after surgery. Results: There was no operative mortality nor postoperative complications. The average hospital stay was two days. Nine patients (10.1%) were lost from follow-up. The mean late follow-up was 17 years (10-26). Visick I and II (success) corresponded to 78.7% of patients and grades III-IV (failure) to 21.3%, mainly due to gastroesophageal reflux disease (GERD). Manometric evaluations showed a significant and permanent decrease in lower esophageal sphincter pressure (LESP). 24-h pH monitoring was normal among Visick I patients and showed pathologic acid reflux in patients with GERD. Two patients (2.5%) developed Barrett's esophagus. Squamous-cell carcinoma (SCC) appeared in three patients (3.7%). Conclusion: LHM controlled symptoms in 79% of achalasia patients very late (17 years) after surgery. This was corroborated by endoscopic, manometric, and functional studies. GERD symptoms developed in 18.7% and SCC in 3.7% in previously asymptomatic patients. Endoscopic surveillance at regular intervals is recommended for all patients who have had surgery. These very long-term results are a real challenge to POEM endoscopic treatment. Unique Identifying Registration Number 3743.

SERVICIO DERMATOLOGÍA

REV CHILENA INFECTOL. 2022 JUN;39(3):349-353. DOI: 10.4067/S0716-10182022000200349.

CROMOBLASTOMICOSIS. PRIMER CASO ALÓCTONO TRATADO EN CHILE

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Chromoblastomycosis is a fungal infection of the skin and subcutaneous tissue, of chronic evolution, caused by dematiaceous fungi. The disease occurs worldwide, mainly in tropical and subtropical regions, but in regions like Chile there is only one report of a human case more than 30 years ago. We present the case of a 46-year-old Haitian man, resident in Chile, with verrucous plaques in the right anterior tibial area of one year of evolution. The diagnosis of chromoblastomycosis was confirmed when muriform cells and dematiaceous colonies were observed in the histopathological analysis and the direct microscopy, respectively. After six months of treatment with systemic antimycotics and cryotherapy, complete remission of the lesions was achieved.

REV MED CHIL. 2022 FEB;150(2):256-260. DOI: 10.4067/S0034-98872022000200256.

PUSTULOSIS AMICROBIANA DE LOS PLIEGUES. INFORME DE DOS CASOS

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Amicrobial Pustulosis of the Folds is a relapsing, chronic and rare neutrophilic dermatosis, characterized by papulopustular, eczematous and aseptic lesions on skin folds. This disorder usually occurs predominantly in females (30 years of age average) with a history of an autoimmune disorder, especially systemic lupus erythematosus. There is no standard therapy, but systemic corticosteroids, alone or in combination with other immunosuppressive drugs, are usually the first-line therapy. We report two females aged 37 and 20 years with the disease but without associated autoimmune diseases. They were successfully treated with non-steroidal treatments.

CENTRO DE IMAGENOLOGÍA

J ANAT. 2022 DEC 30. DOI: 10.1111/JOA.13813.

NEW INSIGHTS INTO THE VARIABILITY OF UPPER AIRWAY MORPHOLOGY IN MODERN HUMANS

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The biological adaptation of the human lineage to its environment is a recurring question in paleoanthropology. Particularly, how eco-geographic factors (e.g., environmental temperature and humidity) have shaped upper airway morphology in hominins have been subject to continuing debate. Nasal shape is the result of many intertwined factors that include, but are not limited to, genetic drift, sexual selection, or adaptation to climate. A quantification of nasal airway (NA) morphological variation in modern human populations is crucial to better understand these multiple factors. In the present research, we study 195 in vivo CT scans of adult individuals collected in five different geographic areas (Chile, France, Cambodia, Russia, and South Africa). After segmentation of the nasal airway, we reconstruct 3D meshes that are analyzed with a landmark-free geometric morphometrics method based on surface deformation. Our results highlight subtle but statistically significant morphological differences between our five samples. The two morphologically closest groups are France and Russia, whose NAs are longer and narrower, with an important protrusion of the supero-anterior part. The Cambodian sample is the most morphologically distinct and clustered sample, with a mean NA that is wider and shorter. On the contrary, the Chilean sample form the most scattered cluster with the greatest intra-population variation. The South African sample is morphologically close to the Cambodian sample, but also partially overlaps the French and Russian variation. Interestingly, we record no correlation between NA volume and geographic groups, which raises the question of climate-related metabolic demands for oxygen consumption. The other factors of variation (sex and age) have no influence on the NA shape in our samples. However, NA volume varies significantly according both to sex and age: it is higher in males than in females and tends to increase with age. In contrast, we observe no effect of temperature or humidity on NA volume. Finally, we highlight the important influence of asymmetries related to nasal septum deviations in NA shape variation.

MEDICINE (BALTIMORE). 2022 SEP 9;101(36):E30216. DOI: 10.1097/MD.0000000000030216.

ETHNICITY INFLUENCES PHENOTYPE AND CLINICAL OUTCOMES: COMPARING A SOUTH AMERICAN WITH A NORTH AMERICAN INFLAMMATORY BOWEL DISEASE COHORT

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Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn disease (CD), has emerged as a global disease with an increasing incidence in developing and newly industrialized regions such as South America. This global rise offers the opportunity to explore the differences and similarities in disease presentation and outcomes across different genetic backgrounds and geographic locations. Our study includes 265 IBD patients. We performed an exploratory analysis of the databases of Chilean and North American IBD patients to compare the clinical phenotypes between the cohorts. We employed an unsupervised machine-learning approach using principal component analysis, uniform manifold approximation, and projection, among others, for each disease. Finally, we predicted the cohort (North American vs Chilean) using a random forest. Several unsupervised machine learning methods have separated the 2 main groups, supporting the differences between North American and Chilean patients with each disease. The variables that explained the loadings of the clinical metadata on the principal components were related to the therapies and disease extension/location at diagnosis. Our random forest models were trained for cohort classification based on clinical characteristics, obtaining high accuracy (0.86 = UC; 0.79 = CD). Similarly, variables related to therapy and disease extension/location had a high Gini index. Similarly, univariate analysis showed a later CD age at diagnosis in Chilean IBD patients (37 vs 24; P = .005). Our study suggests a clinical difference between North American and Chilean IBD patients: later CD age at diagnosis with a predominantly less aggressive phenotype (39% vs 54% B1) and more limited disease, despite fewer biological therapies being used in Chile for both diseases.

J MED RADIAT SCI. 2022 DEC 11. DOI: 10.1002/JMRS.639.

COMPARISON OF VIRTUAL REALITY AND PHYSICAL SIMULATION TRAINING IN FIRST-YEAR RADIOGRAPHY STUDENTS IN SOUTH AMERICA

David Rowe, Alejandra Garcia, Benito Rossi

Introduction: The aim of this study was to comparatively evaluate the learning outcomes achieved by first-year radiography students educated with either virtual reality (VR) simulation training or physical simulation training. The implementation of VR has been proposed to enhance learning in radiography students and provide a more effective and efficient approach to simulation. However, the learning outcomes achieved with this approach have not been widely investigated. Methods: Through stratified randomisation, 188 radiography students were allocated to one of two matched groups: a VR group (using Virtual Medical Coaching's Radiography simulation) and a physical simulation group (using Philips' X-ray equipment). Both groups were taught 31 radiography views over one 25-week semester. Both groups were assessed in an Objective Structured Clinical Examination (OSCE), using actors as patients in a physical

X-ray environment. Assessment was conducted by assigning objective count scores for five assessment criteria. Results: The VR group achieved shorter OSCE duration and fewer errors in moving equipment and patient positioning: these results were statistically significant ($P < 0.00$). There was no significant difference in the frequency of errors in radiographic exposure setting between the VR and the physical simulation group. The current findings concur with the limited number of published studies concerning VR simulation in radiography. Conclusions: The results of this study demonstrated superior effectiveness and efficiency in the VR group. This provides preliminary evidence to introduce VR simulation in the host institution and provide evidence that it may be possible to replace the use of physical simulation across other years of the degree. Further research investigating these possibilities is warranted.

J CLIN MED. 2022 APR 1;11(7):1970. DOI: 10.3390/JCM11071970.

PLASMA THALLIUM CONCENTRATION, KIDNEY FUNCTION, NEPHROTOXICITY AND GRAFT FAILURE IN KIDNEY TRANSPLANT RECIPIENTS

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The nephrotoxic effects of heavy metals have gained increasing scientific attention in the past years. Recent studies suggest that heavy metals, including cadmium, lead, and arsenic, are detrimental to kidney transplant recipients (KTR) even at circulating concentrations within the normal range, posing an increased risk for graft failure. Thallium is another highly toxic heavy metal, yet the potential consequences of the circulating thallium concentrations in KTR are unclear. We measured plasma thallium concentrations in 672 stable KTR enrolled in the prospective TransplantLines Food and Nutrition Biobank and Cohort Study using inductively coupled plasma mass spectrometry. In cross-sectional analyses, plasma thallium concentrations were positively associated with kidney function measures and hemoglobin. We observed no associations of thallium concentration with proteinuria or markers of tubular damage. In prospective analyses, we observed no association of plasma thallium with graft failure and mortality during a median follow-up of 5.4 [interquartile range: 4.8 to 6.1] years. In conclusion, in contrast with other heavy metals such as lead, cadmium, and arsenic, there is no evidence of tubular damage or thallium nephrotoxicity for the range of circulating thallium concentrations observed in this study. This is further evidenced by the absence of associations of plasma thallium with graft failure and mortality in KTR.

DEPARTAMENTO DE MEDICINA

BANCO DE SANGRE

INT J MOL SCI. 2022 AUG 18;23(16):9306. DOI: 10.3390/IJMS23169306.

TNF-A AFFECTS SIGNATURE CYTOKINES OF TH1 AND TH17 T CELL SUBSETS THROUGH DIFFERENTIAL ACTIONS ON TNFR1 AND TNFR2

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Tumor necrosis factor (TNF)-α is a pleiotropic cytokine implicated in the etiology of several autoimmune diseases, including rheumatoid arthritis (RA). TNF-α regulates diverse effector functions through the activation of TNF-α receptor (TNFR)1 and TNFR2. Although the detrimental role of this cytokine has been addressed in distinct disease settings, the effects of TNF-α on cytokine production by isolated CD4+ T helper type 1 (Th1) and Th17 cells, two T cell subpopulations that contribute to the pathogenesis of RA, have not been completely elucidated. Here, we show that TNF-α promotes a reduction and expansion in the frequency of both T cell subsets producing IFN-γ and IL-17, respectively. Selective blockade of TNFR1 or TNFR2 on Th1 and Th17 cells revealed that TNFR2 mediates the decrease in IFN-γ production, while signaling through both receptors augments IL-17 production. We also demonstrate that Th1, but not Th17 cells from RA patients present lower levels of TNFR1 compared to healthy controls, whereas TNFR2 expression on both T cell types is similar between patients and controls. Since TNF-α receptors levels in RA patients are not significantly changed by the therapeutic blockade of TNF-α, we propose that targeting TNFR2 may represent an alternative strategy to normalize the levels of key cytokines that contribute to RA pathogenesis.

INT J MOL SCI. 2022 JUN 21;23(13):6882. DOI: 10.3390/IJMS23136882.

HAPTOGLOBIN INDUCES A SPECIFIC PROTEOMIC PROFILE AND A MATURE-ASSOCIATED PHENOTYPE ON PRIMARY HUMAN MONOCYTE-DERIVED DENDRITIC CELLS

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Damage-associated molecular patterns (DAMPs) play a critical role in dendritic cells (DCs) ability to trigger a specific and efficient adaptive immune response for different physiological and pathological scenarios. We have previously identified constitutive DAMPs (HMGB1 and Calreticulin) as well as new putative inducible DAMPs such as Haptoglobin (HP), from a therapeutically used heat shock-conditioned melanoma cell lysate (called TRIMEL). Remarkably, HP was shown to be the most abundant protein in the proteomic profile of heat shock-conditioned TRIMEL samples. However, its relative contribution to the observed DCs phenotype has not been

fully elucidated. Human DCs were generated from monocytes isolated from PBMC of melanoma patients and healthy donors. DC lineage was induced with rhIL-4 and rhGM-CSF. After additional stimulation with HP, the proteome of these HP-stimulated cells was characterized. In addition, DCs were phenotypically characterized by flow cytometry for canonical maturation markers and cytokine production. Finally, in vitro transmigration capacity was assessed using Transwell plates. Our results showed that the stimulation with HP was associated with the presence of exclusive and higher relative abundance of specific immune-; energy production-; lipid biosynthesis-; and DAMPs-related proteins. Importantly, HP stimulation enhanced the expression of specific DC maturation markers and pro-inflammatory and Th1-associated cytokines, and an in vitro transmigration of primary human DCs. Taken together, these data suggest that HP can be considered as a new inducible DAMP with an important role in in vitro DC activation for cancer immunotherapy.

ENDOCRINOLOGÍA Y DIABETES

FEBS LETT. 2022 DEC 15. DOI: 10.1002/1873-3468.14561.

A CLINICAL MUTATION IN GLUCOKINASE CAUSING MATURITY-ONSET DIABETES IN THE YOUNG TYPE 2 INCREASES ENZYME ACTIVITY

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Glucokinase (GCK) is the pancreatic β-cell glucose sensor, and its kinetics are key to that purpose. A slow transition step, displayed as non-hyperbolic kinetics, and a low affinity for glucose characterize GCK. Mutations in GCK associated with maturity-onset diabetes of the young type 2 (MODY2) previously described reduce the functionality of the human pancreatic β-cell, leading to diabetic clinical phenotypes. We present a kinetic characterization of the G448D mutation identified in a MODY2 patient, which is one of the first mutations to exhibit increased functionality. This mutant displays increased activity, high affinity for both Mg2+ -ATP and glucose, hyperbolic kinetics and increased phosphorylation potential. Hyperbolic kinetics and assays in the presence of glycerol indicate that G448D lacks the slow transition step crucial for the pancreatic β-cell glucose sensor function.

ARCH ENDOCRIN METAB. 2023 JAN 17;2359-3997000000580. DOI: 10.20945/2359-3997000000580.

CLINICAL AND HISTOPATHOLOGICAL FEATURES OF FOLLICULAR THYROID CANCER IN CHILE

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Objective: Follicular thyroid carcinoma (FTC) is less frequent but has a worse prognosis than papillary carcinoma. The available evidence on pre-operative characteristics of FTC is controversial. Our objective was to characterize the clinical, ultrasound and histopathological presentation of FTC patients treated Chile. Subjects and methods: Retrospective analysis of 97 patients treated for FTC in 6 large centers in Chile. We analyzed their ultrasonographic features and classified the nodules according to ATA risk of malignancy and TI-RADS score, as well as the cytological findings according to the Bethesda system. We described their clinical and histopathological findings at diagnosis and classified their risk of recurrence and mortality according to ATA 2015 recurrence risk category and the eighth edition of the AJCC/UICC staging system, respectively. Results: Median age was 48 years and 73.2% were females. The median diameter was 38.8 mm; only 9.5% of them were microtumors. According to ATA risk of malignancy, 86% of the nodules were low or intermediate suspicious, while 78% were category 3 or 4A nodules according to the TI-RADS. Regarding the Bethesda system, 65.9% had indeterminate cytology (20.6% category III and 45.3% category IV). At histological examination, most were minimally-invasive and angio-invasive tumors with less than 4 foci (54.7% and 28.4% respectively). More than 90% of FTC were unifocal and there was no lymphovascular or extrathyroidal invasion or lymph node involvement. Four patients (4.1%) had distant metastases at diagnosis. Most patients (95%) had stage I or II disease according to the AJCC/UICC staging system, while the risk of recurrence was low at 51.5% when using the ATA risk of recurrence scale. Conclusion: At diagnosis, most FTCs were nodules of low or intermediate suspicion at ultrasound, nearly two thirds had indeterminate cytology according to the Bethesda system, and nearly 50% of them were of low risk of recurrence.

GASTROENTEROLOGÍA

CAN J GASTROENTEROL HEPATOL. 2022 SEP 26;2022:6470847. DOI: 10.1155/2022/6470847. ECOLLECTION 2022.

AUTOIMMUNE HEPATITIS WITH ACUTE PRESENTATION: CLINICAL, BIOCHEMICAL, AND HISTOLOGICAL FEATURES OF 126 PATIENTS

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Introduction: Autoimmune hepatitis (AIH) is a chronic liver disease with a relevant inflammatory component and an unknown etiology. Evidence for clinical characteristics and risk factors in large cohorts of patients with acute AIH (AAIH) is lacking. We clinically characterized patients with AAIH, the prevalence of a combined adverse outcome (death or liver transplantation (LT)), and its risk factors. Methods: A retrospective study of adult patients diagnosed with AAIH at three centers (Santiago, Chile; 2000-2018) was

conducted. Clinical and laboratory characteristics were obtained. A liver biopsy was performed for all patients. Descriptive statistics and logistic regression models were used. Results: A total of 126 patients were admitted; 77% were female, 33 (26.2%) had a severe presentation, and 14 (11.1%) had a fulminant presentation. Overall, 24 patients (19.0%) lacked typical autoantibodies, and 26.2% had immunoglobulin G levels in the normal range. The most frequent histological findings were plasma cells (86.5%), interface hepatitis (81.7%), and chronic hepatitis (81.0%). Rosettes were uncommon (35.6%). Advanced fibrosis was present in 27% of patients. Combined adverse outcomes occurred in 7.9% of cases, all fulminant with histological cholestasis. Alkaline phosphatase, bilirubin, and prothrombin less than 50% were independent risk factors for in-hospital death or LT (p value <0.05). Although corticosteroid treatment was associated with better outcomes (OR 0.095, p value = 0.013), more severe patients were less likely to receive this therapy. Discussion. In this large cohort of patients with AAIH, clinical characteristics differ from those reported in patients with chronic AIH. Fulminant hepatitis, histological cholestasis, alkaline phosphatase, bilirubin, and prothrombin were associated with death/LT.

GASTROENTEROL HEPATOL. 2022 JAN;45(1):66-76. DOI: 10.1016/J.GASTROHEP.2021.02.022.

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

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

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

ANIMALS (BASEL). 2022 JUN 27;12(13):1645. DOI: 10.3390/ANI12131645.

ELUCIDATING THE ROLE OF INNATE AND ADAPTIVE IMMUNE RESPONSES IN THE PATHOGENESIS OF CANINE CHRONIC INFLAMMATORY ENTEROPATHY-A SEARCH FOR POTENTIAL BIOMARKERS

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Canine chronic inflammatory enteropathy (CIE) is one of the most common chronic gastrointestinal diseases affecting dogs worldwide. Genetic and environmental factors, as well as intestinal microbiota and dysregulated host immune responses, participate in this multifactorial disease. Despite advances explaining the immunological and molecular mechanisms involved in CIE development, the exact pathogenesis is still unknown. This review compiles the latest reports and advances that describe the main molecular and cellular mechanisms of both the innate and adaptive immune responses involved in canine CIE pathogenesis. Future studies should focus research on the characterization of the immunopathogenesis of canine CIE in order to advance the establishment of biomarkers and molecular targets of diagnostic, prognostic, or therapeutic utility.

BMC MED. 2022 JUN 9;20(1):216. DOI: 10.1186/S12916-022-02406-0.

SEROLOGICAL STUDY OF CORONAVAC VACCINE AND BOOSTER DOSES IN CHILE: IMMUNOGENICITY AND PERSISTENCE OF ANTI-SARS-COV-2 SPIKE ANTIBODIES

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Background: Chile was severely affected by COVID19 outbreaks but was also one of the first countries to start a nationwide program to vaccinate against the disease. Furthermore, Chile became one of the fastest countries to inoculate a high percentage of the target population and implemented homologous and heterologous booster schemes in late 2021 to prevent potential immunological waning. The aim of this study is to compare the immunogenicity and time course of the humoral response elicited by the CoronaVac vaccine in combination with homologous versus heterologous boosters. Methods: We compared the immunogenicity of two doses of CoronaVac and BNT162b2 vaccines and one homologous or heterologous booster through an ELISA assay directed against the ancestral spike protein of SARS-CoV-2. Sera were collected from individuals during the vaccination schedule and throughout the implementation of homologous and heterologous booster programs in Chile. Results: Our findings demonstrate that a two-dose vaccination scheme with CoronaVac induces lower levels of anti-SARS-CoV-2 spike antibodies than BNT162b2 in a broad age range (median age 42 years;

interquartile range (IQR) 27-61). Furthermore, antibody production declines with time in individuals vaccinated with CoronaVac and less noticeably, with BNT162b2. Analysis of booster schemes revealed that individuals vaccinated with two doses of CoronaVac generate immunological memory against the SARS-CoV-2 ancestral strain, which can be re-activated with homologous or heterologous (BNT162b2 and ChAdOx1) boosters. Nevertheless, the magnitude of the antibody response with the heterologous booster regime was considerably higher (induction fold BNT162b2: 11.2x; ChAdoX1; 12.4x; CoronaVac: 6.0x) than the responses induced by the homologous scheme. Both homologous and heterologous boosters induced persistent humoral responses (median 122 days, IQR (108-133)), although heterologous boosters remained superior in activating a humoral response after 100 days. Conclusions: Two doses of CoronaVac induces antibody titers against the SARS-CoV-2 ancestral strain which are lower in magnitude than those induced by the BNT162b2 vaccine. However, the response induced by CoronaVac can be greatly potentiated with a heterologous booster scheme with BNT162b2 or ChAdOx1 vaccines. Furthermore, the heterologous and homologous booster regimes induce a durable antibody response which does not show signs of decay 3 months after the booster dose.

HEPATOLOGY. 2022 DEC;76(6):1576-1586. DOI: 10.1002/HEP.32572.

LIVER INJURY AFTER SARS-COV-2 VACCINATION: FEATURES OF IMMUNE-MEDIATED HEPATITIS, ROLE OF CORTICOSTEROID THERAPY AND OUTCOME

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Background and aims: A few case reports of autoimmune hepatitis-like liver injury have been reported after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. We evaluated clinical features, treatment response and outcomes of liver injury following SARS-CoV-2 vaccination in a large case series. Approach and results: We collected data from cases in 18 countries. The type of liver injury was assessed with the R-value. The study population was categorized according to features of immune-mediated hepatitis (positive autoantibodies and elevated immunoglobulin G levels) and corticosteroid therapy for the liver injury. We identified 87 patients (63%, female), median age 48 (range: 18-79) years at presentation. Liver injury was diagnosed a median 15 (range: 3-65) days after vaccination. Fifty-one cases (59%) were attributed to the Pfizer-BioNTech (BNT162b2) vaccine, 20 (23%) cases to the Oxford-AstraZeneca (ChAdOX1 nCoV-19) vaccine and 16 (18%) cases to the Moderna (mRNA-1273) vaccine. The liver injury was predominantly hepatocellular (84%) and 57% of patients showed features of immune-mediated hepatitis. Corticosteroids were given to 46 (53%) patients, more often for grade 3-4 liver injury than for grade 1-2 liver injury (88.9% vs. 43.5%, p = 0.001) and more often for patients with than without immune-mediated hepatitis (71.1% vs. 38.2%, p = 0.003). All patients showed resolution of liver injury except for one man (1.1%) who developed liver failure and underwent liver transplantation. Steroid therapy was withdrawn during the observation period in 12 (26%) patients after complete biochemical resolution. None had a relapse during follow-up. Conclusions: SARS-CoV-2 vaccination can be associated with liver injury. Corticosteroid therapy may be beneficial in those with immune-mediated features or severe hepatitis. Outcome was generally favorable, but vaccine-associated liver injury led to fulminant liver failure in one patient.

LIVER INT. 2022 MAR;42(3):607-614. DOI: 10.1111/LIV.15121.

EFFECTS OF IMMUNOSUPPRESSIVE DRUGS ON COVID-19 SEVERITY IN PATIENTS WITH AUTOIMMUNE HEPATITIS

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Background: We investigated associations between baseline use of immunosuppressive drugs and severity of Coronavirus Disease 2019 (COVID-19) in autoimmune hepatitis (AIH). Patients and methods: Data of AIH patients with laboratory confirmed COVID-19 were retrospectively collected from 15 countries. The outcomes of AIH patients who were on immunosuppression at the time of COVID-19 were compared to patients who were not on AIH medication. The clinical courses of COVID-19 were classified as (i)-no hospitalization, (ii)-hospitalization without oxygen supplementation, (iii)-hospitalization with oxygen supplementation by nasal cannula or mask, (iv)-intensive care unit (ICU) admission with non-invasive mechanical ventilation, (v)-ICU admission with invasive mechanical ventilation or (vi)-death and analysed using ordinal logistic regression. Results: We included 254 AIH patients (79.5%, female) with a median age of 50 (range, 17-85) years. At the onset of COVID-19, 234 patients (92.1%) were on treatment with glucocorticoids (n = 156), thiopurines (n = 151), mycophenolate mofetil (n = 22) or tacrolimus (n = 16), alone or in combinations. Overall, 94 (37%) patients were hospitalized and 18 (7.1%) patients died. Use of systemic glucocorticoids (adjusted odds ratio [aOR] 4.73, 95% CI 1.12-25.89) and thiopurines (aOR 4.78, 95% CI 1.33-23.50) for AIH was associated with worse COVID-19 severity, after adjusting for age-sex, comorbidities and presence of cirrhosis. Baseline treatment with mycophenolate mofetil (aOR 3.56, 95% CI 0.76-20.56) and tacrolimus (aOR 4.09, 95% CI 0.69-27.00) were also associated with more severe COVID-19 courses in a smaller subset of treated patients. Conclusion: Baseline treatment with systemic glucocorticoids or thiopurines prior to the onset of COVID-19 was significantly associated with COVID-19 severity in patients with AIH.

LANCET GASTROENTEROL HEPATOL. 2022 JUN;7(6):552-559. DOI: 10.1016/S2468-1253(22)00008-5.

THE ESTABLISHMENT OF PUBLIC HEALTH POLICIES AND THE BURDEN OF NON-ALCOHOLIC FATTY LIVER DISEASE IN THE AMERICAS

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Non-alcoholic fatty liver disease (NAFLD) affects 20-25% of the general population and is associated with morbidity, increased mortality, and elevated health-care costs. Most NAFLD risk factors are modifiable and, therefore, potentially amenable to being reduced by public health policies. To date, there is no information about NAFLD-related public health policies in the Americas. In this study, we analysed data from 17 American countries and found that none have established national public health policies to decrease NAFLD-related burden. There is notable heterogeneity in the existence of public health policies to prevent NAFLD-related conditions. The most common public health policies were related to diabetes (15 [88%] countries), hypertension (14 [82%] countries), cardiovascular diseases (14 [82%] countries), obesity (nine [53%] countries), and dyslipidaemia (six [35%] of countries). Only seven (41%) countries had a registry of the burden of NAFLD, and efforts to raise awareness in the Americas were scarce. The implementation of public health policies are urgently needed in the Americas to decrease the burden of NAFLD.

FRONT IMMUNOL. 2022 OCT 10;13:954869. DOI: 10.3389/FIMMU.2022.954869. ECOLLECTION 2022.

THE IMMUNE RESPONSE AS A THERAPEUTIC TARGET IN NON-ALCOHOLIC FATTY LIVER DISEASE

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Non-alcoholic fatty liver disease (NAFLD) is a complex and heterogeneous disorder considered a liver-damaging manifestation of metabolic syndrome. Its prevalence has increased in the last decades due to modern-day lifestyle factors associated with overweight and obesity, making it a relevant public health problem worldwide. The clinical progression of NAFLD is associated with advanced forms of liver injury such as fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). As such, diverse pharmacological strategies have been implemented over the last few years, principally focused on metabolic pathways involved in NAFLD progression. However, a variable response rate has been observed in NAFLD patients, which is explained by the interindividual heterogeneity of susceptibility to liver damage. In this scenario, it is necessary to search for different therapeutic approaches. It is worth noting that chronic low-grade inflammation constitutes a central mechanism in the pathogenesis and progression of NAFLD, associated with abnormal composition of the intestinal microbiota, increased lymphocyte activation in the intestine and immune effector mechanisms in liver. This review aims to discuss the current knowledge about the role of the immune response in NAFLD development. We have focused mainly on the impact of altered gut-liver-microbiota axis communication on immune cell activation in the intestinal mucosa and the role of subsequent lymphocyte homing to the liver in NAFLD development. We further discuss novel clinical trials that addressed the control of the liver and intestinal immune response to complement current NAFLD therapies.

PLOS ONE. 2022 NOV 10;17(11):E0271929. DOI: 10.1371/JOURNAL.PONE.0271929. ECOLLECTION 2022.

COLORECTAL CANCER TRENDS IN CHILE: A LATIN-AMERICAN COUNTRY WITH MARKED SOCIOECONOMIC INEQUITIES

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Introduction: Colorectal cancer (CRC) is the third most frequent malignant disease in the world. In some countries with established screening programs, its incidence and mortality have decreased, and survival has improved. Aims: To obtain reliable data about the epidemiology of CRC in Chile, we analyzed the trends in the last ten years and the influence of observable factors on survival, including a nationwide health program for CRC treatment access (GES program). Methods: Publicly available data published by the Ministry of Health and National Institute of Statistics were used. Data were obtained from registries of mortality and hospital discharges, making follow-up of the individuals possible. Crude and age-standardized incidence and mortality rates were calculated, and individual survival was studied by constructing Kaplan-Meier curves. Finally, a Cox statistical model was established to estimate the impact of the observable factors. Results: We found 37,217 newly identified CRC patients between 2008 and 2019 in Chile, corresponding to 103,239 hospital discharges. In the same period, 24,217 people died of CRC. A nearly linear, steady increase in crude incidence, mortality and prevalence was observed. CRC incidence was the lowest in the North of the country, increasing toward the South and reaching a maximum value of 34.6/100,000 inhabitants/year in terms of crude incidence and 20.7/100,000 inhabitants/year in terms of crude mortality in the XII region in 2018. We found that older patients had lower survival rates, as well as men compared to women. Survival was significantly better for patients with private insurance than those under the public insurance system, and the treating hospital also played a significant role in the survival of patients. Patients in the capital region survived longer than those in almost every other part of the country. We found no significant effect on survival associated with the GES program. Conclusions: We found important inequalities in the survival probabilities for CRC patients in Chile. Survival depends mainly on the type of insurance, access to more complex hospitals, and geographical location; all three factors correlated with socioeconomic status of the population. Our work emphasized the need to create specific programs addressing primary causes to decrease the differences in CRC survival.

J MOL MED (BERL). 2022 NOV;100(11):1617-1627. DOI: 10.1007/S00109-022-02244-W.

THE SEROTONIN RECEPTOR 3E VARIANT IS A RISK FACTOR FOR FEMALE IBS-D

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Irritable bowel syndrome (IBS) is a gut-brain disorder of multifactorial origin. Evidence of disturbed serotonergic function in IBS accumulated for the 5-HT3 receptor family. 5-HT3Rs are encoded by HTR3 genes and control GI function, and peristalsis and secretion, in particular. Moreover, 5-HT3R antagonists are beneficial in the treatment of diarrhea predominant IBS (IBS-D). We previously reported on functionally relevant SNPs in HTR3A c.-42C > T (rs1062613), HTR3C p.N163K (rs6766410), and HTR3E c.*76G > A (rs56109847 = rs62625044) being associated with IBS-D, and the HTR3B variant p.Y129S (rs1176744) was also described within the context of IBS. We performed a multi-center study to validate previous results and provide further evidence for the relevance of HTR3 genes in IBS pathogenesis. Therefore, genotype data of 2682 IBS patients and 9650 controls from 14 cohorts (Chile, Germany (2), Greece, Ireland, Spain, Sweden (2), the UK (3), and the USA (3)) were taken into account. Subsequent meta-analysis confirmed HTR3E c.*76G > A (rs56109847 = rs62625044) to be associated with female IBS-D (OR = 1.58; 95% CI (1.18, 2.12)). Complementary expression studies of four GI regions (jejunum, ileum, colon, sigmoid colon) of 66 IBS patients and 42 controls revealed only HTR3E to be robustly expressed. On top, HTR3E transcript levels were significantly reduced in the sigma of IBS patients (p = 0.0187); more specifically, in those diagnosed with IBS-D (p = 0.0145). In conclusion, meta-analysis confirmed rs56109847 = rs62625044 as a risk factor for female IBS-D. Expression analysis revealed reduced HTR3E levels in the sigmoid colon of IBS-D patients, which underlines the relevance of HTR3E in the pathogenesis of IBS-D.

TURK J GASTROENTEROL. 2022 AUG;33(8):704-709. DOI: 10.5152/TJG.2022.21864.

NEOSTIGMINE® IMPROVES PANCREATIC DUCT VISUALIZATION IN MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY AND COULD BE A CHEAP ALTERNATIVE FOR SECRETIN

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Background: To determine the effect of intramuscular administration of Neostigmine® on the visualization of the pancreatic duct on magnetic resonance cholangiopancreatography in patients with recurrent acute pancreatitis or abdominal pain. Methods: We reviewed patients undergoing magnetic resonance cholangiopancreatography followed by a Neostigmine®-enhanced magnetic resonance cholangiopancreatography. Patients with a history of recurrent acute pancreatitis or abdominal pain who had a magnetic resonance cholangiopancreatography where the pancreatic duct was not entirely seen, were selected to undergo a second magnetic resonance cholangiopancreatography 40 minutes after 0.5 mg Neostigmine®. Images were analyzed by 2 radiologists. The diameter of the pancreatic duct was measured in the head, body, and tail of the pancreas on the baseline images and after Neostigmine®. Results: Ten patients were included, with a median age of 33 years (range 15-61). The maximum diameter of the pancreatic duct increased significantly after Neostigmine® administration in all patients, from 1.84 ± 0.98 to 3.41 ± 1.27 mm in the head, 1.34 ± 0.42 mm to 2.5 ± 0.49 mm in the body and 0.72 ± 0.52 mm to 1.78 ± 0.43 mm in the tail (mean ± SD, P < .0001). Neostigmine® helped to provide better detail of the pancreatic duct anatomy in 4 patients. In 2 patients we confirmed pancreas divisum, in another the Santorini duct was not seen on the baseline images but it was clearly visualized after Neostigmine®, and in the fourth patient, Neostigmine® improved visualization of multiple pancreatic duct stenosis. Conclusion: Neostigmine®-magnetic resonance cholangiopancreatography significantly increases the diameter of the pancreatic duct, allowing an accurate morphological evaluation. It could be a cheap alternative to secretin, which is expensive and hardly available.

JHEP REP. 2022 DEC 5;5(2):100644. DOI: 10.1016/J.JHEPR.2022.100644. ECOLLECTION 2023 FEB.

AFP SCORE AND METROTICKET 2.0 PERFORM SIMILARLY AND COULD BE USED IN A "WITHIN-ALL" CLINICAL DECISION TOOL

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Background & aims: Two recently developed composite models, the alpha-fetoprotein (AFP) score and Metroticket 2.0, could be used to select patients with hepatocellular carcinoma (HCC) who are candidates for liver transplantation (LT). The aim of this study was to compare the predictive performance of both models and to evaluate the net risk reclassification of post-LT recurrence between them using each model's original thresholds. Methods: This multicenter cohort study included 2,444 adult patients who underwent LT for HCC in 47 centers from Europe and Latin America. A competing risk regression analysis estimating sub-distribution hazard ratios (SHRs) and 95% CIs for recurrence was used (Fine and Gray method). Harrell's adapted c-statistics were estimated. The net reclassification index for recurrence was compared based on each model's original thresholds. Results: During a median follow-up of 3.8 years, there were 310 recurrences and 496 competing events (20.3%). Both models predicted recurrence, HCC survival and survival better than Milan

criteria (p <0.0001). At last tumor reassessment before LT, c-statistics did not significantly differ between the two composite models, either as original or threshold versions, for recurrence (0.72 vs. 0.68; p = 0.06), HCC survival, and overall survival after LT. We observed predictive gaps and overlaps between the model's thresholds, and no significant gain on reclassification. Patients meeting both models ("within-ALL") at last tumor reassessment presented the lowest 5-year cumulative incidence of HCC recurrence (7.7%; 95% CI 5.1-11.5) and higher 5-year post-LT survival (70.0%; 95% CI 64.9-74.6). Conclusions: In this multicenter cohort, Metroticket 2.0 and the AFP score demonstrated a similar ability to predict HCC recurrence post-LT. The combination of these composite models might be a promising clinical approach. Impact and implications: Composite models were recently proposed for the selection of liver transplant (LT) candidates among individuals with hepatocellular carcinoma (HCC). We found that both the AFP score and Metroticket 2.0 predicted post-LT HCC recurrence and survival better than Milan criteria; the Metroticket 2.0 did not result in better reclassification for transplant selection compared to the AFP score, with predictive gaps and overlaps between the two models; patients who met low-risk thresholds for both models had the lowest 5-year recurrence rate. We propose prospectively testing the combination of both models, to further optimize the LT selection process for candidates with HCC.

J HEPATOBILIARY PANCREAT SCI. 2023 MAR;30(3):325-337. DOI: 10.1002/JHBP.1201.

INTERNATIONAL MULTIDISCIPLINARY SURVEY ON THE INITIAL MANAGEMENT OF ACUTE PANCREATITIS: PERSPECTIVE OF POINT-OF-CARE SPECIALISTS FOCUSED ON DAILY PRACTICE

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Background: The initial management of patients with acute pancreatitis impacts both morbidity and mortality. Point-of-care decisions have been reported to differ from clinical guideline recommendations. Methods: An online anonymous questionnaire was distributed through scientific associations and social media using REDCap. Multivariable logistic regression was used to identify the characteristics of participants associated with compliance with the recommendations. Results: A total of 1054 participants from 94 countries completed the questionnaire; median age (IQR) was 39 (32-47) years; 30.7% were women. Among the participants, 37% opted for nonmoderate flow of i.v. fluid, 31% for fluid type other than Ringer's lactate; 73.4% were in favor of nil per os to patients who could eat, 75.5% for other than enteral feeding to patients with oral intolerance; 15.5% used prophylactic antibiotic in patients with severe acute pancreatitis, 34.1% in necrotizing acute pancreatitis, and 27.4% in patients with systemic inflammatory response syndrome; 27.8% delayed cholecystectomy after biliary acute pancreatitis. Participants with publications in PubMed on acute pancreatitis showed better compliance (OR, 1.62; 95% CI: 1.15-2.32; P = .007) with recommendations of the clinical guidelines. Conclusions: Feeding and nutrition require the greatest improvement efforts, but also the use of prophylactic antibiotics and timing of cholecystectomy should be improved.

GASTROENTEROL HEPATOL. 2022 OCT 13;S0210-5705(22)00233-3. DOI: 10.1016/J.GASTROHEP.2022.10.007.

GASTROINTESTINAL SYMPTOMS AND COMPLICATIONS IN PATIENTS HOSPITALIZED DUE TO COVID-19, AN INTERNATIONAL MULTICENTRE PROSPECTIVE COHORT STUDY (TIVURON PROJECT)

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Background: Retrospective studies suggest that coronavirus disease (COVID-19) commonly involves gastrointestinal (GI) symptoms and complications. Our aim was to prospectively evaluate GI manifestations in patients hospitalized for COVID-19. Methods: This international multicentre prospective cohort study recruited COVID-19 patients hospitalized at 31 centres in Spain, Mexico, Chile, and Poland, between May and September 2020. Patients were followed-up until 15 days post-discharge and completed comprehensive questionnaires assessing GI symptoms and complications. A descriptive analysis as well as a bivariate and multivariate analysis were performer using binary logistic regression. p<0.05 was considered significant. Results: Eight hundred twenty-nine patients were enrolled; 129 (15.6%) had severe COVID-19, 113 (13.7%) required ICU admission, and 43 (5.2%) died. Upon admission, the most prevalent GI symptoms were anorexia (n=413; 49.8%), diarrhoea (n=327; 39.4%), nausea/vomiting (n=227; 27.4%), and abdominal pain (n=172; 20.7%), which were mild/moderate throughout the disease and resolved during follow-up. One-third of patients exhibited liver injury. Non-severe COVID-19 was associated with ≥2 GI symptoms upon admission (OR 0.679; 95% CI 0.464-0.995; p=0.046) or diarrhoea during hospitalization (OR 0.531; 95% CI 0.328-0.860; p=0.009). Multivariate analysis revealed that worse hospital outcomes were not independently associated with liver injury or GI symptoms. Conclusion: GI symptoms were more common than previously documented, and were mild, rapidly resolved, and not independently associated with COVID-19 severity. Liver injury was a frequent complication in hospitalized patients not independently associated with COVID-19 severity.

CUIDADOS PALIATIVOS

MULT SCLER RELAT DISORD. 2022 MAY;61:103751. DOI: 10.1016/J.MSARD.2022.103751.

DECISION MAKING PROCESS IN MULTIPLE SCLEROSIS: AN ARGENTINE PILOT STUDY

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Background: There is scarce information regarding the decision-making process (DMP) in people with MS (PwMS) from Latin America. Objective: To evaluate the DMP in Argentinean PwMS and to assess its relationship with patient preferences, and clinical-demographic characteristics. Methods: PwMS from the patient organization Esclerosis Múltiple Argentina (n = 1275) were invited to participate in a self-administered web-based survey. Participants were asked to provide clinical-demographic information and to complete a questionnaire on their perceptions about the information provided by their physician, the Control Preference Scale, and the Satisfaction with the Decisions and Care Questionnaire, and were inquired on their preferred sources of information about MS. Results: The survey was completed by 379 PwMS. Most were females (67%); mean age: 40.3 (SD = 11.1) years; mean disease duration: 7.9 (SD = 7.2) years. Patients' decisional control preferred role was active in 47%, shared in 27%, and passive in 26%. A moderate concordance (weighted kappa 0.55) was observed between patients' preferences and self-reported DMP. Seventy-two percent participated in the DMP according to their preferences (concordance rates: active 66%, shared 87%, passive 51%). Most (83%) declared receiving information from their neurologists, matching their preferences (94%). Conclusions: Argentinian PwMS have distinctive preferences regarding information management and decision making.

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

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

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

GENÉTICA

FRONT GENET. 2022 APR 12;13:652454. DOI: 10.3389/FGENE.2022.652454. ECOLLECTION 2022.

VARIABILITY IN PHELAN-MCDERMID SYNDROME IN A COHORT OF 210 INDIVIDUALS

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Phelan-McDermid syndrome (PMS, OMIM# 606232) results from either different rearrangements at the distal region of the long arm of chromosome 22 (22q13.3) or pathogenic sequence variants in the SHANK3 gene. SHANK3 codes for a structural protein that plays a central role in the formation of the postsynaptic terminals and the maintenance of synaptic structures. Clinically, patients with PMS often present with global developmental delay, absent or severely delayed speech, neonatal hypotonia, minor dysmorphic features, and autism spectrum disorders (ASD), among other findings. Here, we describe a cohort of 210 patients with genetically confirmed PMS. We observed multiple variant types, including a significant number of small deletions (<0.5 Mb, 64/189) and SHANK3 sequence variants (21 cases). We also detected multiple types of rearrangements among microdeletion cases, including a significant number with post-zygotic mosaicism (9.0%, 17/189), ring chromosome 22 (10.6%, 20/189), unbalanced translocations (de novo or inherited, 6.4%), and additional rearrangements at 22q13 (6.3%, 12/189) as well as other copy number variations in other chromosomes, unrelated to 22q deletions (14.8%, 28/189). We compared the clinical and genetic characteristics among patients with different sizes of deletions and with SHANK3 variants. Our findings suggest that SHANK3 plays an important role in this syndrome but is probably not uniquely responsible for all the spectrum features in PMS. We emphasize that only an adequate combination of different molecular and cytogenetic approaches allows an accurate genetic diagnosis in PMS patients. Thus, a diagnostic algorithm is proposed.

FRONT GENET. 2022 DEC 8;13:1053559. DOI: 10.3389/FGENE.2022.1053559. ECOLLECTION 2022.

OPPORTUNITIES AND CHALLENGES FOR NEWBORN SCREENING AND EARLY DIAGNOSIS OF RARE DISEASES IN LATIN AMERICA

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Rare diseases (RDs) cause considerable death and disability in Latin America. Still, there is no consensus on their definition across the region. Patients with RDs face a diagnostic odyssey to find a correct diagnosis, which may last many years and creates a burden for caregivers, healthcare systems, and society. These diagnostic delays have repercussions on the health and economic burden created by RDs and continue to represent an unmet medical need. This review analyzes barriers to the widespread adoption of newborn screening (NBS) programs and early diagnostic methods for RDs in Latin America and provides recommendations to achieve this critical objective. Increasing the adoption of NBS programs and promoting early diagnosis of RDs are the first steps to improving health outcomes for patients living with RDs. A coordinated, multistakeholder effort from leaders of patient organizations, government, industry, medical societies, academia, and healthcare services is required to increase the adoption of NBS programs. Patients' best interests should remain the guiding principle for decisions regarding NBS implementation and early diagnosis for RDs.

EPIGENOMICS. 2022 SEP;14(17):987-993. DOI: 10.2217/EPI-2022-0180.

PEMT VARIANTS ARE ASSOCIATED WITH NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN CHILE

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Aim: To assess the association between PEMT variants and nonsyndromic cleft lip with or without cleft palate in Chile and the effects of these variants on global DNA methylation. Subjects & methods: The authors obtained genotypes for nine variants from 247 cases and 453 controls for genotype-phenotype associations. The effect of significant polymorphisms on global DNA methylation (percentage of long interspersed element-1 methylation) was evaluated in a subsample of 95 controls. Results: After multiple comparison corrections, variants rs7649 and rs4646409 were associated with nonsyndromic cleft lip with or without cleft palate. Carriers of risk alleles presented lower DNA methylation levels than noncarriers. Conclusion: According to functional analysis for risk variants from previous reports, the authors infer that a decrease of methyl group availability is occurring in affected subjects.

REPROD SCI. 2022 OCT;29(10):2921-2926. DOI: 10.1007/S43032-022-00957-4.

VITAMIN B12 TRANSPORT GENES AND NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN CHILE

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The aims of this study were to assess the association between polymorphisms within genes involved in vitamin B12 transport and nonsyndromic cleft lip with or without cleft palate (NSCL/P) and global DNA methylation in Chile. From 247 cases and 453 controls, we obtained variant genotypes for CBLIF, CUBN, AMN, ABCC1, CD320, and TCN2 from a single nucleotide polymorphisms array. Global DNA methylation in 95 controls was obtained through LINE-1 methylation. After multiple comparison corrections, only rs780807 in CUBN remains associated with NSCL/P at dominant model (OR 0.564, p-value = 0.0006, q-value = 0.0450). Carriers of protective allele showed lower levels of DNA methylation than non-carriers (p = 0.0259). Further studies are necessary in order to explain relations with the phenotype and DNA methylation due to the absence of functional evidence for rs780807 in CUBN.

BIRTH DEFECTS RES. 2022 APR;114(7):259-266. DOI: 10.1002/BDR2.1994.

NEURAL TUBE DEFECTS PREVALENCE DOES NOT INCREASE AFTER MODIFICATION OF THE FOLIC ACID FORTIFICATION PROGRAM IN CHILE

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Background: In 2000, Chile's Ministry of Health mandated fortification of wheat flour with folic acid at a concentration of 2.2 mg/kg to prevent neural tube defects (NTDs), resulting in a 50% reduction in NTD prevalence. Concerns about possible collateral effects of high folic acid intake led, in 2009, to decrease the folic acid fortification to 1.8 mg/kg of flour. Our study evaluated the impact of this modification on the prevalence of NTDs in Santiago. Methods: This study measured the prevalence of NTDs in live births and stillbirths born in Santiago. We calculated prevalence ratios (PR) and 95% confidence intervals (CI) between pre-folic acid fortification (1999-2000), post-folic acid fortification (2001-2009), and post-modified folic acid fortification (2010-2015) periods for all NTDs and their specific types. We used chi-square tests to analyze proportions, and a Joinpoint regression to visualize prevalence time trends. Results: The NTD prevalence for the period 2001-2015 was 8.9 per 10,000 births, which represents a 48% reduction (PR = 0.52; 95% CI = 0.45-0.61; p < .001) from the pre-folic acid fortification period. During 2010-2015, the NTD prevalence was 9.5/10,000 births, which was higher, but not statistically significantly different from 2001 to 2009 prevalence of 8.6/10,000 (PR = 1.11; 95% CI = 0.96-1.30, p = .17). Conclusions: Decreasing the concentration of folic acid fortification was not associated with a statistically significant change in the prevalence of NTDs. Mandatory folic acid fortification continues to be a safe and highly effective policy to prevent NTDs. Future studies should evaluate the prevalence of NTDs across Chile and adherence to folic acid fortification mandates.

GERIATRÍA

ACTA PSYCHIATR SCAND. 2022 JUL 5. DOI: 10.1111/ACPS.13468.

EPIDEMIOLOGY OF DELIRIUM IN HOSPITALIZED PATIENTS IN LATIN AMERICA: A SYSTEMATIC REVIEW

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Background: Accurate epidemiological data are essential for the planning of policies aimed at the identification, prevention, and management of delirium. The reported occurrence of delirium in hospitalized patients varies widely among studies, ranging between 5% to more than 80% in the international literature. The exact occurrence in Latin America is not well described. Objective: The aim of this study is to conduct a systematic analysis of the published data on the epidemiology of delirium in hospitalized patients in Latin America. Methods: We conducted a systematic review following PRISMA guidelines. Both MEDLINE and LILACS databases were searched for original research articles reporting the occurrence of delirium among adult hospitalized patients in Latin American countries. Studies including pediatric populations were excluded from this analysis. Two authors independently applied eligibility criteria, assessed quality, and extracted data. The corresponding authors of the original articles were contacted to obtain relevant information about the study when this was not present in the published manuscripts. Results: Seven hundred and eighteen original articles were identified. After screening titles and abstracts, 149 studies were included in the final analysis. The occurrence of delirium varied depending on the clinical scenario: (1) in the general medico-surgical wards, it ranged from 2.1% to 60.4%, (2) in the Intensive Care Units (ICUs), from 9.6% to 94.8%, (3) in the post-operatory population, from 5.45% and 52.3%, and (4) it was found to be between 10.7% and 62% in the emergency department setting. The most used delirium assessment tools were the "Confusion Assessment Method" (CAM; in the general population), and the "Confusion Assessment Method for the ICU" (CAM-ICU). Fourteen out of 149 studies were conducted in clinical settings who actively implemented some form of non-pharmacological delirium prevention bundles, most of them as part of ICU sedation-analgesia protocols. Conclusion: Delirium occurs frequently in hospitalized patients in Latin America throughout a variety of clinical scenarios, including ICU, general wards, post-operatory populations, and among the emergency department setting. The CAM and the CAM-ICU are the most used delirium assessment tools. Bundles of non-pharmacological interventions to prevent delirium are not universally implemented.

AGING CLIN EXP RES. 2022 OCT;34(10):2317-2333. DOI: 10.1007/S40520-022-02190-0.

THE EFFECT OF RAPAMYCIN AND ITS ANALOGUES ON AGE-RELATED MUSCULOSKELETAL DISEASES: A SYSTEMATIC REVIEW

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Background: Preclinical studies have shown a therapeutic role of the mechanistic/mammalian target of rapamycin complex 1 (mTORC1) inhibition with rapamycin and its analogues (rapalogues) on several age-related musculoskeletal disorders (MSKD). However, the applicability to humans of these findings is unknown. Objective: To assess the efficacy of rapalogues on age-related MSKD in humans. Methods: We conducted a systematic review according to the PRISMA guidelines. MEDLINE, EMBase, EMCare, and Cochrane Central Registry of Controlled Trials were searched for original studies examining the effects of rapalogues on outcomes linked to the age-related MSKD in humans. This review is registered in the PROSPERO database (University of New York; registration number CRD42020208167). Results: Fourteen studies met the inclusion criteria and were analyzed. The effect of rapamycin and other rapalogues, including everolimus and temsirolimus, on bone, muscle and joints have been evaluated in humans; however, considerable variability concerning the subjects' age, inclusion criteria, and drug administration protocols was identified. In bone, the use of rapamycin is associated with a decrease in bone resorption markers dependent on osteoclastic activity. In muscle, rapamycin and rapalogues are associated with a reduction in muscle protein synthesis in response to exercise. In the context of rheumatoid arthritis, rapamycin and rapalogues have been associated with clinical improvement and a decrease in inflammatory activity. Conclusion: Although there are studies that have evaluated the effect of rapamycin and rapalogues on MSKD in humans, the evidence supporting its use is still incipient, and the clinical implication of these results on the development of osteoporosis, sarcopenia, or osteosarcopenia has not been studied, opening an interesting field for future research.

ARCH CLIN NEUROPSYCH. 2022 FEB 22;37(3):553-567. DOI: 10.1093/ARCLIN/ACAB080.

WORKING GROUP RECOMMENDATIONS FOR THE PRACTICE OF TELENEUROPSYCHOLOGY IN LATIN AMERICA

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Objective: Teleneuropsychology (teleNP) could potentially expand access to services for patients who are confined, have limited personal access to healthcare, or live in remote areas. The tranexrationale of the COVID-19 pandemic has significantly increased the use of teleNP for cognitive assessments. The main objective of these recommendations is to identify which procedures can be potentially best adapted to the practice of teleNP in Latin America, and thereby facilitate professional decision-making in the region. Method: Steps taken to develop these recommendations included (1) formation of an international working group with representatives

from 12 Latin American countries; (2) assessment of rationale, scope, and objectives; (3) formulation of clinical questions; (4) evidence search and selection; (5) evaluation of existing evidence and summary; and (6) formulation of recommendations. Levels of evidence were graded following the Oxford Centre for Evidence-Based Medicine system. Databases examined included PubMed, WHO-IRIS, WHO and PAHO-IRIS, Índice Bibliográfico Español en Ciencias de la Salud (IBCS), and LILACS. Results: Working group members reviewed 18,400 titles and 422 abstracts and identified 19 articles meeting the criteria for level of evidence, categorization, and elaboration of recommendations. The vast majority of the literature included teleNP tests in the English language. The working group proposed a series of recommendations that can be potentially best adapted to the practice of teleNP in Latin America. Conclusions: There is currently sufficient evidence to support the use of videoconferencing technology for remote neuropsychological assessments. These recommendations will likely contribute to the advancement of teleNP research and practice in the region.

HEMATOLOGÍA

REV MED CHIL. 2022 MAR;150(3):331-338. DOI: 10.4067/S0034-98872022000300331.

MIELOMA MÚLTIPLE EN CHILE. USO DE DROGAS NOVELES EN DOS CENTROS NACIONALES

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Background: The incorporation of novel drugs, such as proteasome inhibitors and immunomodulators, improved considerably the survival of patients with multiple myeloma. Aim: To evaluate the effect on survival of proteasome inhibitors and immunomodulators in patients with multiple myeloma in two national hospitals. Material and methods: Review of clinical records from two hospitals of Santiago. Epidemiological, clinical, laboratory and therapeutic data was obtained from 144 patients with multiple myeloma diagnosed between 2002 and 2016. Results: Information was retrieved from 78 patients at one center and from 66 at the other center. The mean age at diagnosis was 58 and 62 years, the proportion of males was 53% and 52%, and presentation at stage III was 34% and 46%, respectively. The use of novel drugs, mainly bortezomib, was 90% in one of the centers and 3% in the other one. The use of autologous stem-cell transplantation was 47% and 3% respectively. The median overall survival of patients from the centers with and without access to novel drugs was 117 and 71 months respectively ($p < 0.05$). The five-year overall survival was 93 and 43% respectively ($p < 0.05$). Conclusions: The use of novel drugs, especially bortezomib, and autologous stem-cell transplantation significantly improved the survival of multiple myeloma patients treated in national hospitals. It is necessary to include them as a first line treatment.

INFECTOLOGÍA

REV CHILENA INFECTOL. 2022 JUN;39(3):260-264. DOI: 10.4067/S0716-10182022000200260.

SEROPREVALENCIA DE TOXOPLASMA GONDII EN ESTUDIANTES CON RIESGO OCUPACIONAL

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Background: Toxoplasmosis is a disease that results from infection with the Toxoplasma gondii parasite, one of the world's most common parasites. The zoonotic infection usually occurs by eating undercooked contaminated meat or by contact with contaminated cat feces. A few studies of toxoplasmosis in healthy and immuno-compromised persons were done in Chile, but investigations related to occupational risk groups, such as Veterinary Medicine students were not studied. Aim: Determine the seroprevalence for T. gondii in Veterinary Medicine students at a university located in the center-south of the country, and evaluated to association with intrinsic variables. Methods: Peripheral blood samples were taken from 74 veterinary students from a university in south-central Chile. Immunoassay with sequential chemiluminescent was used as diagnostic technique. Results: Of the total number of students, 16 were seropositive, which is equivalent to 21.6%, the largest number of seropositive students was female (75%), they were in the age range between 24 and 26 years of age (43.7%), all consumed meat and vegetables (100%) and collected pet cat feces without protection 50 (68,7%). Conclusions: The results obtained show the presence of antibodies against T. gondii in Veterinary Medicine students. To the authors' knowledge, it is the first serological study for toxoplasmosis performed in university students of Veterinary Medicine in Chile.

REV CHILENA INFECTOL. 2022 APR;39(2):132-137. DOI: 10.4067/S0716-10182022000200132.

RECOMENDACIONES PARA EL DIAGNÓSTICO Y TRATAMIENTO DE LA INFECCIÓN POR TOXOPLASMA GONDII

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Toxoplasmosis is one of the most prevalent parasitosis in the world. It is associated with perinatal morbidity and in immunocompromised population. Currently, there are several diagnostic tests, both serological and molecular, that can help confirm the diagnosis and differentiate a recent infection of a pass. We propose some recommendations for the diagnosis and treatment of toxoplasmosis in different clinical scenarios based on the currently available evidence.

REV CHILENA INFECTOL. 2022 FEB;39(1):100-102. DOI: 10.4067/S0716-10182022000100100.
ERITEMA INDURADO DE BAZIN COMO UNA REACTIVACIÓN DE UNA TUBERCULOSIS LATENTE EN UNA PACIENTE CON TRATAMIENTO BIOLÓGICO ANTI-FACTOR DE NECROSIS TUMORAL.
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Erythema induratum of Bazin is a rare form of cutaneous tuberculosis, considered as part of the spectrum of tuberculids or hipersensitivity reactions to Mycobacterium tuberculosis. Treatment with biologic agents is a known risk factor for tuberculosis reactivation, especially in areas of high incidence like Latin America, which is why screening and treatment protocols must be followed before these therapies are initiated. We present a case of erythema induratum of Bazin as a reactivation of latent tuberculosis infection in a patient with rheumatoid arthritis treated with golimumab.

REV CHILENA INFECTOL. 2022 JUN;39(3):294-303. DOI: 10.4067/S0716-10182022000200294.
INFECCIÓN POR SARS-COV-2 EN PERSONAS VIVIENDO CON VIH. TÓPICOS DEL PANORAMA MUNDIAL Y EN CHILE
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The COVID-19 disease is caused by the SARS-CoV-2 virus and was declared a pandemic by the WHO on March 11, 2020. To date, more than 500 million people have been infected and it has caused over 6 million deaths worldwide. People that belong to the most vulnerable risk groups, such as those at the extremes of life, patients with chronic comorbidities and those with severe immunosuppression, are especially susceptible to developing a severe form of COVID-19 infection and death. Subjects living with HIV, especially those in precarious immunological conditions or those in whom antiretroviral therapy is yet to be started, may be at risk of developing complications related to COVID-19, as observed with other infectious diseases. This review aims to determine the magnitude of the impact of the SARS-CoV-2 virus on people living with HIV in Chile.

INMUNOLOGÍA

WORLD ALLERGY ORGAN J. 2022 MAY 31;15(6):100640. DOI: 10.1016/J.WAOJOU.2022.100640. ECOLLECTION 2022 JUN.
STANDARDS FOR PRACTICAL INTRAVENOUS RAPID DRUG DESENSITIZATION & DELABELING: A WAO COMMITTEE STATEMENT
Emilio Alvarez-Cuesta, Ricardo Madrigal-Burgaleta, Ana D Broyles, Javier Cuesta-Herranz, Maria Antonieta Guzman-Melendez, Michelle C Maciag, Elizabeth J Phillips, Jason A Trubiano, Johnson T Wong, Ignacio Ansotegui; Steering Committee Authors; Review Panel Members

Drug hypersensitivity reactions (DHRs) to intravenous drugs can be severe and might leave patients and doctors in a difficult position where an essential treatment or intervention has to be suspended. Even if virtually any intravenous medication can potentially trigger a life-threatening DHR, chemotherapeutics, biologics, and antibiotics are amongst the intravenous drugs most frequently involved in these reactions. Admittedly, suspending such treatments may negatively impact the survival outcomes or the quality of life of affected patients. Delabeling pathways and rapid drug desensitization (RDD) can help reactive patients stay on first-choice therapies instead of turning to less efficacious, less cost-effective, or more toxic alternatives. However, these are high-complexity and high-risk techniques, which usually need expert teams and allergy-specific techniques (skin testing, in vitro testing, drug provocation testing) to ensure safety, an accurate diagnosis, and personalized management. Unfortunately, there are significant inequalities within and among countries in access to allergy departments with the necessary expertise and resources to offer these techniques and tackle these DHRs optimally. The main objective of this consensus document is to create a great benefit for patients worldwide by aiding allergists to expand the scope of their practice and support them with evidence, data, and experience from leading groups from around the globe. This statement of the Drug Hypersensitivity Committee of the World Allergy Organization (WAO) aims to be a comprehensive practical guide on the technical aspects of implementing acute-onset intravenous hypersensitivity delabeling and RDD for a wide range of drugs. Thus, the manuscript does not only focus on clinical pathways. Instead, it also provides guidance on topics usually left unaddressed, namely, internal validation, continuous quality improvement, creating a healthy multidisciplinary environment, and redesigning care (including a specific supplemental section on a real-life example of how to design a dedicated space that can combine basic and complex diagnostic and therapeutic techniques in allergy).

CURR OPIN ALLERGY CLIN IMMUNOL. 2022 JUN 1;22(3):167-174. DOI: 10.1097/ACI.0000000000000821.
DRUG ALLERGY DESENSITIZATION IS NOT A UNIQUE RECIPE
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Purpose of review: Drug desensitization is the only therapeutic option for patients with drug allergies who need to receive the drugs they are allergic to, and it is especially critical in patients with an urgent need for chemotherapy, biologics, or antibiotics, where equally effective alternatives might not be available. However, drug desensitization is not a cookbook where anyone with no experience or specific training can find a general recipe. This review article will approach the singularities that make personalized

and highly specialized care essential in this field. Recent findings: Drug desensitization needs to be personalized for each individual patient bearing in mind countless factors. Recent articles have tried to define the optimal resources and the most important factors to account for in personalization. However, drug desensitization is only a tool within the wider management pathway, and we will discuss recent findings in allergy delabelling in chemotherapy, biologics, and antibiotics. Summary: Risk-assessment, delabelling, and desensitization protocols, as a part of wider management pathways, can be adapted locally along with comprehensive and multifactorial risk-management strategies. These high-complexity and high-risk procedures, such as drug desensitization, need to be managed by expert allergists who can provide personalization, innovation, continuous improvement, research, and teaching in expert centres.

LABORATORIO CLÍNICO

ANTIBIOTICS (BASEL). 2022 SEP 7;11(9):1207. DOI: 10.3390/ANTIBIOTICS11091207.

NOVEL MEGAPLASMID DRIVING NDM-1-MEDIATED CARBAPENEM RESISTANCE IN KLEBSIELLA PNEUMONIAE ST1588 IN SOUTH AMERICA

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Carbapenem-resistant Enterobacterales (CRE) is a critical public health problem in South America, where the prevalence of NDM metallo-betalactamases has increased substantially in recent years. In this study, we used whole genome sequencing to characterize a multidrug-resistant (MDR) Klebsiella pneumoniae (UCO-361 strain) clinical isolate from a teaching hospital in Chile. Using long-read (Nanopore) and short-read (Illumina) sequence data, we identified a novel un-typeable megaplasmid (314,976 kb, pNDM-1_UCO-361) carrying the blaNDM-1 carbapenem resistance gene within a Tn3000 transposon. Strikingly, conjugal transfer of pNDM-1_UCO-361 plasmid only occurs at low temperatures with a high frequency of 4.3 × 10-6 transconjugants/receptors at 27 °C. UCO-361 belonged to the ST1588 clone, previously identified in Latin America, and harbored aminoglycoside, extended-spectrum β-lactamases (ESBLs), carbapenem, and quinolone-resistance determinants. These findings suggest that blaNDM-1-bearing megaplasmids can be adapted to carriage by some K. pneumoniae lineages, whereas its conjugation at low temperatures could contribute to rapid dissemination at the human-environmental interface.

LIFE (BASEL). 2022 APR 5;12(4):534. DOI: 10.3390/LIFE12040534.

CELLULAR IMMUNE RESPONSE IN PATIENTS IMMUNIZED WITH THREE VACCINE DOSES OF DIFFERENT VACCINATION SCHEMES AUTHORIZED BY THE CHILEAN MINISTRY OF HEALTH IN JANUARY 2022

Paz Beatriz Tabilo Valenzuela, Gabriela Flores Balter, Gustavo Saint-Pierre Contreras, Daniel Conei Valencia, Catalina Moreno Calderón, Constanza Bohle Venegas, Marcia Guajardo Rivera, Francisco Silva Ojeda, Maria Jesus Vial Covarrubias

In December 2019, a case of atypical pneumonia was reported in Wuhan, China. It was named COVID-19 and caused by SARS-CoV-2. In a few months, scientific groups around the world developed vaccines to reduce the disease's severity. The objective was to evaluate the humoral and cellular immune response post immunization with three different vaccination schedules administered in Chile until January 2022. Sixty volunteers were recruited with a three-dose schedule, who had no history of infection nor close contact with a positive patient. IgG against the spike antigenic domain was detected, and the neutralization capacity against two groups of variants, Original/Alpha and Beta/Gamma, was also measured. Finally, the cellular response with interferon release was measured through IGRA. Results showed that there were significant differences in the neutralizing antibodies for the original and alpha variant when comparing three Comirnaty doses with Coronavac and Vaxzevria. A high number of reactive subjects against the different SARS-CoV-2 variants, alpha, gamma, and delta, were observed, with no significant differences between any of the three schemes, confirming the existence of a cellular immune response against SARS-CoV-2. In conclusion, the three vaccine schemes generated a cellular immune response in these volunteers.

MEDICINA FÍSICA Y REHABILITACIÓN

BRAIN STIMUL. 2023 JAN-FEB;16(1):40-47. DOI: 10.1016/J.BRS.2022.12.008.

EARLY TRANSCRANIAL DIRECT CURRENT STIMULATION WITH MODIFIED CONSTRAINT-INDUCED MOVEMENT THERAPY FOR MOTOR AND FUNCTIONAL UPPER LIMB RECOVERY IN HOSPITALIZED PATIENTS WITH STROKE: A RANDOMIZED, MULTICENTRE, DOUBLE-BLIND, CLINICAL TRIAL

Maricel Garrido M, Evelyn Álvarez E, Fabrizio Acevedo P, Álvaro Moyano V, Natalia Castillo N, Gabriel Cavada Ch

Background: Constraint-induced movement therapy (CIMT) and transcranial direct current stimulation (tDCS) are used to reduce interhemispheric imbalance after stroke, which is why the combination of these therapies has been used for neurological recovery, but not in the acute phase. Objectives: To evaluate the effectiveness of combining active or sham bihemispheric tDCS with modified

CIMT (mCIMT) for the recovery of the Upper Limb (UL) in hospitalized patients with acute and subacute stroke. Methods: This randomized controlled, double-blind, placebo-controlled, parallel group clinical trial was executed between September 2018 to March 2021 recruited 70 patients. The patients were randomized to one of two groups to receive treatment for 7 consecutive days, which included 20 min of active or sham bihemispheric tDCS daily (anodal ipsilesional and cathodal contralesional), with an mCIMT protocol. The primary outcome was the difference in the evolution of motor and functional upper limb recovery with assessment on days 0, 5, 7, 10 and 90. The secondary outcomes were independence in activities of daily living (ADL) and quality of life. Results: The active group presented a statistically significant gap compared to the simulated group throughout the trend in the scores of the FMA (motor function and joint pain) and WMFT (functional ability and weight to box) ($p < 0.05$) and showed a minimal clinically important difference (FMA: difference between groups of 4.9 points [CI: 0.007- 9.799]; WMFT: difference between groups of 6.54 points [CI: 1.10-14.15]). In the secondary outcomes, there was a significant difference between the groups in ADL independence (Functional Independence Measure: difference of 8.63 [CI: 1.37-18.64]) and perceived recovery of quality of life evaluated at 90 days ($p = 0.0176$). Conclusions: Combining mCIMT with bihemispheric tDCS in patients hospitalized with acute-subacute stroke allows us to maximize the motor and functional recovery of the paretic upper limb in the early stages and independence in ADL, maintaining the effects over time.

MEDICINA INTERNA

REV MED CHIL. 2022 APR;150(4):439-449. DOI: 10.4067/S0034-98872022000400439.

EVALUACIÓN DE LA PERCEPCIÓN DE LOS ESTUDIANTES ACERCA DE LOS ATRIBUTOS DE SUS TUTORES EN LOS PRIMEROS CURSOS CLÍNICOS

Nicolás Ortiz-López, Carolina Olea-Gangas, Sofía Ponce-Arancibia, Sara Arancibia-Carvajal, Jonathan Rodríguez-Cabello, Felipe Cortés-Chau, Iván Solís

Background: The clinical teachers' attributes can be grouped into physician competencies, teacher competencies, and personal characteristics. Global performance is considered the clinical teacher's capacity to facilitate an active and stimulating learning process for medical students and a warm, supportive, and pleasant environment. Aim: To determine which attributes of the clinical teacher influence their global performance from the students' point of view. Material and methods: The Role Model Apperception Tool questionnaire (RoMAT) was answered by 133 second-year medical students at the University of Chile during 2018. Results: The students assessed 37 clinical teachers. Teaching competencies had the higher influence in global performance. Personal characteristics also had a significant influence. Physician competencies had an indirect influence on teaching competencies. The model obtained 88% of the explained variance of the teacher's global performance. Conclusions: This study showed that teacher competencies, personal characteristics, and physician competencies are qualities that influence the perception of the global performance of clinical teachers.

HEALTH SOC CARE COMMUNITY. 2022 JUL;30(4):E1202-E1211. DOI: 10.1111/HSC.13527.

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

Nicolás Ortiz-López, Sofía Ponce-Arancibia, Carolina Olea-Gangas, Rodrigo Chacano-Muñoz, Sara Arancibia-Carvajal, Ivan Solis

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

MEDICINA NUCLEAR

J NUCL CARDIOL. 2022 JUN;29(3):1166-1174. DOI: 10.1007/S12350-020-02414-8.

CLINICAL AND GATED SPECT MPI PARAMETERS ASSOCIATED WITH SUPER-RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

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Purpose: We sought to evaluate the behavior of cardiac mechanical synchrony as measured by phase SD (PSD) derived from gated MPI SPECT (gSPECT) in patients with super-response after CRT and to evaluate the clinical and imaging characteristics associated with super-response. Methods: 158 subjects were evaluated with gSPECT before and 6 months after CRT. Patients with an improvement of LVEF > 15% and NYHA class I/II or reduction in LV end-systolic volume > 30% and NYHA class I/II were labeled as super-responders (SR). Results: 34 patients were classified as super-responders (22%) and had lower PSD (32° ± 17°) at 6 months after CRT compared to responders (45° ± 24°) and non-responders 46° ± 28° (P = .02 for both comparisons). Regression analysis identified predictors independently associated with super-response to CRT: absence of previous history of CAD (odds ratio 18.7; P = .002), absence of diabetes mellitus (odds ratio 13; P = .03), and history of hypertension (odds ratio .2; P = .01). Conclusion: LV dyssynchrony after CRT implantation, but not at baseline, was significantly better among super-responders compared to non-super-responders. The absence of diabetes, absence of CAD, and history of hypertension were independently associated with super-response after CRT.

J NUCL CARDIOL. 2022 JUN;29(3):952-961. DOI: 10.1007/S12350-020-02397-6.

REPRODUCIBILITY OF GLOBAL LV FUNCTION AND DYSSYNCHRONY PARAMETERS DERIVED FROM PHASE ANALYSIS OF GATED MYOCARDIAL PERFUSION SPECT: A MULTICENTER COMPARISON WITH CORE LABORATORY SETTING

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Background: Gated myocardial perfusion scintigraphy (GMPS) phase analysis is an important tool to investigate the physiology of left ventricular (LV) dyssynchrony. We aimed to test the performance of GMPS LV function and phase analysis in different clinical settings and on a diverse population. Methods: This is a post hoc analysis of a prospective, non-randomized, multinational, multicenter cohort study. Clinical evaluation and GMPS prior to cardiac resynchronization therapy (CRT)(baseline) and 6-month post CRT (follow-up) were done. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), LV ejection fraction (LVEF), LV phase standard deviation (LVPSD), and percentage of left ventricle non-viable (PLVNV) were obtained by 10 centers and compared to the core lab. Results: 276 GMPS studies had all data available from individual sites and from core lab. There were no statistically significant differences between all variables except for LVPSD. When subjects with no mechanical dyssynchrony were excluded, LVPSD difference became non-significant. LVESV, LVEF, LVPSD and PLVNV had strong correlation in site against core lab comparison. Bland-Altman plots demonstrated good agreement. Conclusions: The presented correlation and agreement of LV function and dyssynchrony analysis over different sites with a diverse sample corroborate the strength of GMPS in the management of heart failure in clinical practice.

NUCL MED COMMUN. 2022 DEC 1;43(12):1163-1170. DOI: 10.1097/MNM.0000000000001630.

CURRENT STATUS OF NUCLEAR CARDIOLOGY PRACTICE IN LATIN AMERICA AND THE CARIBBEAN, IN THE ERA OF MULTIMODALITY CARDIAC IMAGING APPROACH: 2022 UPDATE

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Cardiovascular diseases (CVDs) are the leading cause of mortality in Latin America and the Caribbean (LAC), with the risk in men being slightly higher than in women. The coronavirus disease 2019 (COVID-19) pandemic caused a significant reduction in the number of cardiac diagnostic procedures globally and in particular in LAC. Nuclear cardiology is available in the region, but there is variability in terms of existing technology, radiopharmaceuticals, and human resources. In the region, there are 2385 single photon emission computed tomography (SPECT) and 315 PET scanners, Argentina and Brazil have the largest number. There is an increasing number of new technologies such as cadmium-zinc-telluride (CZT) cardiac-dedicated gamma cameras, SPECT/computed tomography (CT), and PET/CT. All countries performed myocardial perfusion imaging studies, mainly gated-SPECT; the rest are multi-gated acquisition, mainly for cardiac toxicity; detection of viability; rest gated SPECT in patients with dilated cardiomyopathy, and bone-avid tracer cardiac scintigraphy for transthyretin cardiac amyloidosis diagnosis. Regarding other non-nuclear cardiac imaging modalities, Argentina, Colombia, and Chile have the highest ratio of CT scanners, while Brazil, Argentina, and Chile show the highest ratio of MRI scanners. The development of nuclear cardiology and other advanced imaging modalities is challenged by the high cost of equipment, lack of equipment maintenance and service, insufficient-specific training both for imaging specialists and referring

clinicians, and lack of awareness of cardiologists or other referring physicians on the clinical applications of nuclear cardiology. Another important aspect to consider is the necessity of implementing cardiac imaging multimodality training. A joint work of nuclear medicine specialists, radiologists, cardiologists, and clinicians, in general, is mandatory to achieve this goal. National, regional, and international cooperation including support from scientific professional societies such as the American Society of Nuclear Cardiology and Latin American Association of Biology and Nuclear Medicine Societies, cardiological societies, and organizations such as the International Atomic Energy Agency, and Pan American Health Organization, as well as government commitment are key factors in the overall efforts to tackle the burden of cardiovascular diseases in the region.

NEFROLOGÍA

KIDNEY INT REP. 2022 OCT;7(10):2176-2185. DOI: 10.1016/J.EKIR.2022.07.007.

CLINICAL EFFICACY OF SARS-COV-2 VACCINATION IN HEMODIALYSIS PATIENTS

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Introduction: The COVID-19 pandemic is a global public health problem. Patients with end-stage renal disease on hemodialysis are at a higher risk of infection and mortality than the general population. Worldwide, a vaccination campaign has been developed that has been shown to reduce severe infections and deaths in the general population. However, there are currently limited data on the clinical efficacy of vaccinations in the hemodialysis population. Methods: A national multicenter observational cohort was performed in Chile to evaluate the clinical efficacy of anti-SARS-CoV-2 vaccination in end-stage renal disease patients on chronic hemodialysis from February 2021 to August 2021. In addition, the BNT162b2 (Pfizer-BioNTech) and CoronaVac (Sinovac) vaccines were evaluated. The efficacy of vaccination in preventing SARS-CoV-2 infection, hospitalizations, and deaths associated with COVID-19 was determined. Results: A total of 12,301 patients were evaluated; 10,615 (86.3%) received a complete vaccination (2 doses), 490 (4.0%) received incomplete vaccination, and 1196 (9.7%) were not vaccinated. During follow-up, 1362 (11.0%) patients developed COVID-19, and 150 died (case fatality rate: 11.0%). The efficacy of the complete vaccination in preventing infection was 18.1% (95% confidence interval [CI]:11.8-23.8%), and prevention of death was 66.0% (95% CI:60.6-70.7%). When comparing both vaccines, BNT162b2 and CoronaVac were effective in reducing infection and deaths associated with COVID-19. Nevertheless, the BNT162b2 vaccine had higher efficacy in preventing infection (42.6% vs. 15.0%) and deaths (90.4% vs. 64.8%) compared to CoronaVac. Conclusion: The results of our study suggest that vaccination against SARS-CoV-2 in patients on chronic hemodialysis was effective in preventing infection and death associated with COVID-19.

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EFECTIVIDAD DE ANTICOAGULACIÓN REGIONAL CON CITRATO EN TERAPIA DE REEMPLAZO RENAL CONTINUA

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Background: Anticoagulation in continuous renal replacement therapy (CRRT) is essential to counteract the coagulation cascade activation, induced by the dialysis circuit. Heparin is the most widely used anticoagulant, followed by regional citrate anticoagulation (RCA). Aim: To determine the effectiveness and safety of anticoagulant treatment with citrate in CRRT. Material and methods: Retrospective study of adults in CRRT hospitalized between the years 2014 and 2020 in critical units, who required change to RCA according to established protocols. Results: We studied 24 patients aged 63 ± 13 years (12 females). The reasons for admission were acute kidney injury (AKI) in 80% and stage 5 chronic kidney disease in 20%. The indication of RCA in 75% of patients was by coagulation of more than 3 circuits in 24 hours. The duration of the circuit in RCA was 18.5 ± 4.8 hours versus 11.9 ± 4.9 hours with heparin ($p < 0.0001$). There were 19 mild complications that did not affect the RCA. Conclusions: RCA is feasible to perform, it is a safe and efficient procedure if it is protocolized, allowing a longer duration of the dialysis circuit.

VACCINES (BASEL). 2022 SEP 16;10(9):1542. DOI: 10.3390/VACCINES10091542.

HUMORAL IMMUNE RESPONSE OF BNT162B2 AND CORONAVAC VACCINATIONS IN HEMODIALYSIS PATIENTS: A MULTICENTER PROSPECTIVE COHORT

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The CoronaVac vaccine is the most used anti-SARS-CoV-2 vaccine worldwide. Previous data indicate that this vaccine produces a lower immune response than RNA vaccines such as BNT162b2. End-stage renal disease (ESRD) patients have an increased rate of COVID-19 and a reduced immune response to vaccinations. Currently, there is little data on this population's immune response induced

by CoronaVac. Methods: This study involved a prospective cohort of ESRD patients in chronic hemodialysis who received a two-dose immunization scheme of either CoronaVac (Sinovac Biotech) or BNT162b2 vaccines (Pfizer-BioNTech). We measured the plasma levels of anti-SARS-CoV-2 IgG antibodies. We determined antibody titers before immunization, 2 and 4 months after two doses, plus 4 months after a booster dose. Results: We evaluated 208 patients in three hemodialysis centers. The mean age was 62.6 ± 15.6 years, of whom 91 were female (41.75%). Eighty-one patients (38.94%) received the BNT162b2 vaccine and 127 (61.06%) received the CoronaVac vaccine. Patients who received the BNT162b2 vaccine had a higher humoral response compared to those who received the CoronaVac vaccine (4 months after the second dose: BNT162b2: 88.89%, CoronaVac: 51.97%, $p < 0.001$; 4 months after the booster: BNT162b2: 98.77%, CoronaVac: 86.61%, $p < 0.001$). Conclusions: Our results suggest that the CoronaVac vaccine induced a lower humoral response than the BNT162b2 vaccine in ESRD patients on hemodialysis.

AM J KIDNEY DIS. 2022 JUL;80(1):87-97.E1. DOI: 10.1053/J.AJKD.2021.10.009.

PLASMA LEAD CONCENTRATION AND RISK OF LATE KIDNEY ALLOGRAFT FAILURE: FINDINGS FROM THE TRANSPLANTLINES BIOBANK AND COHORT STUDIES

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Rationale & objective: Heavy metals are known to induce kidney damage, and recent studies have linked minor exposures to cadmium and arsenic with increased risk of kidney allograft failure, yet the potential association of lead with late graft failure in kidney transplant recipients (KTRs) remains unknown. Study design: Prospective cohort study in The Netherlands. Setting & participants: We studied outpatient KTRs (n = 670) with a functioning graft for ≥1 year recruited at a university setting (2008-2011) and followed for a median of 4.9 (interquartile range, 3.4-5.5) years. Additionally, patients with chronic kidney disease (n = 46) enrolled in the ongoing TransplantLines Cohort and Biobank Study (2016-2017, ClinicalTrials.gov identifier NCT03272841) were studied at admission for transplant and at 3, 6, 12, and 24 months after transplant. Exposure: Plasma lead concentration was log2-transformed to estimate the association with outcomes per doubling of plasma lead concentration and also considered categorically as tertiles of lead distribution. Outcome: Kidney graft failure (restart of dialysis or repeat transplant) with the competing event of death with a functioning graft. Analytical approach: Multivariable-adjusted cause-specific hazards models in which follow-up of KTRs who died with a functioning graft was censored. Results: Median baseline plasma lead concentration was 0.31 (interquartile range, 0.22-0.45) μg/L among all KTRs. During follow-up, 78 (12%) KTRs experienced graft failure. Higher plasma lead concentration was associated with increased risk of graft failure (hazard ratio, 1.59 [95% CI, 1.14-2.21] per doubling; P = 0.006) independent of age, sex, transplant characteristics, estimated glomerular filtration rate, proteinuria, smoking status, alcohol intake, and plasma concentrations of cadmium and arsenic. These findings remained materially unchanged after additional adjustment for dietary intake and were consistent with those of analyses examining lead categorically. In serial measurements, plasma lead concentration was significantly higher at admission for transplant than at 3 months after transplant (P = 0.001), after which it remained stable over 2 years of follow-up (P = 0.2). Limitations: Observational study design. Conclusions: Pretransplant plasma lead concentrations, which decrease after transplant, are associated with increased risk of late kidney allograft failure. These findings warrant further studies to evaluate whether preventive or therapeutic interventions to decrease plasma lead concentration may represent novel risk-management strategies to decrease the rate of kidney allograft failure.

ONCOLOGÍA

CANCERS (BASEL). 2022 JAN 27;14(3):634. DOI: 10.3390/CANCERS14030634.

IDENTIFICATION OF CIRCULATING LNCRNAS ASSOCIATED WITH GALLBLADDER CANCER RISK BY TISSUE-BASED PRESELECTION, CIS-EQTL VALIDATION, AND ANALYSIS OF ASSOCIATION WITH GENOTYPE-BASED EXPRESSION

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Long noncoding RNAs (lncRNAs) play key roles in cell processes and are good candidates for cancer risk prediction. Few studies have investigated the association between individual genotypes and lncRNA expression. Here we integrate three separate datasets with information on lncRNA expression only, both lncRNA expression and genotype, and genotype information only to identify circulating lncRNAs associated with the risk of gallbladder cancer (GBC) using robust linear and logistic regression techniques. In the first dataset, we preselect lncRNAs based on expression changes along the sequence "gallstones → dysplasia → GBC". In the second dataset, we validate associations between genetic variants and serum expression levels of the preselected lncRNAs (cis-lncRNA-eQTLs) and build lncRNA expression prediction models. In the third dataset, we predict serum lncRNA expression based on individual genotypes and assess the association between genotype-based expression and GBC risk. AC084082.3 and LINC00662 showed increasing expression levels (p-value = 0.009), while C22orf34 expression decreased in the sequence from gallstones to GBC (p-value = 0.04).

We identified and validated two cis-LINC00662-eQTLs (r2 = 0.26) and three cis-C22orf34-eQTLs (r2 = 0.24). Only LINC00662 showed a genotyped-based serum expression associated with GBC risk (OR = 1.25 per log2 expression unit, 95% CI 1.04-1.52, p-value = 0.02). Our results suggest that preselection of lncRNAs based on tissue samples and exploitation of cis-lncRNA-eQTLs may facilitate the identification of circulating noncoding RNAs linked to cancer risk.

RESPIRATORIO

BMC PULM MED. 2022 JUL 19;22(1):278. DOI: 10.1186/S12890-022-02061-4.

EFFECTS OF ECCENTRIC, CONCENTRIC AND ECCENTRIC/CONCENTRIC TRAINING ON MUSCLE FUNCTION AND MASS, FUNCTIONAL PERFORMANCE, CARDIOMETABOLIC HEALTH, QUALITY OF LIFE AND MOLECULAR ADAPTATIONS OF SKELETAL MUSCLE IN COPD PATIENTS: A MULTICENTRE RANDOMISED TRIAL

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Background: Chronic obstructive pulmonary disease (COPD) is the third cause of death worldwide. COPD is characterised by dyspnoea, limited exercise tolerance, and muscle dysfunction. Muscle dysfunction has been linked to dysregulation between muscle protein synthesis, myogenesis and degradation mechanisms. Conventional concentric cycling has been shown to improve several clinical outcomes and reduce muscle wasting in COPD patients. Eccentric cycling is a less explored exercise modality that allows higher training workloads imposing lower cardio-metabolic demand during exercise, which has shown to induce greater muscle mass and strength gains after training. Interestingly, the combination of eccentric and concentric cycling training has scarcely been explored. The molecular adaptations of skeletal muscle after exercise interventions in COPD have shown equivocal results. The mechanisms of muscle wasting in COPD and whether it can be reversed by exercise training are unclear. Therefore, this study aims two-fold: (1) to compare the effects of 12 weeks of eccentric (ECC), concentric (CONC), and combined eccentric/concentric (ECC/CONC) cycling training on muscle mass and function, cardiometabolic health, physical activity levels and quality of life in severe COPD patients; and (2) to examine the molecular adaptations regulating muscle growth after training, and whether they occur similarly in specific muscle fibres (i.e., I, IIa and IIx). methods: Study 1 will compare the effects of 12 weeks of CONC, ECC, versus ECC/CONC training on muscle mass and function, cardiometabolic health, levels of physical activity and quality of life of severe COPD patients using a multicentre randomised trial. Study 2 will investigate the effects of these training modalities on the molecular adaptations regulating muscle protein synthesis, myogenesis and muscle degradation in a subgroup of patients from Study 1. Changes in muscle fibres morphology, protein content, genes, and microRNA expression involved in skeletal muscle growth will be analysed in specific fibre-type pools. Discussion: We aim to demonstrate that a combination of eccentric and concentric exercise could maximise the improvements in clinical outcomes and may be ideal for COPD patients. We also expect to unravel the molecular mechanisms underpinning muscle mass regulation after training in severe COPD patients.

SCI REP. 2022 JUL 30;12(1):13145. DOI: 10.1038/S41598-022-13063-X.

IL-7/IL7R AXIS DYSFUNCTION IN ADULTS WITH SEVERE COMMUNITY-ACQUIRED PNEUMONIA (CAP): A CROSS-SECTIONAL STUDY

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Community-acquired pneumonia (CAP) is a worldwide leading cause of death. Recognized risk factors in some severe cases have not been identified. Lymphocytopenia has been frequently described in CAP. Since IL-7, membrane-bound receptor (IL7Rα;CD127) and soluble IL7Rα (sIL7R) are critical in lymphocytes homeostasis, in this work we aimed to evaluate the involvement of the IL-7/IL7Rα axis in the severity of adult CAP, since it has not been explored. The IL7Rα SNPs rs6897932, rs987106, and rs3194051 SNPs in IL7α were genotyped, the systemic expression of the IL7R gene, sIL7R, IL-7, and levels of peripheral IL7Rα+ T lymphocytes were quantified in 202 hospitalized CAP cases. rs3194051GG was more frequent in non-survivors than in survivors; rs987106TT was more frequent and rs3194051AA less frequent in patients at intensive care unit (ICU) than in those not admitted to ICU. IL7Rα gene expression was lower in non-survivors than in survivors, and in severe than in mild cases. CD3+CD127+ lymphocytes were lower in severe than in mild cases; in non-survivors than in survivors and in ICU than in non- ICU admitted cases. sIL7Rα plasmatic levels were higher in non-survivors than in survivors, and in severe than in mild cases. rs6897932CC, rs987106AA and rs3194051GG carriers showed the highest while rs6897932TT showed the lowest sIL7Rα levels. The AUC of sIL7Rα levels predicting 30-day mortality was 0.71. Plasma IL-7 levels were lower in ICU-admitted than in not ICU-admitted and in non-survivors than in survivors. No additional association was detected. In conclusion, rs3194051GG and rs987106TT IL7R genotypes were associated with a poorer prognosis. A significant association between sIL7R levels and SNPs of the IL7R gene is described for the first time in adult CAP. Increased plasmatic sIL7R could contribute to identifying adult CAP cases at risk of death.

REUMATOLOGÍA

REV MED CHIL. 2022 APR;150(4):505-511. DOI: 10.4067/S0034-98872022000400505.

COMPROMISO PULMONAR EN VASCULITIS ASOCIADAS A ANTICUERPOS ANTICITOPLASMA DE NEUTRÓFILOS

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This article reviews the pulmonary manifestations of anti-neutrophil cytoplasmic antibody associated vasculitis (AAV). Its frequency in the different phenotypes of the disease, clinical manifestations and updated therapeutic recommendations are reviewed, aiming to alert the medical community about the existence of these diseases. We pretend to stimulate a timely suspicion, diagnostic precision, and the implementation of effective therapies, to reduce the eventual sequelae derived from a diagnostic omission or an inappropriate treatment for the different clinical scenarios in which these diseases appear.

ANN RHEUM DIS. 2022 AUG;81(8):1096-1105. DOI: 10.1136/ANNRHEUMDIS-2021-220371.

EPITOPES FOR RHEUMATOID ARTHRITIS

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Objective: Rheumatoid arthritis (RA) immunopathogenesis revolves around the presentation of poorly characterised self-peptides by human leucocyte antigen (HLA)-class II molecules on the surface of antigen-presenting cells to autoreactive CD4 +T cells. Here, we analysed the HLA-DR-associated peptidome of synovial tissue (ST) and of dendritic cells (DCs) pulsed with synovial fluid (SF) or ST, to identify potential T-cell epitopes for RA. Methods: HLA-DR/peptide complexes were isolated from RA ST samples (n=3) and monocyte-derived DCs, generated from healthy donors carrying RA-associated shared epitope positive HLA-DR molecules and pulsed with RA SF (n=7) or ST (n=2). Peptide sequencing was performed by high-resolution mass spectrometry. The immunostimulatory capacity of selected peptides was evaluated on peripheral blood mononuclear cells from patients with RA (n=29) and healthy subjects (n=12) by flow cytometry. Results: We identified between 103 and 888 HLA-DR-naturally presented peptides per sample. We selected 37 native and six citrullinated (cit)-peptides for stimulation assays. Six of these peptides increased the expression of CD40L on CD4 +T cells patients with RA, and specifically triggered IFN-γ expression on RA CD4 +T cells compared with healthy subjects. Finally, the frequency of IFN-γ–producing CD4 +T cells specific for a myeloperoxidase-derived peptide showed a positive correlation with disease activity. Conclusions: We significantly expanded the peptide repertoire presented by HLA-DR molecules in a physiologically relevant context, identifying six new epitopes recognised by CD4 +T cells from patients with RA. This information is important for a better understanding of the disease immunopathology, as well as for designing tolerising antigen-specific immunotherapies.

J CLIN RHEUMATOL. 2022 SEP 1;28(6):285-292. DOI: 10.1097/RHU.0000000000001858.

CLINICAL AND SEROLOGICAL FEATURES IN LATIN AMERICAN IGG4-RELATED DISEASE PATIENTS DIFFER ACCORDING TO SEX, ETHNICITY, AND CLINICAL PHENOTYPE

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Background/objective: Data on IgG4-related disease (IgG4-RD) come almost exclusively from cohorts from Asia, Europe, and North America. We conducted this study to describe the clinical presentation, phenotype distribution, and association with sex, ethnicity, and serological markers in a large cohort of Latin American patients with IgG4-RD. Methods: We performed a multicenter medical records review study including 184 Latin American IgG4-RD patients. We assigned patients to clinical phenotypes: group 1 (pancreato-hepato-biliary), group 2 (retroperitoneal/aortic), group 3 (head and neck-limited), group 4 (Mikulicz/systemic), and group 5 (undefined). We focused the analysis on how sex, ethnicity, and clinical phenotype may influence the clinical and serological presentation. Results: The mean age was 50.8 ± 15 years. Men and women were equally affected (52.2% vs 48.8%). Fifty-four patients (29.3%) were assigned to group 1, 21 (11.4%) to group 2, 57 (30.9%) to group 3, 32 (17.4%) to group 4, and 20 (10.8%) to group 5. Male sex was associated with biliary tract (odds ratio [OR], 3.4; 95% confidence interval [CI], 1.36-8.26), kidney (OR, 3.4; 95% CI, 1.28-9.25), and retroperitoneal involvement (OR, 5.3; 95% CI, 1.45-20). Amerindian patients presented more frequently with atopy history and gallbladder involvement. Group 3 had a female predominance. Conclusions: Latin American patients with IgG4-RD were younger, and men and women were equally affected compared with White and Asian cohorts. They belonged more commonly to group 1 and group 3. Retroperitoneal and aortic involvement was infrequent. Clinical and serological features differed according to sex, ethnicity, and clinical phenotype.

UNIDAD PACIENTES CRÍTICOS

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

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

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

BIOMEDICINES. 2022 DEC 27;11(1):70. DOI: 10.3390/BIOMEDICINES11010070.

NEW OPPORTUNITIES IN HEART FAILURE WITH PRESERVED EJECTION FRACTION: FROM BENCH TO BEDSIDE… AND BACK

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Heart failure with preserved ejection fraction (HFpEF) is a growing public health problem in nearly 50% of patients with heart failure. Therefore, research on new strategies for its diagnosis and management has become imperative in recent years. Few drugs have successfully improved clinical outcomes in this population. Therefore, numerous attempts are being made to find new pharmacological interventions that target the main mechanisms responsible for this disease. In recent years, pathological mechanisms such as cardiac fibrosis and inflammation, alterations in calcium handling, NO pathway disturbance, and neurohumoral or mechanic impairment have been evaluated as new pharmacological targets showing promising results in preliminary studies. This review aims to analyze the new strategies and mechanical devices, along with their initial results in pre-clinical and different phases of ongoing clinical trials for HFpEF patients. Understanding new mechanisms to generate interventions will allow us to create methods to prevent the adverse outcomes of this silent pandemic.

SCI REP. 2022 JUL 25;12(1):12648. DOI: 10.1038/S41598-022-16446-2.

SPONTANEOUS BREATHING PROMOTES LUNG INJURY IN AN EXPERIMENTAL MODEL OF ALVEOLAR COLLAPSE

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Vigorous spontaneous breathing has emerged as a promotor of lung damage in acute lung injury, an entity known as "patient self-inflicted lung injury". Mechanical ventilation may prevent this second injury by decreasing intrathoracic pressure swings and improving regional air distribution. Therefore, we aimed to determine the effects of spontaneous breathing during the early stage of acute respiratory failure on lung injury and determine whether early and late controlled mechanical ventilation may avoid or revert these harmful effects. A model of partial surfactant depletion and lung collapse was induced in eighteen intubated pigs of 32 ±4 kg. Then, animals were randomized to (1) SB-group: spontaneous breathing with very low levels of pressure support for the whole experiment (eight hours), (2) Early MV-group: controlled mechanical ventilation for eight hours, or (3) Late MV-group: first half of the experiment on spontaneous breathing (four hours) and the second half on controlled mechanical ventilation (four hours). Respiratory, hemodynamic, and electric impedance tomography data were collected. After the protocol, animals were euthanized, and lungs

were extracted for histologic tissue analysis and cytokines quantification. SB-group presented larger esophageal pressure swings, progressive hypoxemia, lung injury, and more dorsal and inhomogeneous ventilation compared to the early MV-group. In the late MV-group switch to controlled mechanical ventilation improved the lung inhomogeneity and esophageal pressure swings but failed to prevent hypoxemia and lung injury. In a lung collapse model, spontaneous breathing is associated to large esophageal pressure swings and lung inhomogeneity, resulting in progressive hypoxemia and lung injury. Mechanical ventilation prevents these mechanisms of patient self-inflicted lung injury if applied early, before spontaneous breathing occurs, but not when applied late.

SCI REP. 2022 NOV 23;12(1):20233. DOI: 10.1038/S41598-022-24412-1.

INFLAMMATORY BIOMARKERS AND PENDELLUFT MAGNITUDE IN ARDS PATIENTS TRANSITIONING FROM CONTROLLED TO PARTIAL SUPPORT VENTILATION

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The transition from controlled to partial support ventilation is a challenge in acute respiratory distress syndrome (ARDS) patients due to the risks of patient-self-inflicted lung injury. The magnitude of tidal volume (VT) and intrapulmonary dyssynchrony (pendelluft) are suggested mechanisms of lung injury. We conducted a prospective, observational, physiological study in a tertiary academic intensive care unit. ARDS patients transitioning from controlled to partial support ventilation were included. On these, we evaluated the association between changes in inflammatory biomarkers and esophageal pressure swing (ΔPes), transpulmonary driving pressure (ΔPL), VT, and pendelluft. Pendelluft was defined as the percentage of the tidal volume that moves from the non-dependent to the dependent lung region during inspiration, and its frequency at different thresholds (- 15, - 20 and - 25%) was also registered. Blood concentrations of inflammatory biomarkers (IL-6, IL-8, TNF-α, ANGPT2, RAGE, IL-18, Caspase-1) were measured before (T0) and after 4-h (T4) of partial support ventilation. Pendelluft, ΔPes, ΔPL and VT were recorded. Nine out of twenty-four patients (37.5%) showed a pendelluft mean ≥ 10%. The mean values of ΔPes, ΔPL, and VT were - 8.4 [- 6.7; - 10.2] cmH2O, 15.2 [12.3-16.5] cmH2O and 8.1 [7.3-8.9] m/kg PBW, respectively. Significant associations were observed between the frequency of high-magnitude pendelluft and IL-8, IL-18, and Caspase-1 changes (T0/T4 ratio). These results suggest that the frequency of high magnitude pendelluft may be a potential determinant of inflammatory response related to inspiratory efforts in ARDS patients transitioning to partial support ventilation. Future studies are needed to confirm these results.

J ULTRASOUND. 2022 DEC;25(4):855-859. DOI: 10.1007/S40477-022-00652-9.

CRITICAL CARE ECHOCARDIOGRAPHY IN PRONE POSITION PATIENTS DURING COVID-19 PANDEMIC: A FEASIBILITY STUDY

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Purpose: Critical care echocardiography is a fundamental tool in the hemodynamic evaluation of critically ill patients and prone position ventilation might limit its application. We aim to evaluate the feasibility of transthoracic echocardiography to assess different measurements performed in prone vs supine position in patients during COVID-19 pandemic to answer our research question: What is the feasibility of classic echocardiographic measurements in COVID-19 patients in prone position ventilation? Methods: Patients with covid-19 admitted to ICUs in four academic hospitals with respiratory failure and on mechanical ventilation were evaluated with critical care echocardiography. The first ultrasound assessment was compared between prone and supine patients recording feasibility of several echocardiographic measurements, using Fisher's exact test complementing with Crombach's Alpha. Results: 139 patients were included. Sixty-eight (49%) were evaluated in prone position and seventy one (51%) in supine position. Most variables were highly feasible, left ventricular volumes and ejection fraction were more possible to obtain in prone position, while cardiac output was in supine position. Tricuspid regurgitation was the least feasible overall measurement. Conclusion: Prone position ultrasound achieved a high feasibility of measurements compared with supine ultrasound in critically ill patients with COVID-19 respiratory failure and on mechanical ventilation.

J CRIT CARE. 2022 DEC;72:154166. DOI: 10.1016/J.JCRC.2022.154166.

CARDIAC FUNCTION IN CRITICALLY ILL PATIENTS WITH SEVERE COVID: A PROSPECTIVE CROSS-SECTIONAL STUDY IN MECHANICALLY VENTILATED PATIENTS

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Purpose: To evaluate cardiac function in mechanically ventilated patients with COVID-19. Materials and methods: Prospective, cross-sectional multicenter study in four university-affiliated hospitals in Chile. All consecutive patients with COVID-19 ARDS requiring mechanical ventilation admitted between April and July 2020 were included. We performed systematic transthoracic echocardiography

assessing right and left ventricular function within 24 h of intubation. Results: 140 patients aged 57 ± 11, 29% female were included. Cardiac output was 5.1 L/min [IQR 4.5-6.2] and 86% of the patients required norepinephrine. ICU mortality was 29% (40 patients). Fifty-four patients (39%) exhibited right ventricle dilation out of whom 20 patients (14%) exhibited acute cor pulmonale (ACP). Eight out of the twenty patients with ACP exhibited pulmonary embolism (40%). Thirteen patients (9%) exhibited left ventricular systolic dysfunction (ejection fraction <45%). In the multivariate analysis acute cor pulmonale and PaO2/FiO2 ratio were independent predictors of ICU mortality. Conclusions: Right ventricular dilation is highly prevalent in mechanically ventilated patients with COVID-19 ARDS. Acute cor pulmonale was associated with reduced pulmonary function and, in only 40% of patients, with co-existing pulmonary embolism. Acute cor pulmonale is an independent risk factor for ICU mortality.

ANN INTENSIVE CARE. 2022 NOV 28;12(1):109. DOI: 10.1186/S13613-022-01082-W.

CONTINUOUS PROLONGED PRONE POSITIONING IN COVID-19-RELATED ARDS: A MULTICENTER COHORT STUDY FROM CHILE

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Background: Prone positioning is currently applied in time-limited daily sessions up to 24 h which determines that most patients require several sessions. Although longer prone sessions have been reported, there is scarce evidence about the feasibility and safety of such approach. We analyzed feasibility and safety of a continuous prolonged prone positioning strategy implemented nationwide, in a large cohort of COVID-19 patients in Chile. Methods: Retrospective cohort study of mechanically ventilated COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS), conducted in 15 Intensive Care Units, which adhered to a national protocol of continuous prone sessions ≥ 48 h and until PaO2:FiO2 increased above 200 mm Hg. The number and extension of prone sessions were registered, along with relevant physiologic data and adverse events related to prone positioning. The cohort was stratified according to the first prone session duration: Group A, 2-3 days; Group B, 4-5 days; and Group C, > 5 days. Multivariable regression analyses were performed to assess whether the duration of prone sessions could impact safety. Results: We included 417 patients who required a first prone session of 4 (3-5) days, of whom 318 (76.3%) received only one session. During the first prone session the main adverse event was grade 1-2 pressure sores in 97 (23.9%) patients; severe adverse events were infrequent with 17 non-scheduled extubations (4.2%). 90-day mortality was 36.2%. Ninety-eight patients (24%) were classified as group C; they exhibited a more severe ARDS at baseline, as reflected by lower PaO2:FiO2 ratio and higher ventilatory ratio, and had a higher rate of pressure sores (44%) and higher 90-day mortality (48%). However, after adjustment for severity and several relevant confounders, prone session duration was not associated with mortality or pressure sores. Conclusions: Nationwide implementation of a continuous prolonged prone positioning strategy for COVID-19 ARDS patients was feasible. Minor pressure sores were frequent but within the ranges previously described, while severe adverse events were infrequent. The duration of prone session did not have an adverse effect on safety.

LANCET REG HEALTH AM. 2021 NOV 1;5:100082. DOI: 10.1016/J.LANA.2021.100082. ECOLLECTION 2022 JAN.

EFFECTS OF 2019'S SOCIAL PROTESTS ON EMERGENCY HEALTH SERVICES UTILIZATION AND CASE SEVERITY IN SANTIAGO, CHILE: A TIME-SERIES ANALYSIS

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Background: On October 18th, 2019, protestors gathered across Chile to call for social equity, resulting in widespread civil unrest and violent confrontation with the police. In this study, we quantify the effects of the 2019 Chilean protests on emergency health services utilization and inpatient admission in Santiago. Methods: We used weekly emergency department (ED) admissions (2015-2019) from three large public hospitals near the focal point of protests in Santiago. The exposure period was from October 18th to December 31st, 2019. The outcomes were the number of weekly consultations and hospitalizations by trauma and respiratory causes and the proportion of hospitalizations among consultants per 1,000. We implemented Bayesian structural time series models to calculate the absolute and relative effects and 95% credible intervals (CrI). Findings: During the first ten weeks of protests ED consultations declined on average by 14% for trauma (95%CrI: -40·2%, 11·5%) and 30% for respiratory causes (95%CrI: -89·4%, 30·2%), 7% for respiratory hospitalizations (95%CrI: -43·6%, 30·8%); however, none of these three results were statistically distinguishable from the null. Trauma hospitalizations, on the other hand, increased by 15% (95%CrI: 4·0%, 26·4%), and the proportion of hospitalizations per consultations increased by 40% for trauma (95%CrI: 13·1%, 68·0%) and 59% for respiratory causes (95%CrI: 29·4%, 87·9%). Interpretation: The 2019 Chilean protests affected the use of emergency health services by increasing the trauma hospitalizations and the case hospitalization ratio per 1,000 consultations for trauma and respiratory causes. Crowd-control protocols must be reviewed to prevent the negative effects of civil unrest.

FRONT MED (LAUSANNE). 2022 NOV 4;9:1013430. DOI: 10.3389/FMED.2022.1013430. ECOLLECTION 2022.

ELECTROENCEPHALOGRAPHY SPECTRAL EDGE FREQUENCY AND SUPPRESSION RATE-GUIDED SEDATION IN PATIENTS WITH COVID-19: A RANDOMIZED CONTROLLED TRIAL

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Background: Sedation in coronavirus disease 2019 (COVID-19) patients has been identified as a major challenge. We aimed to investigate whether the use of a multiparameter electroencephalogram (EEG) protocol to guide sedation in COVID-19 patients would increase the 30-day mechanical ventilation-free days (VFD). Methods: We conducted a double-blind randomized clinical trial. We included patients with severe pneumonia due to COVID-19 who required mechanical ventilation (MV) and deep sedation. We randomized to the control (n = 25) or multiparameter group (n = 25). Sedation in the intervention group was administered following the standard institutional protocols together with a flow chart designed to reduce the propofol administration dose if the EEG suppression rate was over 2% or the spectral edge frequency 95 (SEF95) was below 10 Hz. We performed an intention-to-treat analysis to evaluate our primary outcome (30-day VFD). Results: There was no difference in VFD at day 30 (median: 11 [IQR 0-20] days in the control group vs. 0 [IQR 0-21] days in the BIS multiparameter group, p = 0.87). Among secondary outcomes, we documented a 17% reduction in the total adjusted propofol administered during the first 5 days of the protocol [median: 2.3 (IQR 1.9-2.8) mg/k/h in the control group vs. 1.9(IQR 1.5-2.2) mg/k/h in the MP group, p = 0.005]. This was accompanied by a higher average BIS value in the intervention group throughout the treatment period. Conclusion: A sedation protocol guided by multivariate EEG-derived parameters did not increase the 30-day VFD. However, the intervention led to a reduction in total propofol administration.

DEPARTAMENTO DE OBSTETRICIA Y GINECOLOGÍA

INT J MOL SCI. 2022 FEB 15;23(4):2124. DOI: 10.3390/IJMS23042124.

NGF/TRKA PROMOTES ADAM17-DEPENDENT CLEAVAGE OF P75 IN OVARIAN CELLS: ELUCIDATING A PRO-TUMORAL MECHANISM

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Nerve growth factor (NGF) and its high-affinity receptor TRKA are overexpressed in epithelial ovarian cancer (EOC) displaying a crucial role in the disease progression. Otherwise, NGF interacts with its low-affinity receptor P75, activating pro-apoptotic pathways. In neurons, P75 could be cleaved by metalloproteinases (α and γ-secretases), leading to a decrease in P75 signaling. Therefore, this study aimed to evaluate whether the shedding of P75 occurs in EOC cells and whether NGF/TRKA could promote the cleavage of the P75 receptor. The immunodetection of the α-secretase, ADAM17, TRKA, P75, and P75 fragments was assessed by immunohisto/cytochemistry and Western blot in biopsies and ovarian cell lines. The TRKA and secretases' inhibition was performed using specific inhibitors. The results show that P75 immunodetection decreased during EOC progression and was negatively correlated with the presence of TRKA in EOC biopsies. NGF/TRKA increases ADAM17 levels and the fragments of P75 in ovarian cells. This effect is abolished when cells are previously treated with ADAM17, γ-secretase, and TRKA inhibitors. These results indicate that NGF/TRKA promotes the shedding of P75, involving the activation of secretases such as ADAM17. Since ADAM17 has been proposed as a screening marker for early detection of EOC, our results contribute to understanding better the role of ADAM17 and NGF/TRKA in EOC pathogenesis, which includes the NGF/TRKA-mediated cleavage of P75.

J CLIN ULTRASOUND. 2023 FEB;51(2):249-264. DOI: 10.1002/JCU.23336.

CARDIAC REMODELING FROM THE FETUS TO ADULTHOOD

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Prenatal cardiac remodeling refers to in utero changes in the fetal heart that occur as a response to an adverse intrauterine environment. In this article, we will review the main mechanisms leading to cardiac remodeling and dysfunction, summarizing and describing the major pathological conditions that have been reported to be related to this in utero plastic adaptive process. We will also recap the current evidence regarding the persistence of fetal cardiac remodeling and dysfunction, both in infancy and later in adult life. Moreover, we will discuss primary, secondary, and tertiary preventive measures and future clinical and research aspects.

J OBSTET GYNAECOL RES. 2022 JUL;48(7):1658-1667. DOI: 10.1111/JOG.15283.

FETAL CARDIAC DYSFUNCTION IN PREGNANCIES AFFECTED BY INTRAHEPATIC CHOLESTASIS OF PREGNANCY: A COHORT STUDY

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Aim: To analyze the presence of fetal myocardial dysfunction in intrahepatic cholestasis of pregnancy (ICP) at diagnosis. Methods: This prospective cohort study included 49 pregnant participants with ICP at diagnosis and 49 nonaffected controls from a single

public hospital. ICP was diagnosed based on clinical symptoms after excluding other causes of pruritus and presence of autoimmune diseases. Total bile acids were not obtained in this cohort. ICP pregnancies were assessed with a functional echocardiography at diagnosis including PR-interval, isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT) for electrical, systolic, and diastolic function, respectively. Controls were assessed at recruitment. Perinatal outcomes were obtained from delivery books. The main outcome was the presence of PR-interval prolongation or first-degree fetal heart block, and echographic signs of diastolic and systolic dysfunction. Results: Compared to controls, ICP were above upper limit in conjugated bilirubin (2.0% vs. 20.4%; p = 0.008), aspartate aminotransferase (2.0% vs. 24.5%; p = 0.002), and alanine aminotransferase (4.1% vs. 28.6%; p = 0.002). ICP was associated with a higher PR-interval (130 ± 12 ms vs. 121 ± 6 ms; p < 0.0001) with five first-degree fetal heart blocks. IRT was significantly higher in ICP (42 ± 6 ms vs. 37 ± 5 ms; p = 0.0001), with no differences in ICT and ET. PR-interval trend was only positively correlated with IRT in ICP pregnancies (p = 0.04 and p = 0.34, in ICP and controls, respectively). Conclusions: Our study demonstrates that fetuses affected by maternal ICP are associated with electrical and diastolic myocardial dysfunction. More studies focused on antenatal and postnatal functional echocardiography are necessary to validate our results and consider these markers in the clinical management of ICP pregnancies.

BMJ OPEN. 2022 FEB 4;12(2):E051700. DOI: 10.1136/BMJOPEN-2021-051700.

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

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

SCI REP. 2022 MAY 30;12(1):9016. DOI: 10.1038/S41598-022-13047-X.

CONCORDANCE OF THE RISK OF NEONATAL RESPIRATORY MORBIDITY ASSESSED BY QUANTITATIVE ULTRASOUND LUNG TEXTURE ANALYSIS IN FETUSES OF TWIN PREGNANCIES

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To evaluate the concordance of the risk of neonatal respiratory morbidity (NRM) assessed by quantitative ultrasound lung texture analysis (QuantusFLM) between twin fetuses of the same pregnancy. Prospective study conducted in twin pregnancies. Fetal ultrasound lung images were obtained at 26.0-38.6 weeks of gestation. Categorical (high or low) and continuous results of the risk of NRM were compared between twins. Fetal ultrasound lung images from 131 pairs (262 images) of twins were included. The images were classified into three gestational age ranges: Group 1 (26.0-29.6 weeks, 78 images, 39 pairs [29.8%]); Group 2 (30.0-33.6 weeks, 98 images, 49 pairs [37.4%]) and Group 3 (34.0-38.6 weeks, 86 images, 43 pairs [32.8%]). Concordance was good in Groups 1 and 3 and moderate in Group 2. In Groups 2 and 3 at least one fetus presented high-risk results in 26.5% and 11.6% of twin pairs, respectively. Only gestational age < 32 weeks, gestational diabetes mellitus, and spontaneous conception were associated with a high risk of NRM in Group 2. There was good concordance of the risk of NRM between twins < 30.0 weeks and > 34.0 weeks. From 30.0 to 33.6 weeks 26.5% of the twin pairs had discordant results, with moderate concordance of the risk of NRM.

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PERINATAL OUTCOMES OF PREGESTATIONAL HYPERTENSION ACCORDING TO BLOOD PRESSURE RANGE AT 11-14 WEEK SCAN: IMPACT OF THE 2017 ACC/AHA GUIDELINES

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Objective: The aim of this study was to evaluate the impact on perinatal outcomes related to placental insufficiency with the application of the new 2017 ACC/AHA guidelines to a group of chronic hypertensive pregnancies during their first-trimester assessment. Study design: This retrospective cohort study included pregnancies with preconceptional hypertension and known perinatal outcomes. In the first trimester, a combined screening for preterm preeclampsia (p-PE) was performed, including blood pressure (BP), mean uterine artery Doppler, and maternal characteristics. Patients were divided, according to the 2017 ACC/AHA consensus, into the following groups: elevated or less, Stage 1, and Stage 2. For adverse perinatal outcome assessment, univariate and multivariate regression analyses were performed, considering the "elevated or less" group as a reference. Odds ratios (OR) were compared with linear trend analysis. The main outcomes measured were preterm PE and FGR < 3 rd percentile. Results: Of the 130 included patients, 59 (45.4%) were classified as elevated or less, 47 (36.2%) as Stage 1, and 24 (18.4%) as Stage 2. p-PE showed a significant increase according to BP range [7% (OR = 1.0), 19.6% (OR = 3.2), and 21.7% (OR = 3.7)]; trend p = 0.02, for elevated or less, Stage 1, and Stage 2, respectively. There was a non-significant increased trend of FGR < 3 rd percentile according to the BP stage. The best multivariate predictive model for p-PE included a previous PE background (OR = 15) and mean arterial pressure in mmHg (OR = 1.1). Conclusion: The use of the 2017 ACC/AHA consensus in pregnancies with chronic hypertension identifies an intermediate risk group for placental-mediated diseases.

EUR J IMMUNOL. 2022 JUL;52(7):1069-1076. DOI: 10.1002/EJI.202149774.

HUMAN CDC1S DISPLAY CONSTITUTIVE ACTIVATION OF THE UPR SENSOR IRE1

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The intracellular mechanisms safeguarding DC function are of biomedical interest in several immune-related diseases. Type 1 conventional DCs (cDC1s) are prominent targets of immunotherapy typified by constitutive activation of the unfolded protein response (UPR) sensor IRE1. Through its RNase domain, IRE1 regulates key processes in cDC1s including survival, ER architecture and function. However, most evidence linking IRE1 RNase with cDC1 biology emerges from mouse studies and it is currently unknown whether human cDC1s also activate the enzyme to preserve cellular homeostasis. In this work, we report that human cDC1s constitutively activate IRE1 RNase in steady state, which is evidenced by marked expression of IRE1, XBP1s, and target genes, and low levels of mRNA substrates of the IRE1 RNase domain. On a functional level, pharmacological inhibition of the IRE1 RNase domain curtailed IL-12 and TNF production by cDC1s upon stimulation with TLR agonists. Altogether, this work demonstrates that activation of the IRE1/XBP1s axis is a conserved feature of cDC1s across species and suggests that the UPR sensor may also play a relevant role in the biology of the human lineage.

EUR J OBSTET GYNECOL REPROD BIOL. 2022 SEP;276:161-167. DOI: 10.1016/J.EJOGRB.2022.07.010.

LONG-TERM OUTCOMES OF COVID-19: THE PAN-COVID STUDY

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Objective: To assess perinatal outcomes for pregnancies affected by suspected or confirmed SARS-CoV-2 infection. Methods: Prospective, web-based registry. Pregnant women were invited to participate if they had suspected or confirmed SARS-CoV-2 infection between 1st January 2020 and 31st March 2021 to assess the impact of infection on maternal and perinatal outcomes including miscarriage, stillbirth, fetal growth restriction, pre-term birth and transmission to the infant. Results: Between April 2020 and March 2021, the study recruited 8239 participants who had suspected or confirmed SARs-CoV-2 infection episodes in pregnancy between January 2020 and March 2021. Maternal death affected 14/8197 (0.2%) participants, 176/8187 (2.2%) of participants required ventilatory support. Pre-eclampsia affected 389/8189 (4.8%) participants, eclampsia was reported in 40/ 8024 (0.5%) of all participants. Stillbirth affected 35/8187 (0.4 %) participants. In participants delivering within 2 weeks of delivery 21/2686 (0.8 %) were affected by stillbirth compared with 8/4596 (0.2 %) delivering ≥ 2 weeks after infection (95 % CI 0.3-1.0). SGA affected 744/7696 (9.3 %) of livebirths, FGR affected 360/8175 (4.4 %) of all pregnancies. Pre-term birth occurred in 922/8066 (11.5%), the majority of these were indicated pre-term births, 220/7987 (2.8%) participants experienced spontaneous pre-term births. Early neonatal deaths affected 11/8050 livebirths. Of all neonates, 80/7993 (1.0%) tested positive for SARS-CoV-2. Conclusions: Infection was associated with indicated pre-term birth, most commonly for fetal compromise. The overall proportions of women affected by SGA and FGR were not higher than expected, however there was the proportion affected by stillbirth in participants delivering within 2 weeks of infection was significantly higher than those delivering ≥ 2 weeks after infection. We suggest that clinicians' threshold for delivery should be low if there are concerns with fetal movements or fetal heart rate monitoring in the time around infection. The proportion affected by

pre-eclampsia amongst participants was not higher than would be expected, although we report a higher than expected proportion affected by eclampsia. There appears to be no effect on birthweight or congenital malformations in women affected by SARS-CoV-2 infection in pregnancy and neonatal infection is uncommon. This study reflects a population with a range of infection severity for SARS-COV-2 in pregnancy, generalisable to whole obstetric populations.

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OCUL IMMUNOL INFLAMM. 2022 JAN 2;30(1):174-179. DOI: 10.1080/09273948.2020.1793369.

DEFINITION OF UVEITIS REFRACTORY TO TREATMENT: A SYSTEMATIC REVIEW IN THE ABSENCE OF A CONSENSUS

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Purpose: To evaluate the different definition of refractoriness in uveitis in the literature. Methods: We systematically searched the literature in order to identify definitions of refractory noninfectious uveitis in adult patients. A search strategy in the databases of MEDLINE and Scopus was used to find articles published between January 2005 and October 2018. Results: Definitions of corticosteroids-refractoriness were related to two main concepts: persistence of inflammation despite the use of corticosteroid and recurrences above a dosage threshold. In terms of immunomodulatory therapy and biologic agents, we observed a great variety of definitions: persistence of inflammation, number of attacks, side effects or complications, symptoms, and best-corrected visual acuity. Conclusions: The results of this systematic review demonstrate the current lack of consensus on the definition for refractory uveitis, regardless of the treatment being used and revealed a new terminology based on a comprehensive and operational definition for each specific category of refractoriness.

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DISABIL REHABIL. 2022 APR;44(8):1419-1426. DOI: 10.1080/09638288.2020.1795279.

THE SPANISH 12-ITEM VERSION OF THE SPEECH, SPATIAL AND QUALITIES OF HEARING SCALE (SP-SSQ12): ADAPTATION, RELIABILITY, AND DISCRIMINANT VALIDITY FOR PEOPLE WITH AND WITHOUT HEARING LOSS

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Purpose: Because of the limited number of Spanish validated questionnaires available to assess auditory functionality in daily life situations in adults, the purpose of this study was to investigate the validity and the reliability of the Spanish version of the Speech, Spatial and Qualities of Hearing 12 items scale (sp-SSQ12), adapted from the published Spanish SSQ49, and to provide reference data for normal and hearing-impaired populations. Methods: The SSQ12 is a self-report questionnaire, consisting of 12 items assessing a range of daily life listening situations. One hundred fifty adults (101 female) with a mean age of 53.9 years (SD 20.3; range 20-88 years) took part in the study. Internal consistency, test-retest reliability, validity, and floor and ceiling effects were investigated. Results: The sp-SSQ12 questionnaire had high internal consistency (Cronbach's alpha = 0.95) and test-retest scores were highly correlated (ICC = 0.79). There was minimal evidence of floor and ceiling effects in our sample. Significant differences were observed overall and for the three subscales between normal and hearing-impaired groups. Although some significant differences in SSQ12 scores between groups of participants from different countries, these differences were minimal. Conclusions: The sp-SSQ12 questionnaire is a valid and reliable tool that is easy to administer and requires a short time to answer. We recommend the use of this tool for the assessment of functional hearing in the Spanish-speaking population.Implication for rehabilitationHearing loss impacts people's lives in a number of ways that are captured in the SSQ.The sp-SSQ12 is a valid and reliable tool for assessing everyday listening abilities and limitations experienced by Spanish-speaking adults with hearing loss.The sp-SSQ12 can be incorporated in the hearing rehabilitation process as a tool for evaluating and improving hearing assessment and rehabilitation programs.The sp-SSQ12 can help to identify adults who require a comprehensive hearing assessment.

VIRUSES. 2022 JUN 2;14(6):1212. DOI: 10.3390/V14061212.

HUMAN PAPILLOMAVIRUS DETECTED IN OROPHARYNGEAL CANCERS FROM CHILEAN SUBJECTS

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High-risk human papillomaviruses (HR-HPV) are the causal agents of an important subset of oropharyngeal cancers that has increased considerably in incidence in recent years. In this study, we evaluated the presence of HPV in 49 oropharyngeal cancers from Chilean subjects. The presence of HPV DNA was analyzed by conventional PCR, the genotypes were identified through sequencing, and the expression of E6/E7 transcripts was evaluated by a reverse transcriptase polymerase chain reaction (RT-

PCR). Additionally, to determine p16 expression-a surrogate marker for oncogenic HPV infection-a tissue array was constructed for immunohistochemistry (IHC). HPV was detected in 61.2% of oropharyngeal carcinomas, the most prevalent genotype being HPV16 (80%). E6 and E7 transcripts were detected in 91.6% and 79.1% of the HPV16-positive specimens, respectively, demonstrating functional HPV infections. Furthermore, p16 expression was positive in 58.3% of cases. These findings show a high prevalence of HR-HPV in oropharyngeal tumors from Chile, suggesting the necessity of additional studies to address this growing public health concern.

FRONT AGING NEUROSCI. 2022 FEB 24;14:786330. DOI: 10.3389/FNAGI.2022.786330. ECOLLECTION 2022.

SPEECH PERCEPTION AND DICHOTIC LISTENING ARE ASSOCIATED WITH HEARING THRESHOLDS AND COGNITION, RESPECTIVELY, IN UNAIDED PRESBYCUSIS

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Presbycusis or age-related hearing loss is a prevalent condition in the elderly population, which affects oral communication, especially in background noise, and has been associated with social isolation, depression, and cognitive decline. However, the mechanisms that relate hearing loss with cognition are complex and still elusive. Importantly, recent studies show that the use of hearing aids in presbycusis, which is its standard management, can induce neuroplasticity and modify performance in cognitive tests. As the majority of the previous studies on audition and cognition obtained their results from a mixed sample of subjects, including presbycusis individuals fitted and not fitted with hearing aids, here, we revisited the associations between hearing loss and cognition in a controlled sample of unaided presbycusis. We performed a cross-sectional study in 116 non-demented Chilean volunteers aged ≥65 years from the Auditory and Dementia study cohort. Specifically, we explored associations between bilateral sensorineural hearing loss, suprathreshold auditory brain stem responses, auditory processing (AP), and cognition with a comprehensive neuropsychological examination. The AP assessment included speech perception in noise (SIN), dichotic listening (dichotic digits and staggered spondaic words), and temporal processing [frequency pattern (FP) and gap-in-noise detection]. The neuropsychological evaluations included attention, memory, language, processing speed, executive function, and visuospatial abilities. We performed an exploratory factor analysis that yielded four composite factors, namely, hearing loss, auditory nerve, midbrain, and cognition. These four factors were used for generalized multiple linear regression models. We found significant models showing that hearing loss is associated with bilateral SIN performance, while dichotic listening was associated with cognition. We concluded that the comprehension of the auditory message in unaided presbycusis is a complex process that relies on audition and cognition. In unaided presbycusis with mild hearing loss (<40 dB HL), speech perception of monosyllabic words in background noise is associated with hearing levels, while cognition is associated with dichotic listening and FP.

FRONT NEUROSCI. 2022 APR 27;16:867034. DOI: 10.3389/FNINS.2022.867034. ECOLLECTION 2022.

SUPPORTING CELLS AND THEIR POTENTIAL ROLES IN CISPLATIN-INDUCED OTOTOXICITY

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Cisplatin is a known ototoxic chemotherapy drug, causing irreversible hearing loss. Evidence has shown that cisplatin causes inner ear damage as a result of adduct formation, a proinflammatory environment and the generation of reactive oxygen species within the inner ear. The main cochlear targets for cisplatin are commonly known to be the outer hair cells, the stria vascularis and the spiral ganglion neurons. Further evidence has shown that certain transporters can mediate cisplatin influx into the inner ear cells including organic cation transporter 2 (OCT2) and the copper transporter Ctr1. However, the expression profiles for these transporters within inner ear cells are not consistent in the literature, and expression of OCT2 and Ctr1 has also been observed in supporting cells. Organ of Corti supporting cells are essential for hair cell activity and survival. Special interest has been devoted to gap junction expression by these cells as certain mutations have been linked to hearing loss. Interestingly, cisplatin appears to affect connexin expression in the inner ear. While investigations regarding cisplatin-induced hearing loss have been focused mainly on the known targets previously mentioned, the role of supporting cells for cisplatin-induced ototoxicity has been overlooked. In this mini review, we discuss the implications of supporting cells expressing OCT2 and Ctr1 as well as the potential role of gap junctions in cisplatin-induced cytotoxicity.

FRONT NEUROSCI. 2022 APR 27;16:866161. DOI: 10.3389/FNINS.2022.866161. ECOLLECTION 2022.

CORTICOFUGAL AND BRAINSTEM FUNCTIONS ASSOCIATED WITH MEDIAL OLIVOCOCHLEAR CHOLINERGIC TRANSMISSION

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Cholinergic transmission is essential for survival and reproduction, as it is involved in several physiological responses. In the auditory system, both ascending and descending auditory pathways are modulated by cholinergic transmission, affecting the perception of sounds. The auditory efferent system is a neuronal network comprised of several feedback loops, including corticofugal and

brainstem pathways to the cochlear receptor. The auditory efferent system's -final and mandatory synapses that connect the brain with the cochlear receptor- involve medial olivocochlear neurons and outer hair cells. A unique cholinergic transmission mediates these synapses through $\alpha 9/\alpha 10$ nicotinic receptors. To study this receptor, it was generated a strain of mice carrying a null mutation of the Chrna9 gene ($\alpha 9$-KO mice), lacking cholinergic transmission between medial olivocochlear neurons and outer hair cells, providing a unique opportunity to study the role of medial olivocochlear cholinergic transmission in auditory and cognitive functions. In this article, we review behavioral and physiological studies carried out to research auditory efferent function in the context of audition, cognition, and hearing impairments. Auditory studies have shown that hearing thresholds in the $\alpha 9$-KO mice are normal, while more complex auditory functions, such as frequency selectivity and sound localization, are altered. The corticofugal pathways have been studied in $\alpha 9$-KO mice using behavioral tasks, evidencing a reduced capacity to suppress auditory distractors during visual selective attention. Finally, we discuss the evolutionary role of the auditory efferent system detecting vocalizations in noise and its role in auditory disorders, such as the prevention of age-related hearing loss.

ACTA OTOLARYNGOL. 2023 JAN;143(1):28-30. DOI: 10.1080/00016489.2022.2162959.

HEARING LOSS IN SCHOOL-AGED CHILDREN

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Background: Hearing loss is a common disability affecting 5% of the world's population. A lack of opportune diagnosis affects both the individual and society. In order to develop public health policies in the field of hearing health, countries must have information about epidemiology. Aims/objectives: In this review, we describe the information available about prevalence and incidence of hearing loss in school-aged children. Material and methods: Review of the literature in PubMed. Results: Reported prevalence of hearing loss in school-aged children varied between 0.2% and 7.8%. Several factors could explain the discrepancy in numbers such as definition of hearing loss, cause, and the inclusion of high-frequency hearing loss. The rate of delayed-onset hearing loss at the age of six years old varied between 0.6 and 0.8 per 1000. Conclusions and significance: The prevalence of hearing loss in school-aged children varied between 0.2% and 7.8%, and the rate of delayed-onset hearing loss at the age of six years old varied between 0.6 and 0.8 per 1000.

DIAGNOSTICS (BASEL). 2022 APR 7;12(4):917. DOI: 10.3390/DIAGNOSTICS12040917.

COLOR DEPENDENCE ANALYSIS IN A CNN-BASED COMPUTER-AIDED DIAGNOSIS SYSTEM FOR MIDDLE AND EXTERNAL EAR DISEASES

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Artificial intelligence-assisted otologic diagnosis has been of growing interest in the scientific community, where middle and external ear disorders are the most frequent diseases in daily ENT practice. There are some efforts focused on reducing medical errors and enhancing physician capabilities using conventional artificial vision systems. However, approaches with multispectral analysis have not yet been addressed. Tissues of the tympanic membrane possess optical properties that define their characteristics in specific light spectra. This work explores color wavelengths dependence in a model that classifies four middle and external ear conditions: normal, chronic otitis media, otitis media with effusion, and earwax plug. The model is constructed under a computer-aided diagnosis system that uses a convolutional neural network architecture. We trained several models using different single-channel images by taking each color wavelength separately. The results showed that a single green channel model achieves the best overall performance in terms of accuracy (92%), sensitivity (85%), specificity (95%), precision (86%), and F1-score (85%). Our findings can be a suitable alternative for artificial intelligence diagnosis systems compared to the 50% of overall misdiagnosis of a non-specialist physician.

INT J AUDIOL. 2023 JAN;62(1):53-61. DOI: 10.1080/14992027.2021.1998675.

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

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

DEPARTAMENTO DE NEUROLOGÍA Y NEUROCIRUGÍA

J NEUROL NEUROSURG PSYCHIATRY. 2022 JUL 27;JNNP-2022-328921. DOI: 10.1136/JNNP-2022-328921.

GENOTYPE-PHENOTYPE CORRELATIONS IN VALOSIN-CONTAINING PROTEIN DISEASE: A RETROSPECTIVE MUTICENTRE STUDY

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Background: Valosin-containing protein (VCP) disease, caused by mutations in the VCP gene, results in myopathy, Paget's disease of bone (PBD) and frontotemporal dementia (FTD). Natural history and genotype-phenotype correlation data are limited. This study characterises patients with mutations in VCP gene and investigates genotype-phenotype correlations. Methods: Descriptive retrospective international study collecting clinical and genetic data of patients with mutations in the VCP gene. Results: Two hundred and fifty-five patients (70.0% males) were included in the study. Mean age was 56.8±9.6 years and mean age of onset 45.6±9.3 years. Mean diagnostic delay was 7.7±6 years. Symmetric lower limb weakness was reported in 50% at onset progressing to generalised muscle weakness. Other common symptoms were ventilatory insufficiency 40.3%, PDB 28.2%, dysautonomia 21.4% and FTD 14.3%. Fifty-seven genetic variants were identified, 18 of these no previously reported. c.464G>A (p.Arg155His) was the most frequent variant, identified in the 28%. Full time wheelchair users accounted for 19.1% with a median time from disease onset to been wheelchair user of 8.5 years. Variant c.463C>T (p.Arg155Cys) showed an earlier onset (37.8±7.6 year) and a higher frequency of axial and upper limb weakness, scapular winging and cognitive impairment. Forced vital capacity (FVC) below 50% was as risk factor for being full-time wheelchair user, while FVC <70% and being a full-time wheelchair user were associated with death. Conclusion: This study expands the knowledge on the phenotypic presentation, natural history, genotype-phenotype correlations and risk factors for disease progression of VCP disease and is useful to improve the care provided to patient with this complex disease.

REV MED CHIL. 2022 JAN;150(1):78-87. DOI: 10.4067/S0034-98872022000100078.

ACTUALIZACIÓN EN EL TRATAMIENTO DEL SÍNDROME DE HIPERTENSIÓN INTRACRANEANA

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Elevated intracranial pressure (ICP) is a devastating complication, with great impact on neurological status and high morbidity and mortality. Intracranial hypertension (ICH) has multiple etiologies. The natural history of this condition can lead to brain death. The successful management of patients with elevated ICP (> 20-25 mmHg) requires fast and timely recognition, judicious use of invasive monitoring and therapies aimed to reversing its underlying cause. Therefore, it must be managed as a neurological emergency. The objective of this review is to present in a friendly way the diagnostic approach and the management of ICH, focused on general practitioners.

J COMMUN DISORD. 2022 MAY-JUN;97:106202. DOI: 10.1016/J.JCOMDIS.2022.106202.

LINGUISTIC PROFILES OF VARIANTS OF PRIMARY PROGRESSIVE APHASIA

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Background: Several subtypes of primary progressive aphasia (PPA) have been proposed. Most reports use small samples, and few have included Spanish-speaking participants. Aim: To analyze the language profile and nonlinguistic deficits in a large sample of PPA Spanish monolingual participants. Method: 177 individuals were diagnosed with PPA in a sample consisting of 69 men and 108 women (Mage = 66.40 years, SD = 9.30). The participants were assessed using the Spanish versions of the Western Aphasia Battery Revised (SWAB-R) and the Boston Diagnostic Aphasia Examination (SBDAE). Non-verbal reasoning was evaluated with the Raven's Colored Progressive Matrices. Results: 41.8% of the sample met the criteria for the logopenic variant (lvPPA), while 28.2% met the criteria for semantic (svPPA), 15.3% for lexical (lxvPPA), and 14.7% for nonfluent/agrammatic (nfvPPA) variants. Language difficulties were similar in all variants except for lxvPPA. Scores on Spontaneous Language, Auditory Comprehension, Repetition, and Naming were significantly higher for the lxvPPA group. Raven's Colored Progressive Matrices scores were significantly lower in lvPPA. Years of education correlated with all test scores, while age was negatively associated with naming. When the PPA variants were classified according to the traditional aphasia classification, discrepancies were evident. Furthermore, the most frequent type of aphasia was Amnesic, while the least frequent was Wernicke's aphasia. Conclusion: The SWAB-R is useful in describing the clinical characteristics of aphasia for each variant of PPA, but quantitative scores from this battery are not capable of distinguishing between variants of PPA, with the exception of lxvPPA.

NEUROLOGY. 2022 SEP 13;10.1212/WNL.0000000000201315. DOI: 10.1212/WNL.0000000000201315.

PEARLS & OY-STERS: MANAGING CHOLESTEROL IN A PATIENT WITH STATIN INTOLERANCE DUE TO ANTI-HMG-COA REDUCTASE-ASSOCIATED MYOPATHY

Eduardo Villa, Rodrigo Naves, Katiuska Bezares, Karen Cobeña, Ana Claudia Villarroel, Carlos Guevara

Statins are the first line of treatment for hypercholesterolemia and of prevention of atherosclerotic cardiovascular disease (ASCVD). It is estimated that one in four Americans over the age of 40 years use statins. In rare cases patients may develop an autoimmune myopathy associated with antibodies against 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR). Anti-HMGCR associated

myopathy requires immediate discontinuation of statins plus initiation of immunosuppressive therapy. Suspension of statin treatment worsens low-density lipoprotein-cholesterol (LDL-C) control, leading to an increased risk of ASCVD and necessitating commencement of another treatment for dyslipidemia. Unfortunately, the management of dyslipidemia in these patients is still unclear. Herein, we describe the case of a 65-year-old woman with dyslipidemia treated with atorvastatin, who consulted for long-standing muscle pain associated with symmetrical proximal weakness. Laboratory tests showed elevated levels of creatine kinase and anti-HMGCR antibodies. She was diagnosed with an anti-HMGCR associated myopathy and was successfully treated with corticosteroids and azathioprine as immunosuppressive therapy, followed by ezetimibe for LDL-C reduction. We present key findings for early recognition and treatment of anti-HMGCR associated myopathy and give recommendations on how to manage hypercholesterolemia in a patient with statin intolerance due to this disease.

GENES (BASEL). 2022 JUN 16;13(6):1076. DOI: 10.3390/GENES13061076.

GENETIC PROFILE OF PATIENTS WITH LIMB-GIRDLE MUSCLE WEAKNESS IN THE CHILEAN POPULATION

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Hereditary myopathies are a group of genetically determined muscle disorders comprising more than 300 entities. In Chile, there are no specific registries of the distinct forms of these myopathies. We now report the genetic findings of a series of Chilean patients presenting with limb-girdle muscle weakness of unknown etiology. Eighty-two patients were explored using high-throughput sequencing approaches with neuromuscular gene panels, establishing a definite genetic diagnosis in 49 patients (59.8%) and a highly probable genetic diagnosis in eight additional cases (9.8%). The most frequent causative genes identified were DYSF and CAPN3, accounting for 22% and 8.5% of the cases, respectively, followed by DMD (4.9%) and RYR1 (4.9%). The remaining 17 causative genes were present in one or two cases only. Twelve novel variants were identified. Five patients (6.1%) carried a variant of uncertain significance in genes partially matching the clinical phenotype. Twenty patients (24.4%) did not carry a pathogenic or likely pathogenic variant in the phenotypically related genes, including five patients (6.1%) presenting an autoimmune neuromuscular disorder. The relative frequency of the different forms of myopathy in Chile is like that of other series reported from different regions of the world with perhaps a relatively higher incidence of dysferlinopathy.

AM J ALZHEIMERS DIS OTHER DEMEN. 2022 JAN-DEC;37:15333175221094396. DOI: 10.1177/15333175221094396.

VALIDATION OF PICTURE FREE AND CUED SELECTIVE REMINDING TEST FOR ILLITERACY IN LIMA, PERU

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Dementia in Latin America is a crucial public health problem. Identifying brief cognitive screening (BCS) tools for the primary care setting is crucial, particularly for illiterate individuals. We evaluated tool performance characteristics and validated the free and total recall sections of the Free and Cued Selective Reminding Test-Picture version (FCSRT-Picture) to discriminate between 63 patients with early Alzheimer's disease dementia (ADD), 60 amnestic mild cognitive impairment (aMCI) and 64 cognitively healthy Peruvian individuals with illiteracy from an urban area. Clinical, functional, and cognitive assessments were performed. FCSRT-Picture performance was assessed using receiver operating characteristic curve analyses. The mean ± standard deviation scores were 7.7 ± 1.0 in ADD, 11.8 ± 1.6 in aMCI, and 29.5 ± 1.8 in controls. The FCSRT-Picture had better performance characteristics for distinguishing controls from aMCI compared with several other BCS tools, but similar characteristics between controls and early ADD. The FCSRT-Picture is a reliable BCS tool for illiteracy in Peru.

ALZHEIMERS DEMENT (AMST). 2022 FEB 23;14(1):E12273. DOI: 10.1002/DAD2.12273. ECOLLECTION 2022.

POPULATION ATTRIBUTABLE FRACTION OF MODIFIABLE RISK FACTORS FOR DEMENTIA IN CHILE

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Introduction: Projected dementia incidence in Latin America and the Caribbean for the next decades is overwhelming. Access to local data, stratified by sex, is imperative for planning precise dementia-prevention strategies. Methods: We analyzed the individual and overall weighted population attributable fraction (PAF) of nine modifiable risk factors for dementia, in dementia-free subjects ≥45-years-old, using the 2016-2017 Chilean National Health Survey. Results: The overall weighted PAF for modifiable risk factors was 45.8% (42.2% to 49.3%). Variables with the highest PAF were lower education, high blood pressure, hearing loss, and obesity. Women showed a greater overall weighted PAF: 50.7% (45.3% to -56.1%), compared to men: 40.2% (35.4% to 45.0%), driven by a higher PAF for physical inactivity and depression in women. Discussion: The PAF for modifiable risk factors for dementia in Chile is higher than in previous world reports, due to a greater prevalence of cardiovascular risk factors. Women have a higher potential for dementia prevention. Highlights: The proportion of dementia associated to modifiable risk factors in Chile is 45.8%.The main modifiable risk

factors are high blood pressure, obesity, and hearing loss.Women had a greater prevalence of physical inactivity and depression than men.Chile had a greater prevalence of metabolic risk factors than other world regions.

NEUROMUSCUL DISORD. 2022 AUG;32(8):687-691. DOI: 10.1016/J.NMD.2022.05.014.

NOVEL AUTOSOMAL DOMINANT TPM3 MUTATION CAUSES A COMBINED CONGENITAL FIBRE TYPE DISPROPORTION-CAP DISEASE HISTOLOGICAL PATTERN

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Tropomyosin 3 (TPM3) gene mutations associate with autosomal dominant and recessive nemaline myopathy 1 (NEM1), congenital fiber type disproportion myopathy (CFTD) and cap myopathy (CAPM1), and a combination of caps and nemaline bodies. We report on a 47-year-old man with polyglobulia, restricted vital capacity and mild apnea hypopnea syndrome, requiring noninvasive ventilation. Physical assessment revealed bilateral ptosis and facial paresis, with high arched palate and retrognathia; global hypotonia and diffuse axial weakness, including neck and upper and lower limb girdle and foot dorsiflexion weakness. Whole body MRI showed a diffuse fatty replacement with an unspecific pattern. A 122 gene NGS neuromuscular disorders panel revealed the heterozygous VUS c.709G>A (p.Glu237Lys) on exon 8 of TMP3. A deltoid muscle biopsy showed a novel histological pattern combining fiber type disproportion and caps. Our findings support the pathogenicity of the novel TPM3 variant and widen the phenotypic gamut of TMP3-related congenital myopathy.

DEPARTAMENTO DE PSIQUIATRÍA Y SALUD MENTAL

INT J DRUG POLICY. 2022 SEP;107:103793. DOI: 10.1016/J.DRUGPO.2022.103793.

THE ALCOHOL PREVENTION MAGNITUDE MEASURE: APPLICATION OF A SPANISH-LANGUAGE VERSION IN SANTIAGO, CHILE

Lorena Contreras, Nicolás Libuy, Viviana Guajardo, Carlos Ibáñez, Paula Donoso, Adrian P Mundt

Background: The Alcohol Prevention Magnitude Measure (APMM) is an instrument to monitor and improve substance use prevention at the community level developed in Sweden. The aim of this study was to produce and apply a Spanish-language version of the APMM. Method: We translated and adapted the APMM using an expert panel. We retained 37 indicators in five dimensions, with total scores ranging from 0 to 100 points and 0 to 20 in each dimension. The instrument was administered to the prevention coordinators in six socioeconomically heterogeneous municipalities of Santiago de Chile, during the pilot implementation of a community-based prevention model in 2019 and 2020. We calculated median scores for the instrument and each dimension. We tested for differences between 2019 and 2020 using the Wilcoxon Test and between municipalities with the Friedman Test. Results: The Spanish version of the APMM was acceptable to stakeholders. The median scores were 49.3 (range: 34.0 to 64.0) in 2019 and 67.3 (range 55.5 to 80.5) in 2020. The median scores for Staff and budget were 14.0 in 2019 and 2020, for Prevention policy 5.0 in 2019 and 16.0 in 2020, for Cooperation with key agents 12.0 in both years, for Supervision and alcohol licenses 4.3 in 2019 and 9.0 in 2020, and for Prevention activities 11.0 in 2019 and 15.0 in 2020. The scores in the dimensions Prevention policy and Supervision and alcohol licenses significantly increased in 2020. The differences between the municipalities were not significant. Conclusions: Improvements of the prevention index between 2019 and 2020 in the dimension Prevention policies may be related to the intervention. Improvements in Supervision and alcohol licenses could be related to curfew policies in the context of the COVID-19 pandemic. The Spanish version of the APMM deserves larger scale testing in Latin America.

MOL PSYCHIATRY. 2022 APR;27(4):1873-1879. DOI: 10.1038/S41380-021-01435-0.

MINIMUM AND OPTIMAL NUMBERS OF PSYCHIATRIC BEDS: EXPERT CONSENSUS USING A DELPHI PROCESS

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The required minimum number of psychiatric inpatient beds is highly debated and has substantial resource implications. The present study used the Delphi method to try to reach a global consensus on the minimum and optimal psychiatric bed numbers. An international board of scientific advisors nominated the Delphi panel members. In the first round, the expert panel provided responses exploring estimate ranges for a minimum to optimal numbers of psychiatric beds and three levels of shortage. In a second round, the panel reconsidered their responses using the input from the total group to achieve consensus. The Delphi panel comprised 65 experts (42% women, 54% based in low- and middle-income countries) from 40 countries in the six regions of the World Health Organization. Sixty psychiatric beds per 100 000 population were considered optimal and 30 the minimum, whilst 25-30 was regarded as mild, 15-25 as moderate, and less than 15 as severe shortage. This is the first expert consensus on minimum and optimal bed numbers involving experts from HICs and LMICs. Many high-income countries have psychiatric bed numbers that fall within the recommended range. In contrast, the number of beds in many LMIC is below the minimum recommended rate.

BEHAV SCI (BASEL). 2022 OCT 19;12(10):401. DOI: 10.3390/BS12100401.

CHILDREN'S MENTAL HEALTH: DISCREPANCY BETWEEN CHILD SELF-REPORTING AND PARENTAL REPORTING

Alejandra Caqueo-Urízar, Alfonso Urzúa, Ester Villalonga-Olives, Diego Atencio-Quevedo, Matías Irarrázaval, Jerome Flores, Cristian Ramírez

Background: Discrepancies between children's self-reports and their parents' reports on mental health indicators are associated with measurement errors or informant bias. However, they are a valuable tool in understanding the course of child psychopathology. This study aims to determine the level of discrepancies between parents' perceptions and children's self-reports in mental health indicators in Northern Chile. Methods: A System of Evaluation of Children and Adolescents self-report (Sistema de Evaluación de Niños y Adolescentes, SENA) was responded to by 408 students between 8 and 13 years old and their parents. Results: Children reported a significantly higher frequency of emotional problems, defiant behavior, and executive functions as compared to their parents' responses. Conclusions: There is a disjunction between the report of parents and children, which could originate in poor family communication.

INT J ENVIRON RES PUBLIC HEALTH. 2022 NOV 21;19(22):15374. DOI: 10.3390/IJERPH192215374.

THE IMPACT OF A YOGA-BASED MINDFULNESS INTERVENTION VERSUS PSYCHO-EDUCATIONAL SESSION FOR OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: THE PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

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Background: There is a global agreement in the medical community that a significant proportion of dementia cases could be prevented or postponed. One of the factors behind this agreement comes from scientific evidence showing that mind-body interventions such as mindfulness and yoga for the elderly have been related to a range of positive outcomes, including improved cognition performance in seniors with mild cognitive impairment (MCI). Objective: This study aims to evaluate the effectiveness of a yoga-based mindfulness intervention (YBM) versus psychoeducational sessions for older adults with MCI attending Hospital Clinic Universidad de Chile in Santiago. Method: Two-arm, individually randomized controlled trial (RCT) will be carried out at Clinical Hospital Universidad de Chile in Santiago. Older people over 60 years with any type of MCI using a score < 21 in the Montreal Cognitive Assessment (MoCA) test and a score of 0.05 in the Clinical Dementia Rating (CDR) Scale; and with preserved activities of daily living will be randomly assigned with an allocation ratio of 1:1 in either the yoga-based mindfulness intervention or the active control group based on the psycho-educational program. People who have performed yoga and/or mindfulness in the last 6 months or/and people with a psychiatric clinical diagnosis will be excluded from the study. Montreal Cognitive Assessment, the Lawton Instrumental Activities of Daily Living Scale (IADL), the Barthel Index (BI), the Pemberton happiness index, the Geriatric Anxiety Inventory (GAI) as well as the Geriatric Depression Scale (GDS-5) will be administered by blinded outcomes assessors before random assignment (Pre-test), the week following the last session of the intervention (post-test), and then after 3- and 6-months follow-up. Results: The YBM intervention protocol based on a video recording has been adapted and designed. This is the first RCT to examine the effects of a yoga-based mindfulness intervention in improving cognitive and physical functions and mental health outcomes for Chilean elderly diagnosed with MCI. It is expected to be implemented as an acceptable and effective non-pharmacological option for older people with MCI. Conclusion: Providing evidence-based programs such as preventive therapy for Alzheimer's disease has relevant implications for public mental health services in Chile.

INT J MENT HEALTH SYST. 2022 JAN 28;16(1):5. DOI: 10.1186/S13033-022-00519-W.

THE EFFECTS OF NATIONAL MENTAL HEALTH PLANS ON MENTAL HEALTH SERVICES DEVELOPMENT IN CHILE: RETROSPECTIVE INTERRUPTED TIME SERIES ANALYSES OF NATIONAL DATABASES BETWEEN 1990 AND 2017

Adrian P Mundt, Pablo Martínez, Sebastián Jaque, Matías Irarrázaval

Aims: To describe changes in mental health services in Chile between 1990 and 2017, and to retrospectively assess the effects of national mental health plans (NMHPs) on mental health services development during this period. Methods: Service data (beds in psychiatric hospitals, psychiatric beds in general hospitals, forensic psychiatric beds, beds in protected housing facilities, psychiatric day hospital places, and outpatient mental health care centers) were retrieved from government sources in Chile. Data were reported as rates per 100,000 population. We conducted interrupted time series analyses, using ordinary least-square regressions with Newey-West standard errors, to assess the effects of the 1993 and 2000 NMPHs on mental health services development. Results: Rates of short- and long-stay beds in psychiatric hospitals (per 100,000 population) were reduced from 4.3 to 3.2 and from 19.0 to 2.0 over the entire time span, respectively. The strongest reduction of short- and long-stay beds in psychiatric hospitals was seen between the 1993 and 2000 NMHPs (annual removal of - 0.14 and - 1.03, respectively). We observed increased rates of psychiatric beds in general hospitals from 1.8 to 4.0, beds in protected housing facilities from 0.4 to 10.2, psychiatric day hospital places from 0.4 to 5.0, outpatient mental health care centers from 0.1 to 0.8 and forensic psychiatric beds from 0.3 to 1.1 over the entire time span. The strongest annual increase of rates of psychiatric beds in general hospitals (0.09), beds in protected housing facilities (0.50), psychiatric day hospital places (0.16) and outpatient mental health care centers (0.04) were observed after the 2000 NMHP. Forensic psychiatric beds increased in the year 2007 (0.58) due to the opening of a new facility. Conclusions: The majority of acute care psychiatric beds in Chile now are based in general hospitals. The strong removal of short- and long-stay beds from psychiatric hospitals after the 1993 NMHP preceded substantial expansion of more

modern mental health services in general hospitals and in the community. Only after the 2000 NMHP, the implementation of new mental health services gained momentum. Reiterative policies are needed to readjust mental health services development.

FRONT PSYCHOL. 2022 OCT 10;13:1000059. DOI: 10.3389/FPSYG.2022.1000059. ECOLLECTION 2022.

PHENOMENOLOGICAL CONSIDERATIONS ON EMPATHY AND EMOTIONS IN PSYCHOTHERAPY

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In this article we will present a phenomenological approach to empathy and its relationship with emotions in the context of psychotherapy, highlighting the importance of empathy as a key element of the therapist-client relationship and therapeutic process, regardless of the therapist's approach. We will use a consensus definition of empathy taken from phenomenologically oriented philosophy to analyze therapist's empathy, as well as client's self-empathy and client's empathic communication with others. We will discuss emotions as they usually manifest in the context of psychotherapy, specifically describing how certain emotions can disturb empathic communication in close personal relationships and how it is possible to reestablish empathic communication in psychotherapy. This article it is not only based on evidence from scientific literature but also incorporates the authors' practical knowledge of psychotherapy.

INT J ENVIRON RES PUBLIC HEALTH. 2022 FEB 17;19(4):2262. DOI: 10.3390/IJERPH19042262.

THE MEDIATING ROLE OF CONTEXTUAL PROBLEMS AND SENSATION SEEKING IN THE ASSOCIATION BETWEEN SUBSTANCE USE AND MENTAL HEALTH IN ADOLESCENTS FROM NORTHERN CHILE

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Substance use is a risk behavior that has been associated with adverse mental health outcomes in adolescence. The aim of this study was to determine the relation between behavioral problems, emotional problems, and substance use as well as the mediating role of contextual problems and sensation seeking in this relation. A cross-sectional study of 2277 adolescents from Northern Chile was conducted. The System for the Evaluation of Children and Adolescents (SENA) was used to assess substance use, contextual problems, sensation seeking, and emotional and behavioral problems. Through a mediational model, it was observed that substance use has a positive indirect effect on emotional and behavioral problems when both contextual problems and sensation seeking act as mediating variables. An indirect effect of substance use on contextual problems with sensation seeking as a mediator was also observed. The results suggests that context and sensation seeking are a relevant source of information in understanding adolescents and their propensity to use drugs. Interventions based on addressing contextual problems (problems with school, peers, and family) and enhancing personal resources should be implemented in order to reduce substance use in adolescents as well as the consequences it can generate in the short, medium, and long term.

CLIN NEUROPHYSIOL. 2022 APR;136:13-38. DOI: 10.1016/J.CLINPH.2022.01.002.

REVIEW OF TECHNIQUES USEFUL FOR THE ASSESSMENT OF SENSORY SMALL FIBER NEUROPATHIES: REPORT FROM AN IFCN EXPERT GROUP

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Nerve conduction studies (NCS) are an essential aspect of the assessment of patients with peripheral neuropathies. However, conventional NCS do not reflect activation of small afferent fibers, including Aδ and C fibers. A definitive gold standard for laboratory evaluation of these fibers is still needed and therefore, clinical evaluation remains fundamental in patients with small fiber neuropathies (SFN). Several clinical and research techniques have been developed for the assessment of small fiber function, such as (i) microneurography, (ii) laser evoked potentials, (iii) contact heat evoked potentials, (iv) pain-related electrically evoked potentials, (v) quantitative thermal sensory testing, (vi) skin biopsy-intraepidermal nerve fiber density and (vii) corneal confocal microscopy. The first five are physiological techniques, while the last two are morphological. They all have advantages and limitations, but the combined use of an appropriate selection of each of them would lead to gathering invaluable information for the diagnosis of SFN. In this review, we present an update on techniques available for the study of small afferent fibers and their clinical applicability. A summary of the anatomy and important physiological aspects of these pathways, and the clinical manifestations of their dysfunction is also included, in order to have a minimal common background.

J AFFECT DISORD. 2022 JAN 15;297:381-385. DOI: 10.1016/J.JAD.2021.10.014. EPUB 2021 OCT 14.

STRUCTURAL GENDER INEQUALITIES AND SYMPTOMS OF POSTPARTUM DEPRESSION IN 40 COUNTRIES

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Background: The role of structural gender inequality in macro-level differences in women's perinatal mental health remains largely unexplored. This short communication explores structural gender inequalities and their potential as a macro-level, upstream social determinant of postpartum depression (PPD). Methods: We compiled meta-analytically derived national-level prevalence estimates of PPD symptoms - based on the Edinburgh Postnatal Depression Scale - with economic (e.g., income inequality), health (e.g., infant mortality rate), sociodemographic (e.g., urban population), and structural gender inequality variables (e.g., abortion policies) for 40 countries. Meta-regression techniques and traditional p-value based stepwise procedures, complemented with a Bayesian model averaging approach, were used for a robust selection of variables associated with national-level PPD symptom prevalence. Results:

Income inequality (β = 0.04, 95% CI = 0.02 to 0.07) and abortion policies (β = 0.02, 95% CI = 0.00 to 0.03) were the only variables selected in the final, adjusted model, accounting for 60.7% of cross-national variations in PPD symptoms. Limitations: Study quality of primary studies was not assessed and some national-level meta-analytical estimates were based on few primary studies. A fifth of world countries and territories could be included, with high-income regions overrepresented. High rate of missing national-level data for potential predictors of PPD. Cross-sectional analyses precludes causal inferences. Conclusions: Abortion policies are a significant macro-level social determinant of PPD, and its liberalization might be associated with women's mental health at a population level. Our findings should be a relevant argument for clinicians to advocate for changing discriminatory social norms against women.

AGING MENT HEALTH. 2022 JUL;26(7):1395-1416. DOI: 10.1080/13607863.2021.1958145.

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

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

J GLOB HEALTH. 2022 SEP 3;12:04054. DOI: 10.7189/JOGH.12.04054.

CHANGES IN RATES OF PSYCHIATRIC BEDS AND PRISON POPULATIONS IN SUB-SAHARAN AFRICA FROM 1990 TO 2020

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Background: Psychiatric bed numbers (general, forensic, and residential) and prison populations have been considered indicators of institutionalization. The present study aimed to assess changes of those indicators across sub-Saharan Africa (SSA) from 1990 to 2020. Methods: We retrospectively obtained data on psychiatric bed numbers and prison populations from 46 countries in SSA between 1990 and 2020. Mean and median rates, as well as percentage changes between first and last data points were calculated for all of SSA and for groups of countries based on income levels. Results: Primary data were retrieved from 17 out of 48 countries. Data from secondary sources were used for 29 countries. From two countries, data were unavailable. The median rate of psychiatric beds decreased from 3.0 to 2.2 per 100 000 population (median percentage change = -16.1%) between 1990 and 2020. Beds in forensic and residential facilities were nonexistent in most countries of SSA in 2020, and no trend for building those capacities was detected. The median prison population rate also decreased from 77.8 to 71.0 per 100 000 population (-7.8%). There were lower rates of psychiatric beds and prison populations in low-income and lower-middle income countries compared with upper-middle income countries. Conclusions: SSA countries showed, on average, a reduction of psychiatric bed rates from already very low levels, which may correspond to a crisis in acute psychiatric care. Psychiatric bed rates were, on average, about one twenty-fifth of countries in the Organization for Economic Co-operation and Development (OECD), while prison population rates were similar. The heterogeneity of trends among SSA countries over the last three decades indicates that developments in the region may not have been based on coordinated policies and reflects unique circumstances faced by the individual countries.

SCHIZOPHR BULL. 2022 MAR 1;48(2):485-494. DOI: 10.1093/SCHBUL/SBAB139.

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

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22q11.2 deletion syndrome (22q11.2DS) is a genetic neurodevelopmental disorder that represents one of the greatest known risk factors for psychosis. Previous studies in psychotic subjects without the deletion have identified a dopaminergic dysfunction in

striatal regions, and dysconnectivity of striatocortical systems, as an important mechanism in the emergence of psychosis. Here, we used resting-state functional MRI to examine striatocortical functional connectivity in 22q11.2DS patients. We used a 2 × 2 factorial design including 125 subjects (55 healthy controls, 28 22q11.2DS patients without a history of psychosis, 10 22q11.2DS patients with a history of psychosis, and 32 subjects with a history of psychosis without the deletion), allowing us to identify network effects related to the deletion and to the presence of psychosis. In line with previous results from psychotic patients without 22q11.2DS, we found that there was a dorsal to ventral gradient of hypo- to hyperstriatocortical connectivity related to psychosis across both patient groups. The 22q11.2DS was additionally associated with abnormal functional connectivity in ventral striatocortical networks, with no significant differences identified in the dorsal system. Abnormalities in the ventral striatocortical system observed in these individuals with high genetic risk to psychosis may thus reflect a marker of illness risk.

LANCET PUBLIC HEALTH. 2022 JUN;7(6):E557-E568. DOI: 10.1016/S2468-2667(22)00093-7.

THE PREVALENCE OF COMORBID SERIOUS MENTAL ILLNESSES AND SUBSTANCE USE DISORDERS IN PRISON POPULATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Comorbid mental illnesses and substance use disorders are associated with adverse criminal, social, and health outcomes. Yet, their burden is not reliably known among prison populations. We therefore aimed to estimate the prevalence of comorbid serious mental illnesses and substance use disorders (dual disorders) among people in prison worldwide. Methods: In this systematic review and meta-analysis, we searched 15 electronic databases (ASSIA, CAB Abstracts, Criminal Justice Database, Embase, Global Health, Global Index Medicus, IBSS, MEDLINE, NCJRS, PAIS Index, PsycINFO, Russian Science Citation Index, Scielo, Social Services Abstracts, and Web of Science) and the grey literature (Open Grey and ProQuest Dissertations & Theses Global) for studies reporting the prevalence of serious mental illnesses and substance use disorders in prison populations published between Jan 1, 1980, and Sept 25, 2021, and contacted the authors of relevant studies. Empirical studies among unselected adult prison populations that applied representative sampling strategies and validated diagnostic instruments, and either reported the prevalence of dual disorders or had authors who could provide prevalence data in correspondence, were included. Two reviewers (GB and SDL) independently extracted data from the eligible studies; both current (up to 1 year) and lifetime prevalence were extracted, if available. We sought summary estimates. Our primary outcomes were comorbid non-affective psychosis with substance use disorders and comorbid major depression with substance use disorders. We conducted a random-effects meta-analysis, explored between-sample heterogeneity with meta-regression, and calculated odds ratios (ORs) to assess bidirectional relationships between mental and substance use disorders. Risk of bias was assessed by use of a standard tool. The study protocol was registered with PROSPERO, CRD42020207301. Findings: Of 11 346 records screened, we identified 34 studies reporting the prevalence of dual disorders among individuals in prison and received unpublished prevalence data for 16 studies, totalling 50 eligible studies and 24 915 people. The mean quality score of included studies was 7·8 (SD 1·2). We found that 3·5% (95% CI 2·2-5·0) had current non-affective psychosis with any comorbid substance use disorder, representing 443 (49·2%) of 900 people with non-affective psychosis, and 9·1% (5·6-13·3) had current major depression and comorbid substance use disorders, representing 1105 (51·6%) of 2143 people with major depression. Between-sample heterogeneity was high (I2>80%). People in prison with current non-affective psychosis were significantly more likely to have substance use disorders compared with those without (OR 1·7, 95% CI 1·4-2·2). People with major depression had higher odds of substance use disorders than those without (1·6, 1·3-2·0). Interpretation: Around half of the prison population with non-affective psychosis or major depression have a comorbid substance use disorder. Consideration should be given to screening for dual disorders and implementing integrated and scalable treatments.

SLEEP. 2022 FEB 14;45(2):ZSAB300. DOI: 10.1093/SLEEP/ZSAB300.

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

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Study objectives: Our aim is to evaluate the presence of REM sleep without atonia (RWA), the objective hallmark of REM sleep Behaviour Disorder (RBD), as prodromal marker of Parkinson's disease (PD), in an adult cohort of 22q11.2 deletion syndrome (22qDS). Methods: Sleep quality was assessed by means of Pittsburgh quality scale index (PSQI), and RBD symptoms by means of RBD questionnaire-Hong-Kong (RBDQ-HK). Attended domiciliary video-Polysomnography (v-PSG) were performed in 26 adults (18-51 years, 14 females) 22qDS patients. Electromyogram during REM sleep was analyzed by means of SINBAR procedure at 3-second time resolution (miniepochs). Results: An overall poor sleep quality was observed in the cohort and high RBDQ-HK score in 7 of the 26 patients, two additional patients with positive dream enactment reported by close relatives had low score of RBDQ-HK. Nevertheless, SINBAR RWA scores were lower than cut-off threshold for RWA (mean 5.5%, range 0-12.2%). TST and the percentage of light sleep (N1) were increased, with preserved proportions of N2 and N3. Participants reported poor quality of sleep (mean PSQI > 5), with prolonged

sleep latency in the v-PSG. No subjects exhibit evident dream enactment episodes during recording sessions. Conclusions: RWA was absent in the studied cohort of 22qDS adult volunteers according to validated polysomnographic criteria. High RBDQ-HK scores do not correlate with v-PSG results among 22qDS individuals.

J IMMIGR MINOR HEALTH. 2023 FEB;25(1):151-160. DOI: 10.1007/S10903-022-01374-0.

MENTAL HEALTH IN INDIGENOUS CHILDREN AND ADOLESCENTS: THE CONTRIBUTION OF CULTURAL BACKGROUD

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The purpose of this study is to describe and compare the prevalence of mental health problems in Aymara and non-Aymara children and adolescent. The study sample comprised 1839 students from 8 to 19 years, from educational institutions of Northern Chile. Forty-nine percent of students identified with the Aymara ethnic group. The Child and Adolescent Evaluation System was used to evaluate internal and external problems. In Elementary school, Aymara students showed significantly lower scores in externalized problems and in high school, there were significantly lower scores in interiorized, exteriorized and other problems than Non-Aymara students. It seems that the legacy of the Aymara culture has favored the development of protective factors in relation to the mental health of these students. In a context of growing recognition and appreciation of this culture, greater involvement with Aymara culture could promote better mental health of school children.

PSYCHIATR SERV. 2022 NOV 1;73(11):1225-1231. DOI: 10.1176/APPI.PS.202000843.

A RECOVERY-ORIENTED INTERVENTION FOR PEOPLE WITH PSYCHOSIS: A PILOT RANDOMIZED CONTROLLED TRIAL

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Objective: This pilot randomized controlled trial evaluated the effectiveness of critical time intervention-task shifting (CTI-TS) for people with psychosis in Santiago, Chile, and Rio de Janeiro. CTI-TS is a 9-month intervention involving peer support workers and is designed to maintain treatment effects up to 18 months. Methods: A total of 110 people with psychosis were recruited when they enrolled in community mental health clinics (Santiago, N=60; Rio de Janeiro, N=50). Participants within each city were randomly assigned to either CTI-TS or usual care for 9 months. Primary outcomes were quality of life, measured with the World Health Organization Quality of Life Assessment-Brief Version (WHOQOL-BREF), and unmet needs, measured with the Camberwell Assessment of Need (CAN), at 18-month follow-up. Results were analyzed according to intention-to-treat guidelines. Generalized estimating equations, with observations clustered within cities, and multiple imputation for missing data were used. Results: At 18 months, both groups showed improved primary outcomes. In both unadjusted and fully adjusted analyses, no significant differences between CTI-TS and usual care (WHOQOL-BREF question on quality of life and CAN mean number of unmet needs) were found. Conclusions: Three factors might explain the lack of difference between CTI-TS and usual care: first-contact enrollment precluded rapport prior to randomization, a minority of patients were uncomfortable with peers being on the treatment team, and primary outcome measures may not have been sensitive enough to capture the effects of a recovery-oriented intervention. The results have implications for the design of transitional services for people with psychosis, especially in Latin America.

INT J BIPOLAR DISORD. 2022 OCT 13;10(1):23. DOI: 10.1186/S40345-022-00267-3.

CLINICAL RESEARCH DIAGNOSTIC CRITERIA FOR BIPOLAR ILLNESS (CRDC-BP): RATIONALE AND VALIDITY

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Background: In the 1970 s, scientific research on psychiatric nosology was summarized in Research Diagnostic Criteria (RDC), based solely on empirical data, an important source for the third revision of the official nomenclature of the American Psychiatric Association in 1980, the Diagnostic and Statistical Manual, Third Edition (DSM-III). The intervening years, especially with the fourth edition in 1994, saw a shift to a more overtly "pragmatic" approach to diagnostic definitions, which were constructed for many purposes, with research evidence being only one consideration. The latest editions have been criticized as failing to be useful for research. Biological and clinical research rests on the validity of diagnostic definitions that are supported by firm empirical foundations, but critics note that DSM criteria have failed to prioritize research data in favor of "pragmatic" considerations. Results: Based on prior work of the International Society for Bipolar Diagnostic Guidelines Task Force, we propose here Clinical Research Diagnostic Criteria for Bipolar Illness (CRDC-BP) for use in research studies, with the hope that these criteria may lead to further refinement of diagnostic definitions for other major mental illnesses in the future. New proposals are provided for mixed states, mood temperaments, and duration of episodes. Conclusions: A new CRDC could provide guidance toward an empirically-based, scientific psychiatric nosology, and provide an alternative clinical diagnostic approach to the DSM system.

PSYCHOL MED. 2022 APR;52(5):914-923. DOI: 10.1017/S0033291720002664.

THE INCIDENCE OF NON-AFFECTIVE PSYCHOTIC DISORDERS IN CHILE BETWEEN 2005 AND 2018: RESULTS FROM A NATIONAL REGISTER OF OVER 30 000 CASES

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Background: Evidence suggests the incidence of non-affective psychotic disorders (NAPDs) varies across persons and places, but data from the Global South is scarce. We aimed to estimate the treated incidence of NAPD in Chile, and variance by person, place and time. Methods: We used national register data from Chile including all people, 10-65 years, with the first episode of NAPD (International Classification of Diseases, Tenth Revision: F20-F29) between 1 January 2005 and 29 August 2018. Denominators were estimated from Chilean National Census data. Our main outcome was treated incidence of NAPD and age group, sex, calendar year and regional-level population density, multidimensional poverty and latitude were exposures of interest. Results: We identified 32 358 NAPD cases [12 136 (39.5%) women; median age-at-first-contact: 24 years (interquartile range 18-39 years)] during 171.1 million person-years [crude incidence: 18.9 per 100 000 person-years; 95% confidence interval (CI) 18.7-19.1]. Multilevel Poisson regression identified a strong age-sex interaction in incidence, with rates peaking in men (57.6 per 100 000 person-years; 95% CI 56.0-59.2) and women (29.5 per 100 000 person-years; 95% CI 28.4-30.7) between 15 and 19 years old. Rates also decreased (non-linearly) over time for women, but not men. We observed a non-linear association with multidimensional poverty and latitude, with the highest rates in the poorest regions and those immediately south of Santiago; no association with regional population density was observed. Conclusion: Our findings inform the aetiology of NAPDs, replicating typical associations with age, sex and multidimensional poverty in a Global South context. The absence of association with population density suggests this risk may be context-dependent.

INT J NEUROPSYCHOPHARMACOL. 2022 SEP 28;25(9):701-708. DOI: 10.1093/IJNP/PYAC025.

POLYMORPHISMS IN SCHIZOPHRENIA-RELATED GENES ARE POTENTIAL PREDICTORS OF ANTIPSYCHOTIC TREATMENT RESISTANCE AND REFRACTORINESS

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Background: Approximately 30% of individuals with schizophrenia (SZ) are resistant to conventional antipsychotic drug therapy (AP). Of these, one-third are also resistant to the second-line treatment, clozapine. Treatment resistance and refractoriness are associated with increased morbidity and disability, making timely detection of these issues critical. Variability in treatment responsiveness is partly genetic, but research has yet to identify variants suitable for personalizing antipsychotic prescriptions. Methods: We evaluated potential associations between response to AP and candidate gene variants previously linked to SZ or treatment response. Two groups of patients with SZ were evaluated: one receiving clozapine (n = 135) and the other receiving another second-generation AP (n = 61). Single-nucleotide polymorphisms (SNPs) in the genes OXT, OXTR, CNR1, DDC, and DRD2 were analyzed. Results: Several SNPs were associated with response vs. resistance to AP or clozapine. Conclusions: This is the first study of its kind, to our knowledge, in our admixed Chilean population to address the complete treatment response spectrum. We identified SNPs predictive of treatment-resistant SZ in the genes OXT, CNR1, DDC, and DRD2.

PSYCHOL MED. 2022 AUG;52(11):2177-2188. DOI: 10.1017/S0033291721002403.

EFFECTS OF SOCIOECONOMIC STATUS IN COGNITION OF PEOPLE WITH SCHIZOPHRENIA: RESULTS FROM A LATIN AMERICAN COLLABORATION NETWORK WITH 1175 SUBJECTS

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Background: Cognition heavily relies on social determinants and genetic background. Latin America comprises approximately 8% of the global population and faces unique challenges, many derived from specific demographic and socioeconomic variables, such as violence and inequality. While such factors have been described to influence mental health outcomes, no large-scale studies with Latin American population have been carried out. Therefore, we aim to describe the cognitive performance of a representative sample of Latin American individuals with schizophrenia and its relationship to clinical factors. Additionally, we aim to investigate how socioeconomic status (SES) relates to cognitive performance in patients and controls. Methods: We included 1175 participants from five Latin American countries (Argentina, Brazil, Chile, Colombia, and Mexico): 864 individuals with schizophrenia and 311 unaffected

subjects. All participants were part of projects that included cognitive evaluation with MATRICS Consensus Cognitive Battery and clinical assessments. Results: Patients showed worse cognitive performance than controls across all domains. Age and diagnosis were independent predictors, indicating similar trajectories of cognitive aging for both patients and controls. The SES factors of education, parental education, and income were more related to cognition in patients than in controls. Cognition was also influenced by symptomatology. Conclusions: Patients did not show evidence of accelerated cognitive aging; however, they were most impacted by a lower SES suggestive of deprived environment than controls. These findings highlight the vulnerability of cognitive capacity in individuals with psychosis in face of demographic and socioeconomic factors in low- and middle-income countries.

ARCH SUICIDE RES. 2022 NOV 4;1-12. DOI: 10.1080/13811118.2022.2134067.

BRIEF REPORT: THE ASSOCIATION OF ADVERSE CHILDHOOD EXPERIENCES AND SUICIDE-RELATED BEHAVIORS AMONG 10TH-GRADE SECONDARY SCHOOL STUDENTS

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The association between adverse childhood experiences and suicide-related behaviors (SRB) of adolescents has been widely studied in Western high-income countries, but not yet in Latin America. The aim of this study was to determine this association and to explore a dose-response relationship between adverse childhood experiences and SRB in Chile. We conducted a cross-sectional survey to assess adverse childhood experiences up to 1 year prior to the survey and SRB (suicide ideation and attempts) in a sample of secondary school students. Multilevel and multivariable logistic regressions were run with SRB as dependent and adverse childhood experiences as independent variables, adjusted by self-esteem, general mental health, friend and parental support, and the age at onset of cannabis and alcohol use. We included 7,458 adolescents (48.7% girls), mean age = 16.0 (SD = 0.7), and found a prevalence of 78.1% for at least one adverse childhood experience. The 6-month prevalence of suicidal ideation was 18.1% (95% confidence interval [CI]: 17.2%-19.0%), and the prevalence of suicide attempts was 5.0% (95% CI: 4.6-5.6). Among all adverse childhood experiences, only sexual abuse was a risk factor for both SRB. We also found an independent effect of the total number of adverse childhood experiences on suicidal ideation ($p < .001$) and on suicide attempts ($p < .001$). Additionally, ages at onset of alcohol and cannabis use were associated with suicidal ideation and suicidal attempts, respectively. This is the first study exploring the influence of adverse childhood experiences on suicide-related behaviors in adolescents from Latin America.HIGHLIGHTSSexual abuse is associated with suicidal ideation and suicide attempts in 10th-grade secondary school studentsThere is a dose-response effect between adverse childhood experiences and suicide-related behaviorAges at onset of alcohol and cannabis use were associated with suicidal ideation and suicidal attempts, respectively.

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RESTORATION OF ANATOMIC PARAMETERS AND SYNDESMOTIC REDUCTION AFTER INTRAMEDULLARY NAILING OF DISTAL FIBULAR FRACTURES

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Background: Intramedullary nailing of the fibula (FN) is a method of fixation that has proven to be useful for treating distal fibular fractures (DFs). FN minimizes soft tissue complications and provides similar stability to plating, with fewer hardware-related symptoms. Nevertheless, FN has been associated with syndesmotic malreduction and the incapacity of restoring length and rotation of the fibula. We aimed to evaluate the fibular position and syndesmotic reduction after fixation with FN compared with the uninjured ankle in the immediate postoperative period. Methods: Prospective cohort study. Patients with DF fractures treated with IN between January 2017 and January 2020 were included. Immediate postoperative bilateral ankle CT was obtained in all cases. Fibular rotation, length, and translation as well as syndesmotic diastasis were measured on both ankles and compared by 3 independent observers. Results: Twenty-eight patients were included (16 women). The mean age was 46 years (range 16-91). Fracture type distribution according to AO/ASIF classification included 19 patients with 44.B (67.9%), 8 patients with 44.C (28.6%), and 1 patient with a 44.A fracture (3.6%). No significant differences were identified considering fibular rotation ($P = .661$), syndesmotic diastasis ($P = .147$), and fibular length ($P = .115$) between the injured and uninjured ankle. Fibular translation had statistical differences ($P = .01$) compared with the uninjured ankle. The intraclass correlation coefficient showed an excellent concordance between observers except for fibular translation on the injured ankle. Conclusion: In this cohort, fixation of DF fractures with FN allows restoration of anatomical parameters of the ankle in terms of fibular rotation, length, and syndesmotic diastasis. However, fibular translation had significant differences compared with the uninjured ankle based on bilateral CT scan evaluation.

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LATIN AMERICAN FORMAL CONSENSUS ON THE APPROPRIATE INDICATIONS OF EXTRA-ARTICULAR LATERAL PROCEDURES IN PRIMARY ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Objectives: To create a practice guideline for the appropriate indications of an extra-articular procedure in primary anterior cruciate ligament reconstruction (ACLR). Methods: The formal consensus method described by the Haute Autorité de Santé was used. The Latin American Society of Arthroscopy, Articular Replacement, and Sports Injuries (SLARD) recruited three groups of experts on ACLR. Initially, the steering group, consisting of eight surgeons, performed a systematic review of the literature and elaborated on 192 scenarios for primary ACLR. The rating group, composed of 23 surgeons, rated each scenario in two rounds, with an in-between in-person meeting for discussion. Median scores and agreement levels were estimated to classify each scenario as inappropriate, uncertain or appropriate for adding anterolateral reconstruction. Finally, the lecture group, consisting of 10 surgeons, revised each stage of the method, results and interpretation. Results: Of the scenarios, 11.97% were rated as appropriate for adding an extra-articular lateral procedure, 7.81% as inappropriate and 80.21% as uncertain. The key recommendations for the addition of extra-articular lateral techniques were as follows: it is appropriate when the patient is under 25 years of age, has high-grade physical examination findings, practises a pivoting sport and has hyperlaxity; meanwhile, it is inappropriate when the patient has low-grade physical examination findings, has normal laxity and does not practise a pivoting sport. Conclusions: The appropriate indications of extra-articular lateral procedures in primary ACLR were determined on the basis of the best available evidence and expert opinion following a formal consensus method.

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

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Purpose: Management of anterior ring injuries is still a matter of discussion, and there are only few studies reporting anterior external fixator as definitive treatment for unstable pelvic injuries. This study aimed to describe the clinical and radiological outcomes of a consecutive series of mechanically unstable pelvic injuries that were treated with definitive anterior supra-acetabular external fixator for the anterior ring, and to identify risk factors for failure. Methods: We included a consecutive series of patients with unstable pelvic ring fractures who underwent anterior supra-acetabular external fixation for definitive treatment, between January 2012 and January 2020. All demographics, associated injuries and procedures, injury mechanism, and complications were analysed. Pelvic fracture was classified based on Orthopaedic Trauma Association/Tile AO (OTA/AO) and Young-Burgess classifications. Complications associated with the external fixator were revised. All patients were functionally evaluated at final follow-up and asked to report their clinical outcomes using the Majeed score. Results: A total of 47 patients were included, of which 25 were females. The median age was 44 years (interquartile range 23-59). Median follow-up duration was 14 months (interquartile range 6-31). The most frequent aetiology was motor vehicle accident (35), followed by fall from height (8). All fractures required posterior pelvic ring fixation. The median time during which patients had external fixation in situ was 11 weeks (interquartile range 9-13). All patients achieved healing of pelvic fracture at median time of 10 weeks (interquartile range 8-12). At final follow-up, the median displacement of the anterior pelvis was 6 mm (interquartile range 0-11). Superficial infection was the most common complication (n = 7). No washout procedures were needed. No major complication was reported. No patient required reoperation for anterior ring fracture. The median Majeed score was 88 points (range 60-95; interquartile range 80-90) at final follow-up. Conclusion: Our findings suggest that the use of supra-acetabular external fixator is safe and effective for definitive treatment of the anterior ring in unstable pelvic fractures. It is a method with high proportion of excellent results, regardless of the type of fracture. The rate of complications is low, and it does not compromise functional results.

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THE IMPACT OF CONCOMITANT IPSILATERAL KNEE PAIN ON FUNCTIONAL OUTCOMES IN TOTAL ANKLE ARTHROPLASTY

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In end-stage ankle arthritis, little is known about the impact of concomitant knee pathology, including the impact of ipsilateral knee pain on total ankle arthroplasty (TAA) outcomes. The aim of this study was to determine the prevalence of ipsilateral preoperative knee pain in patients undergoing TAA and analyze its impact on patient-reported functional outcome measures (PROMs). A retrospective review was performed on the Vancouver End Stage Ankle Arthritis Database at a single institution. In total, 114 patients were studied, with patient demographics collected preoperatively, including the presence or absence of knee pain. Postoperative follow-up was performed at 5 years, primarily analyzing disease-specific PROMs, including the Ankle Osteoarthritis Score (AOS) and Ankle Arthritis Score (AAS). Multivariate mixed-effects linear regression models compared the scores between the groups. In total, 31 patients

(27.2%) presented with concomitant ipsilateral knee pain. Despite more females in the knee pain group (64.5% vs 36.1%) there were no other significant differences at baseline between the knee pain and no knee pain groups in terms of demographics or baseline primary disease specific PROMs. At 5 years, the patients with knee pain had significantly worse AAS (37.9 ± 23.8 vs 21.2 ± 16.3, P = .004) and AOS total scores (38.1 ± 24.1 vs 21.9 ± 15.5, P = .005) compared with the no-knee pain group. Both groups improved significantly from baseline across all outcome measures; however, the magnitude of improvement was less in the knee pain group. Our study demonstrated that over one-quarter of patients with end-stage ankle arthritis undergoing TAA present with ipsilateral concomitant knee pain. If present, it is associated with worse functional outcomes at the 5-year mark. Further studies are needed to evaluate if knee pain influences complications, implant failure rates, and survival. Levels of Evidence: Level III.

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DROPPED ABDOMINAL PRESSURE AT VOID IN WOMEN

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Introduction and hypothesis: "Dropped pabd at void" occurs when pabd decreases below the previous resting pressure during voiding time. We sought clinical factors associated with this phenomenon and evaluated whether its correction modifies the urodynamic diagnosis. Methods: Retrospective cross-sectional study of non-neurological consecutive symptomatic women. The following definitions were used: "dropped pabd at void": decrease in pabd at Qmax ≥ 5 cmH2O; bladder outflow obstruction (BOO) (pdetQmax ≥ 25 cmH2O + Qmax ≤ 12 ml/s and female BOO index (pdetQmax - 2.2*Qmax) > 18; "low detrusor contraction strength": PIP1 (pdetQmax + Qmax) < 30. In patients with "dropped pabd at void", pdetQmax was corrected. Results: A total of 360 women were analyzed. Ninety-five percent of the women had a variation in pabd at Qmax between -13 and 53 cmH2O. "Dropped pabd at void" was found in 100 women (27.8%). History of stress urinary incontinence (SUI) surgery was significantly higher (p = 0.016) and symptoms of mixed urinary incontinence were significantly lower (p = 0.030) in patients with "dropped pabd at void". On multivariate analysis only the history of SUI surgery maintained its significance (OR = 1.787 [95% CI: 1.058, 3.017], p = 0.030). When correcting pdetQmax in women with "dropped pabd at void", 2 or 5 patients lost BOO diagnosis (depending on how it was diagnosed) and 7 patients gained a "low detrusor contraction strength" diagnosis. Conclusions: Approximately one-quarter of women had "dropped pabd at void", which was associated with a history of SUI surgery. Correction of pdetQmax would lead to a 2.5% to 3.33% diagnostic modification.

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ANTIOXIDANT INTERVENTION AGAINST MALE INFERTILITY: TIME TO DESIGN NOVEL STRATEGIES

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Infertility is a highly prevalent condition, affecting 9-20% of couples worldwide. Among the identifiable causes, the male factor stands out in about half of infertile couples, representing a growing problem. Accordingly, there has been a decline in both global fertility rates and sperm counts in recent years. Remarkably, nearly 80% of cases of male infertility (MI) have no clinically identifiable aetiology. Among the mechanisms likely plausible to account for idiopathic cases, oxidative stress (OS) has currently been increasingly recognized as a key factor in MI, through phenomena such as mitochondrial dysfunction, lipid peroxidation, DNA damage and fragmentation and finally, sperm apoptosis. In addition, elevated reactive oxygen species (ROS) levels in semen are associated with worse reproductive outcomes. However, despite an increasing understanding on the role of OS in the pathophysiology of MI, therapeutic interventions based on antioxidants have not yet provided a consistent benefit for MI, and there is currently no clear consensus on the optimal antioxidant constituents or regimen. Therefore, there is currently no applicable antioxidant treatment against this problem. This review presents an approach aimed at designing an antioxidant strategy based on the particular biological properties of sperm and their relationships with OS.