Cuban Research in Current International Journals

The following selection—alphabetical by title—reflects Cuban medical publishing in international journals over the last quarter on an array of topics. Links to these journal articles may be found at www.medicc.org/mediccreview.

An appraisal of blood-cerebrospinal fluid barrier dysfunction during the course of Guillain Barré syndrome. Gonzalez Quevedo A, Carriera RF, O'Farrill ZL, Luis IS, Bécquer RM, Luis Gonzalez RS. Neurol India. 2009 May–Jun;57(3):288–94.

Background Elevated cerebrospinal fluid (CSF) total protein (TP) concentration (mainly due to a dysfunctional blood-CSF barrier (B-CSFB)) with normal cell count is a hallmark for the diagnosis of Guillain-Barré syndrome (GBS). **Aims** This work presents the evaluation of B-CSFB dysfunction with respect to the course, severity, and clinical features of GBS. **Materials and Methods** A sample of CSF was collected on admission from 68 patients of both genders (15 children and 53 adults) diagnosed with GBS. A follow-up CSF sample was obtained approximately 15 days after admission. TP concentration was determined in the CSF and 7.5% polycrylamide gel electrophoresis was employed for serum and CSF protein fractioning. A low percentage of prealbumin fraction was considered a test of impaired B-CSFB. **Results** Elevated TP concentration and lower prealbumin were observed in almost 70% of the patients on admission, but this percentage was lower (52.4%) during the first week from onset of symptoms. Both variables were directly associated with the time of evolution of the disease and also with a greater clinical severity. Follow-up CSF studies showed higher CSF TP and lower prealbumin percentages, while deceased patients did not display this response pattern in the follow-up CSF. **Conclusions** B-CSFB dysfunction was present in only half of the patients with GBS during the first week from onset and it was directly associated with progression and clinical severity; nevertheless, a low B-CSFB dysfunction response during follow-up was associated with a lethal outcome, suggesting it could also serve a 'protective' effect during regeneration.

Application of a biochemical and clinical model to predict individual survival in patients with end-stage liver disease. Gomez EV, Bertot LC, Oramas BG, Soler EA, Navarro RL, Elias JD, et al. World J Gastroenterol. 2009 Jun 14;15(22):2768–77.

Aim To investigate the capability of a biochemical and clinical model, BioCliM, in predicting the survival of cirrhotic patients. **Methods** We prospectively evaluated the survival of 172 cirrhotic patients. The model was constructed using clinical (ascites, encephalopathy and variceal bleeding) and biochemical (serum creatinine and serum total bilirubin) variables that were selected from a Cox proportional hazards model. It was applied to estimate 12-, 52- and 104-wk survival. The model's calibration using the Hosmer-Lemeshow statistic was computed at 104 wk in a validation dataset. Finally, the model's validity was tested among an independent set of 85 patients who were stratified into 2 risk groups (low risk ≤8 and high risk >8). **Results** In the validation cohort, all measures of fit, discrimination and calibration were improved when the biochemical and clinical model was used. The proposed model had better predictive values (c-statistic: 0.90, 0.91, 0.91) than the Model for End-stage Liver Disease (MELD) and Child-Pugh (CP) scores for 12-, 52- and 104-wk mortality, respectively. In addition, the Hosmer-Lemeshow (H-L) statistic revealed that the biochemical and clinical model (H-L, 4.69) is better calibrated than MELD (H-L, 17.06) and CP (H-L, 14.23). There were no significant differences between the observed and expected survival curves in the stratified risk groups (low risk, P = 0.61; high risk, P = 0.77). **Conclusion** Our data suggest that the proposed model is able to accurately predict survival in cirrhotic patients.

Augmenting frameworks for appraising the practices of community-based health interventions. Pérez D, Lefèvre P, Romero MI, Sánchez L, De Vos P, Van der Stuyft, P. Health Policy Plan. 2009 Jun 23. [Epub ahead of print]

This paper aims at augmenting the frameworks proposed by Rifkin in 1996 to distinguish between target-oriented and empowerment approaches to participation in community-based health interventions. In her paper, Rifkin defined three criteria: who makes decisions on resource allocation, expected outcome and outcome assessment. We propose five additional criteria: the definition of community, the characteristics of the capacity-building process, the leadership characteristics, the documentation process, and ethical issues regarding participation. Derived from our analysis of a community-based project, the proposed criteria are discussed in the light of the principles of Popular Education and other literature on community participation. The augmented frameworks are intended to assist health professionals and planners interested in the empowerment approach of community participation to consciously sharpen their practice.

Burden of Self-reported Acute Gastrointestinal Illness in Cuba. Aguiar Prieto P, Finley RL, Muchaal PK, Guerin MT, Isaacs S, Castro Domínguez A, et al. J Health Popul Nutr. 2009 Jun;27(3):345–57.

Acute gastrointestinal illness is an important public-health issue worldwide. Burden-of-illness studies have not previously been conducted in Cuba. The objective of the study was to determine the magnitude, distribution, and burden of self-reported acute gastrointestinal illness in Cuba. A retrospective, cross-sectional survey was conducted in three sentinel sites during June–July 2005 (rainy season) and during November 2005–January 2006 (dry season). Households were randomly selected from a list maintained by the medical offices in each site. One individual per household was selected to complete a questionnaire in a face-to-face interview. The case definition was three or more bouts of loose stools in a 24-hour period within the last 30 days. In total, 97.3% of 6,576 interviews were completed. The overall prevalence of acute gastrointestinal illness was 10.6%. The risk of acute gastrointestinal illness was higher during the rainy season (odds ratio [OR]=3.85, 95% confidence interval [CI] 3.18–4.66) in children (OR=3.12, 95% CI 2.24–4.36) and teens (OR=2.27, 95% CI 1.51–3.41) compared to people aged 25–54 years, in males (OR=1.24, 95% CI 1.04–1.47), and in the municipality of Santiago de Cuba (OR=1.33, 95% CI 1.11–1.61). Of 680 cases, 17.1–38.1% visited a physician, depending on sentinel site. Of the cases who visited a physician, 33.3–53.9% were requested to submit a stool sample, and of those, 72.7–100.0% complied. Of the cases who sought medical care, 16.7–61.5% and 0–31.6% were treated with antidiarrheals and antibiotics respectively. Acute gastrointestinal illness represented a substantial burden of health compared to developed countries. Targeting the identified risk factors when allocating resources for education, food safety, and infrastructure might lower the morbidity associated with acute gastrointestinal illness.

Clinical trial: Viusid® in combination with diet and exercise in patients with nonalcoholic fatty liver disease. Vilar Gómez E, Rodríguez de Miranda A, Gra Oramas B, Arus Soler E, Llanio Navarro R, Calzadilla Bertot L, et al. Aliment Pharmacol Ther. 2009 Aug 18. [Epub ahead of print]

Background Nonalcoholic fatty liver disease (NAFLD) is a significant health problem for which there is no universally accepted pharmacological treatment. The combination of weight loss and antioxidant drugs to ameliorate insulin resistance and improve steatosis, inflammation, and fibrosis, provide the rational for therapeutic trials. **Aim** Our study evaluated the efficacy and safety of Viusid® in association with diet and ex-

ercise for NAFLD. **Methods** A randomized, controlled, and parallel-group trial was conducted at a tertiary care academic center (National Institute of Gastroenterology, Havana, Cuba). We randomly assigned 60 patients with liver biopsy-proven NAFLD to 6 months of treatment with a hypocaloric diet plus aerobic exercise daily and 3 Viusid® sachets daily or a hypocaloric diet and exercise. End points were improvement in the NAFLD activity score (NAS), fibrosis and normalization of serum aminotransferase levels. **Results** A significant improvement in steatosis, necroinflammation, and fibrosis was seen in each group of treatment ($P < 0.01$ for each feature). The Viusid® group, as compared with the control group, significantly reduced the mean of NAS (from 4.18 to 0.54 points in the Viusid® group versus 4.45 to 2.2 points in the control group [$P < 0.001$]). On between-group comparison, Viusid® was associated with a significantly greater improvement in steatosis ($P < 0.001$), ballooning ($P = 0.002$), and lobular inflammation ($P = 0.025$), but not in fibrosis ($P = 0.07$). Viusid® was well tolerated. **Conclusions** Our results indicate that treatment with diet and exercise leads to a notable improvement in the histological features of NAFLD; however, the administration of Viusid® intensifies the improvements of histological findings, especially of steatosis and inflammation.

Community involvement in dengue vector control: cluster randomised trial. Vanlerberghe V, Toledo ME, Rodríguez M, Gómez D, Baly A, Benítez JR, et al. BMJ. 2009 Jun 9;338:b1959. doi 10.1136/bmj.b1959.

Objective To assess the effectiveness of an integrated community-based environmental management strategy to control *Aedes aegypti*, the vector of dengue, compared with a routine strategy. **Design** Cluster randomized trial. **Setting** Guantánamo, Cuba. **Participants** 32 circumscriptions (around 2000 inhabitants each). **Interventions** The circumscriptions were randomly allocated to control clusters (n=16) comprising routine *Aedes* control program (entomological surveillance, source reduction, selective adulticiding, and health education) and to intervention clusters (n=16) comprising the routine *Aedes* control program combined with a community based environmental management approach. **Main outcome measures** The primary outcome was levels of *Aedes* infestation: house index (number of houses positive for at least one container with immature stages of *Ae aegypti* per 100 inspected houses), Breteau index (number of containers positive for immature stages of *Ae aegypti* per 100 inspected houses), and the pupae per inhabitant statistic (number of *Ae aegypti* pupae per inhabitant). **Results** All clusters were subjected to the intended intervention; all completed the study protocol up to February 2006 and all were included in the analysis. At baseline the Aedes infestation levels were comparable between intervention and control clusters: house index 0.25% v 0.20%, pupae per inhabitant 0.44×10^{-3} v 0.29×10^{-3}. At the end of the intervention these indices were significantly lower in the intervention clusters: rate ratio for house indices 0.49 (95% confidence interval 0.27 to 0.88) and rate ratio for pupae per inhabitant 0.27 (0.09 to 0.76). **Conclusion** A community based environmental management embedded in a routine control program was effective at reducing levels of *Aedes* infestation. **Trial registration** Current Controlled Trials ISRCTN88405796.

Cost-Effectiveness of a Community-Based Approach Intertwined with a Vertical *Aedes* Control Program. Baly A, Toledo ME, Vanlerberghe V, Ceballos E, Reyes A, Sánchez I, et al. Am J Trop Med Hyg. 2009 Jul;81(1):88–93.

We compared in a 5-year intervention study the cost-effectiveness of community-based environmental management intertwined with routine vertical *Aedes* control and of routine vertical control only. At baseline (year 2000), *Aedes* infestation levels and economic costs for vector control were comparable in intervention and control areas (house index, 2.23% versus 2.21% and US$21 versus US$24/yr/inhabitant, respectively). By 2004, house indices became 0.22% versus 2.36% and the costs were 29.8 US$ versus 36.7 US$/yr/inhabitant, respectively. The community cost made up 38.6% of the total economic cost in 2004 in the intervention areas against 23.5% in 2000. The average cost-effectiveness ratio for the intervention period 2001–2004, expressed as the societal cost incurred for the reduction (from baseline) of *Aedes* foci, was US$831.1 per focus in the intervention areas versus US$2,465.6 in the control areas. The intervention produced economic savings and health benefits that were sustained over the whole observation period.

CSF/serum quotient graphs for the evaluation of intrathecal C_4 synthesis. Padilla Docal B, Dorta Contreras AJ, Bu-Coifiu-Fanego R, Rey AR. Cerebrospinal Fluid Res. 2009 Jul 2;6:8.

Background Cerebrospinal fluid (CSF)/serum quotient graphs have been used previously to determine local synthesis in brain of immunoglobulins and C_3 complement component. The aim of this study was to use the same technique to construct quotient graphs, or Reibergrams, for the beta globulin C_4 and to evaluate the method for assessing intrathecal synthesis in neurological disease. **Methods** The constants in the previously defined Reibergram for immunoglobulin IgA were used to calculate the CSF/serum quotient for C_4. CSF and serum were analyzed for C_4, IgA and albumin from a total of 12 patients with meningoencephalitis caused by encapsulated microorganisms and 10 subjects without infections or inflammatory neurological disease, some of which had dysfunction of the blood-CSF barrier. **Results** The formula and C_4 Reibergram with the constants previously found for IgA, determined the intrathecal C_4 synthesis in CSF. The intrathecal C_4 fraction in CSF (C_4 loc in mg/l) was compared to the C_4-Index (fraction of CSF: serum for C_4/fraction of CSF: serum for albumin). There was a significant correlation between the two formulae. The CSF/Serum quotient graph was superior for detecting intrathecal synthesis of C_4 under variable conditions of blood-CSF barrier permeability. **Conclusion** The C_4 Reibergram can be used to quantify the intrathecal synthesis of this component of the complement system in different infectious diseases of the central nervous system and is especially useful for patients with blood-brain barrier dysfunction.

Designing novel antitrypanosomal agents from a mixed graph-theoretical substructural approach. Planche AS, Scotti MT, Emerenciano VD, López AG, Pérez EM, Uriarte E. J Comput Chem. 2009 Jul 17. [Epub ahead of print]

Chagas disease is nowadays the most serious parasitic health problem. This disease is caused by *Trypanosoma cruzi*. The great number of deaths and the insufficient effectiveness of drugs against this parasite have alarmed the scientific community worldwide. In an attempt to overcome this problem, a model for the design and prediction of new antitrypanosomal agents was obtained. This used a mixed approach, containing simple descriptors based on fragments and topological substructural molecular design descriptors. A data set was made up of 188 compounds, 99 of them characterized an antitrypanosomal activity and 88 compounds that belong to other pharmaceutical categories. The model showed sensitivity, specificity and accuracy values above 85%. Quantitative fragmental contributions were also calculated. Then, and to confirm the quality of the model, 15 structures of molecules tested as antitrypanosomal compounds (that we did not include in this study) were predicted, taking into account the information on the abovementioned calculated fragmental contributions. The model showed an accuracy of 100% which means that the "in silico" methodology developed by our team is promising for the rational design of new antitrypanosomal drugs.

Immunoglobulin G antibody response in children and adults with acute dengue 3 infection. Vázquez S, Acosta N, Ruiz D, Calzada N, Alvaréz AM, Guzmán MG. J Virol Methods. 2009 Jul;159(1):6–9. Epub 2009 Feb 24.

Using a serological test, different criteria have been established for classifying a case as primary or secondary dengue virus infection. Considering the dengue epidemiological situation in Cuba, IgG antibody response to dengue virus infection in serum samples from children and adults with a dengue 3 infection, in Havana city during the 2001–2002 epidemic was evaluated. Samples were collected on days 5–7 of fever onset and tested by an ELISA inhibition. A total of 713 serum samples positive for IgM

antibody, 93 from children and 620 from adult patients were studied. Serum samples collected from healthy blood donors and patients not infected with dengue were included as controls. An IgG primary infection pattern was observed in sera collected from children, with titers of ≤20 in the 89.3% of the patients, while both, a primary and secondary patterns were observed in sera collected from adult patients with titers of ≤20 (13.4%) and ≥1280 (83.9%), respectively. These results permitted the definition of a primary or secondary case of dengue virus infection in serum samples collected during the acute phase of dengue virus infection.

Neuromyelitis optica positive antibodies confer a worse course in relapsing-neuromyelitis optica in Cuba and French West Indies. Cabrera-Gómez JA, Bonnan M, González-Quevedo A, Saíz-Hinajeros A, Marignier R, Olindo S, et al. Mult Scler. 2009 Jul;15(7):828–33. Epub 2009 Jun 4.

Background In Caucasian populations neuromyelitis optica (NMO-IgG) antibody has been detected in 27.1%/78.2% of patients with relapsing-NMO (R-NMO). The prevalence reported for the disease in the Caribbean is 3.1/100,000 in the French West Indies (FWI) and 0.52 /100,000 in Cuba, but the NMO antibody status is unknown. **Objective** To assess the NMO-IgG antibody status of Cuban/FWI RNMO patients, comparing with European cases tested at the same laboratories. **Methods** Serum NMO-IgG antibodies were assayed in 48 R-NMO patients (Wingerchucks 1999 criteria): Cuba (24)/FWI (24), employing Lennon et al's method. We compared the demographic, clinical, disability and laboratory data between NMO-IgG +/- patients. All the data were reviewed and collected blinded to the NMO-IgG status. **Results** Seropositivity of the NMO-IgG antibody demonstrated a lower rate in the Caribbean (33.3%), as compared with Caucasian patients from Spain/Italy (62.5%) and France (53.8%). Caribbean patients with NMO-IgG (+) displayed more attacks, more spinal attacks and a higher EDSS than NMO-IgG (-) cases, while brain and spinal cord MRI lesions were more frequent during remission, with more vertebral segments, more gray, white matter and holocord involvement. **Conclusions** NMO IgG positive antibodies in NMO patients had a lower rate in the Caribbean area—where the population has a predominant African ancestry—than in Caucasian Europeans, suggesting the influence of a possible ethnic factor in the pathogenesis of the disease, but they confer a worse course with more attacks, more disability and MRI lesions.

Nimotuzumab, an antitumor antibody that targets the epidermal growth factor receptor, blocks legand binding while permitting the active receptor conformation. Talavera A, Friemann R, Gómez-Puerta S, Martínez-Fleites C, Garrido G, Rabasa A, et al. Cancer Res. 2009 Jul 15;69(14):5851–9. Epub 2009 Jul 7.

Overexpression of the epidermal growth factor (EGF) receptor (EGFR) in cancer cells correlates with tumor malignancy and poor prognosis for cancer patients. For this reason, the EGFR has become one of the main targets of anticancer therapies. Structural data obtained in the last few years have revealed the molecular mechanism for ligand-induced EGFR dimerization and subsequent signal transduction, and also how this signal is blocked by either monoclonal antibodies or small molecules. Nimotuzumab (also known as h-R3) is a humanized antibody that targets the EGFR and has been successful in the clinics. In this work, we report the crystal structure of the Fab fragment of Nimotuzumab, revealing some unique structural features in the heavy variable domain. Furthermore, competition assays show that Nimotuzumab binds to domain III of the extracellular region of the EGFR, within an area that overlaps with both the surface patch recognized by Cetuximab (another anti-EGFR antibody) and the binding site for EGF. A computer model of the Nimotuzumab-EGFR complex, constructed by docking and molecular dynamics simulations and supported by mutagenesis studies, unveils a novel mechanism of action, with Nimotuzumab blocking EGF binding while still allowing the receptor to adopt its active conformation, hence warranting a basal level of signaling.

Nutrition as a Vehicle for Cardiovascular Translational Research. Rodríguez-Leyva D, McCullough RS, Pierce GN. J Cardiovasc Transl Res. 2009 Sep;2(3):328–34.

It is becoming increasingly evident that poor nutrition plays an important role in inducing cardiovascular disease. Just as importantly, data now support the contention that appropriate nutritional interventions may have just as important an effect in preventing or delaying the appearance of cardiovascular disease. If this is indeed true, then it is critical that these advances in our knowledge of the effects of nutritional interventions be translated into effective strategies to combat cardiovascular disease. It is argued in this paper, with a few specific examples, that the translation of nutritional interventions can provide powerful approaches to alleviating the clinical challenges currently facing us today in the cardiovascular field. Furthermore, the value-added economic advantages of translating nutritional strategies on a wide scale into the public become another intriguing argument to further support investigations in this growing field.

Properties and clinical performance of vaccines containing outer membrane vesicles from *Neisseria meningitides*. Holst J, Martin D, Arnold R, Campa Huergo C, Oster P, O'Hallahan J, et al. Vaccine. 2009 June 24;27 Suppl 2:S3–12.

Meningococcal outer membrane proteins have been used for over 20 years in more than 80 million doses; either as carrier protein in a *Haemophilus influenzae* type b (Hib) polysaccharide conjugate vaccine or as vesicle vaccine formulations against meningococcal disease. Conventional wild-type outer membrane vesicle (wtOMV) vaccines are the only formulations that have shown efficacy against serogroup B meningococcal disease. This has been demonstrated in Cuba, Norway and New Zealand; where epidemics, dominated by one particular strain or clone, were causing high rates of disease and wtOMV vaccines have been used for epidemic control. The most significant limitation for widespread use of wtOMV is that the immune response is strain-specific in infants, mostly directed against the immuno-dominant porin protein, PorA. The natural orientation of surface-exposed membrane antigens and the preservation of good physico-chemical stability are key features of OMV vaccines. The efficacy, tolerability and safety of wtOMV vaccines have been well proven. The most recent experience from New Zealand demonstrated a vaccine effectiveness of 80% for children less than 5 years of age, over a period of 24 months. Such results are encouraging for the further use of "tailor-made" OMV vaccines for epidemic control. Moreover, it provides opportunities for development of OMV vaccines with various additional cross-protective potential. There is good reason to believe that in the coming few years the "OMV-concept" will be exploited further and that a number of cross-protective "universal" antigens will be included in vaccines against serogroup B meningococcal disease. The desire to have a global vaccine strategy that enables susceptible individuals to be protected against all the relevant serogroups of meningococcal disease may become a reality.

Treatment of intestinal protozoan infections in children. Escobedo AA, Almirall P, Alfonso M, Cimerman S, Rey S, Terry SL. Arch Dis Child. 2009 Jun;94(6):478–82.

Intestinal protozoan infections are a worldwide problem in both industrialized and unindustrialized countries; in the latter they may be the cause of significant morbidity and mortality. Children, in particular, are more likely to experience considerable morbidity. Most intestinal protozoan infections can cause acute or chronic diarrhea in healthy individuals and may result in intractable, life-threatening illness in patients with immunosuppressive diseases such as AIDS. Adequate identification and treatment of these infections may provide significant benefit for individual patients and public health. This article presents an update on the pharmacotherapy currently available for amebiasis, giardiasis and other intestinal protozoan infections.