

# 3

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## Journée et Prix de la Recherche Clinique

Jeudi 27 mai 2010  
13h30 – 18h30

HUG – Site Cluse-Roseraie  
Auditoire des polycliniques, niveau 2



Programme final  
et  
Recueil des résumés

## PROGRAMME

### 13h30 Nouveautés du Centre de recherche clinique

Pr. Bernard Hirschel, président du comité de gestion du CRC

### 13h45 Présentations orales – Partie I (9 minutes de présentation, suivie de 3 minutes de discussion)

Modérateur: Pr. Pierre Dayer, directeur médical des HUG

- 13h45 Dre M.-I. Vargas: **Diffusion tensor imaging (DTI) and tractography of the brachial plexus: feasibility and initial experience in neoplastic conditions**
- 13h57 Dr J.-L. Rény: **Clinical implications of clopidogrel non-response in cardiovascular patients: a systematic review and meta-analysis**
- 14h09 Dre N. Farpour: **Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children**
- 14h21 Dr A. Finckh: **Adalimumab in severe and acute sciatica. A multicentre, randomised, double-blind, placebo-controlled trial**
- 14h33 Dre M.-J. Guttier: **Moxibustion pour la version des foetus en présentation du siège**
- 14h45 Dr Y. Jackson : **Prévalence, staging de la maladie et risque de transmission par voie sanguine de la Maladie de Chagas chez les migrants latino-américains à Genève, Suisse**

### 15h00 Visite des posters et vote du public du meilleur poster

*Café et douceurs à disposition*

### 16h15 Présentations orales – Partie II

Modérateur: Pr. Antoine Hadengue, médecin-chef du service de gastro-entérologie et hépatologie

- 16h15 Dre E. Rapiti: **Prostate cancer patients of low socioeconomic status have delayed diagnosis, poor tumor assessment, and less aggressive treatments with important disease overmortality as a consequence**
- 16h27 Dre C. Samer: **Genetic polymorphism and drug interactions modulating CYP2D6 and CYP3A activities have a major impact on oxycodone analgesic efficacy, safety and pharmacokinetics**
- 16h39 Dr L. Spinelli: **Electrical source imaging for presurgical focus localization in epilepsy patients with normal MRI**
- 16h51 Dr A. Trombetti: **Music-Based Multitask Training (Jaques-Dalcroze Eurhythmics) Improves Gait, Balance and Reduces Fall Risk in the Elderly: A Randomized Controlled Trial**
- 17h03 Dr C. van Delden: **Cooperation and virulence of clinical Pseudomonas aeruginosa populations**
- 17h15 Dr T. Agoritsas: **Study design attributes influenced patients' willingness to participate in clinical research: a randomized vignette-based study**

### 17h30 Conférence par **Madame Stéphanie Clarke**, Professeure à la Faculté de biologie et médecine du CHUV et Présidente de la Division biologie et médecine du Fonds National :

*La recherche clinique dans le cadre du projet FNS pour la période 2011-2015*

### 18h10 Remise des Prix de la présentation orale et du poster par le Pr Antoine Hadengue, membre du jury

Clôture de la journée par le Pr Pierre Dayer, directeur médical des HUG

### 18h20 Apéritif

## MOT DE BIENVENUE

Cher(e) Collègue,

La Journée de la recherche clinique est dorénavant bien établie dans le programme des manifestations de notre institution : elle a toujours lieu le dernier jeudi du mois de mai et reflète l'activité de recherche par l'intermédiaire des quelques 60 contributions soumises.

Comme dans les années précédentes, un Prix rétribuera le meilleur travail parmi les présentations orales. Cette année, ce n'est pas seulement le Jury du Prix qui peut voter mais également le public qui choisira le meilleur poster. Pour que vous puissiez faire un choix informé, les auteurs des posters seront tous présents pendant la visite entre 15h00 et 16h15.

Par ailleurs, la Journée se terminera par la conférence de Madame Stéphanie Clarke (CHUV) : « La recherche clinique dans le cadre du projet FNS pour la période 2011-2015 ».

Mme Clarke est une neurophysiologiste de renommée mondiale, spécialiste du cortex auditif. Elle est également présidente de la Division III (Biologie et Médecine) du Fonds national, qui est en train de développer un nouveau modèle pour le support d'études cliniques que nous n'oserions ignorer.

Je me réjouis de vous voir nombreux le 27 mai 2010 !



Directeur du Centre de recherche clinique

## INFORMATION GENERALE

### Qui participe?

Tous les chercheurs des HUG et de la Faculté de médecine ayant terminé récemment un projet de recherche clinique dont les résultats sont directement applicables aux soins ou aux patients.

60 recherches provenant de services très variés ont été soumises pour cette troisième édition.

### Le jury :

Pr Thierry Berney, chirurgie (Président)

Pr Jacques Cornuz, pour le CHUV

Pr Claudine Burton-Jeangros, pour l'Université de Genève, section de sociologie

Pr Antoine Hadengue, gastro-entérologie

Pr Gilles Bertschy, psychiatrie

Pr Jean-Paul Vallée, radiologie

Pr Michel Boulvain, gynécologie-obstétrique

Le jury a sélectionné les recherches présentées par oral et a désigné l'équipe de recherche lauréate du Prix.

### Le Prix de la recherche clinique :

Un diplôme ainsi qu'une somme de CHF 1'000.- sont décernés aux auteurs.

### Le Prix du meilleur poster :

Cette année, et pour la première fois, un prix sera attribué au meilleur poster assorti d'une somme de 1'000.- francs, décerné par vote du public.

Pour toute information sur la Journée de la recherche clinique:  
corinne.chaudet@hcuge.ch, tél. 022 372 98 08 /91 34

# RECUEIL DES RESUMES

**PRESENTATIONS ORALES**

ORDRE SELON LE PROGRAMME

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**STUDY DESIGN ATTRIBUTES INFLUENCED PATIENTS' WILLINGNESS TO PARTICIPATE IN CLINICAL RESEARCH: A RANDOMIZED VIGNETTE-BASED STUDY.**

*Thomas Agoritsas, Marie Deom, Thomas V Perneger*

Service d'épidémiologie clinique, Hôpitaux Universitaires de Genève

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**Introduction:** Clinical research depends on patients' willingness to participate. Although both the public and outpatients report globally positive attitudes toward clinical research, recruitment problems are common. Our objective was to identify characteristics of clinical research projects that influence patients' willingness to participate in research.

**Méthode:** We surveyed all patients discharged during one month from a Swiss public teaching hospital. We described 4 hypothetical studies and asked patients whether they would agree to participate. We randomly manipulated 3 study attributes in each vignette, using a factorial design.

**Résultat:** All studies were not equally acceptable to the 1277 respondents. A higher willingness to participate was found when a new drug had no side effects (OR=1.68, 95% CI: 1.37–2.05), when no additional visit was required (OR=1.63, 1.33–2.01), when balanced information was given (OR=1.26, 1.03–1.54), when results stayed in public domain (OR=1.27, 1.04–1.55), and when the project was approved by a research ethics committee (OR=2.13, 1.73–2.63). In contrast, destruction of blood samples at the end of the project (OR=0.80, 0.65–0.98), use of placebo controls (OR=0.79, 0.64–0.96), and random allocation (OR=0.84, 0.69–1.03) were associated with a lower likelihood of participation. The origin of funds, financial reward, the need to complete a questionnaire, and clinical versus economic purpose of the study did not influence willingness to participate.

**Conclusion:** Patients valued safety, convenience, oversight and open communication in research. However, they were put off by some aspects that are valued by health care professionals. Educating the public about research methods may improve participation.

## CLINICAL IMPLICATIONS OF CLOPIDOGREL NON-RESPONSE IN CARDIOVASCULAR PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

C. Combescure\*, P. Fontana†, N. Mallouk‡, P. Berdague§, C. Labruyere‡, I. Barazer§, J.C. Gris, P¶ \*\*, S. Laporte‡, P. Fabbro-Peray††, and J. L. Reny§ \*\* ‡‡ for the CLOVIS study group§§

\* Division of Clinical Epidemiology, Geneva University Hospital, Switzerland, †Division of Angiology and Haemostasis, Geneva University Hospital, Switzerland, ‡EA 3065, Saint-Etienne University Hospital, France, §Internal Medicine, Cardiology and Central Laboratories, Béziers General Hospital, France, ¶Hematology Laboratory, Nîmes University Hospital, France, \*\*EA 2992, Montpellier-Nîmes Medical University, France, ††BESPIIM, Nîmes University Hospital, France, ‡‡Internal Medicine, Geneva University Hospital, Switzerland. §§CLOVIS study group listed in appendix

**Introduction:** Background: Previous studies have shown an important risk of cardiovascular events in patients with clopidogrel biological non-response (NR) and data showed considerable, unexplored heterogeneity. Objectives: To evaluate the magnitude of cardiovascular risk associated with clopidogrel NR and to explore heterogeneity.

**Méthode:** Systematic review and meta-analysis of prospective studies of patients treated with clopidogrel for symptomatic atherothrombosis, evaluated by light transmission aggregometry with adenosine diphosphate and monitored prospectively for clinical ischemic events.

**Résultat:** Fifteen studies were included, totalling 3960 patients, of whom 25% were considered clopidogrel non-responders. The global relative risk (RR) for recurrent ischemic events in clopidogrel non-responders was 3.5 ([2.4-5.2],  $p < 0.0001$ ). The results of the different studies were heterogeneous (Cochran  $p = 0.01$  and  $I^2 = 52\%$ ). The most recent studies yielded lower RRs (global RR=2.9 [2.3 – 3.8] after 2007 and global RR=6.6 [3.7–11.9] before 2007,  $p = 0.01$ ). Heterogeneity was present in the group of studies in which more than 10% of patients took GPIIb/IIIa inhibitors (Cochran  $p = 0.003$  and  $I^2 = 70\%$ ; RR=3.8 [2.9–5.1]) and was absent in the other studies (Cochran  $p = 0.88$  and  $I^2 = 0$ ; RR=2.5 [1.7–3.6]). The RR was significantly higher in studies using higher ADP maximal aggregation cut-offs (>65%) for clopidogrel NR than the RR found in studies using lower cut-offs (RR=5.8 [3.2-10.3] and RR=2.9 [2.2-3.7], respectively  $p = 0.03$ ).

**Conclusion:** The risk of ischemic events associated with clopidogrel NR is now more precisely defined. The risk is heterogeneous across studies, possibly because of an interaction with GPIIb/IIIa inhibitors and the use of different cut-offs to identify non-responders.

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**PHYSICAL ACTIVITY REDUCES SYSTEMIC BLOOD PRESSURE AND IMPROVES EARLY MARKERS OF ATHEROSCLEROSIS IN PRE-PUBERTAL OBESE CHILDREN**

*Nathalie J. Farpour-Lambert, Yacine Aggoun, Laetitia M. Marchand, Xavier E. Martin, François R. Herrmann, Maurice Beghetti*

Unité de cardiologie, Service des spécialités pédiatriques, Département de l'enfant et de l'adolescent

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**Introduction:** Hypertension and endothelial dysfunction are premature complications of obesity. The aims of this study were to determine the effects of physical activity on systemic blood pressure (BP) and early markers of atherosclerosis in pre-pubertal obese children.

**Méthode:** We performed a 3-month RCT with a modified cross-over design: 44 pre-pubertal obese children (8.9+/-1.5 yr) were randomly assigned (1:1) to an Exercise (n=22) or a Control group (n=22). We recruited 22 lean children (8.5+/-1.5 yr) for baseline comparison. The Exercise group trained 60 minutes 3 times per week during 3 months, while Controls remained relatively inactive. Then, both groups trained twice a week during 3 months. We assessed changes at 3 and 6 months in office and 24-hour BP, arterial intima-media thickness and stiffness, endothelial function (flow-mediated dilation), body mass index (BMI), body fat (DXA), cardiorespiratory fitness (VO<sub>2</sub>max), physical activity and biological markers.

**Résultat:** Obese children had higher BP, arterial stiffness, body weight, BMI, abdominal fat, insulin resistance indices, C-reactive protein levels and lower flow-mediated dilation, VO<sub>2</sub>max, physical activity and HDL-cholesterol levels than lean subjects. At 3 months, we observed significant changes in 24-hour systolic BP (Exercise -6.9+/-13.5 vs Control 3.8+/-7.9 mmHg, -0.8+/-1.5 vs 0.4+/-0.8 standard deviation score-SDS), diastolic BP (-0.5+/-1.0 vs 0+/-1.4 SDS), hypertension rate (-12 vs -1%), office BP, BMI z-score, abdominal fat and VO<sub>2</sub>max. At 6 months, change differences in arterial stiffness and intima-media thickness were significant.

**Conclusion:** Regular physical activity reduces blood pressure, arterial stiffness and abdominal fat, increases cardiorespiratory fitness, and delays arterial wall remodeling in pre-pubertal obese children.



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**ADALIMUMAB IN SEVERE AND ACUTE SCIATICA. A MULTICENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL**

*Stephane Genevay, Sébastien Viatte, Axel Finckh, Pascal Zufferey, Federico Balagué, Cem Gabay*

Rhumatologie HUG Rhumatologie, Hôpital Intercantonal de la broie Rhumatologie, Hôpital Cantonal de Fribourg

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**Introduction:** Based on several experimental results and on a preliminary study, a trial was undertaken to assess the efficacy of adalimumab, a TNF- $\alpha$  inhibitor, in patients with radicular pain due to lumbar disc herniation.

**Méthode:** A multicentre, double-blind, randomised controlled trial was conducted between May 2005 and December 2007 in Switzerland. Patients with acute (< 12 weeks) and severe (Oswestry Disability index > 50) radicular leg pain and imaging-confirmed lumbar disc herniation were randomised to receive as adjuvant therapy either two subcutaneous injections of adalimumab (40 mg) at 7 days interval or matching placebo. The primary outcome was leg pain, which was recorded every day for 10 days and at 6-weeks and 6-months based on a visual analogue scale (0 to 100).

**Résultat:** Of the 265 patients screened, 61 were enrolled (adalimumab= 31) and 4 were lost to follow-up. Over time, the evolution of leg pain was more favourable in the adalimumab group than in the placebo group ( $p < 0.001$ ). However, the effect size was relatively small and at last follow-up the difference was 13.8 (CI95% -11.5 – 39.0). In the adalimumab group twice as many patients fulfilled the criteria for “responders” and for “low residual disease impact” ( $p < 0.05$ ) and fewer surgical discectomies were performed (6 versus 13,  $p = 0.04$ ).

**Conclusion:** The addition of a short course of adalimumab to the treatment regimen of patients suffering from acute and severe sciatica resulted in a small decrease in leg pain and in significantly fewer surgical procedures.

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## MOXIBUSTION POUR LA VERSION DES FOETUS EN PRESENTATION DU SIEGE

*Marie-Julia Guittier, Michèle Pichon, Hongguang Dong, Olivier Irion, Michel Boulvain*

Service d'obstétrique, HUG

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**Introduction:** Notre objectif était d'évaluer l'efficacité de la moxibustion du point d'acupuncture BL 67 entre 34 et 38 semaines pour faciliter la version foetus en présentation du siège. Une étude réalisée en Chine avait montré une efficacité importante, mais d'autres essais avaient mis en doute ces résultats.

**Méthode:** Nous avons inclus dans notre essai clinique randomisé 212 femmes entre 34 et 36 semaines avec un fœtus en siège. Les critères d'exclusion étaient une malformation de l'utérus, un placenta praevia ou une présentation transverse. La stimulation du point BL 67 par moxibustion était réalisée 3 fois par semaine pendant 2 semaines à l'hôpital et par la patiente elle-même à domicile les autres jours. Le groupe témoin n'a pas reçu de traitement particulier. Pour les 2 groupes, une version céphalique par manœuvres externes (VCE) était proposée, à 37 semaines. La mesure d'issue principale était la présentation du fœtus à l'accouchement ou avant la VCE.

**Résultat:** Les caractéristiques lors de la randomisation étaient similaires entre les groupes, excepté plus de nullipares dans le groupe moxibustion. Le pourcentage de versions était similaire entre les groupes (18% moxibustion versus 16% témoin), comme le pourcentage de césariennes (64% versus 58%, respectivement). L'ajustement pour la parité n'a pas changé les résultats. L'acceptabilité de l'intervention était bonne et les femmes avaient une opinion favorable de la moxibustion.

**Conclusion:** Nous n'avons pas mis en évidence d'effet bénéfique de la moxibustion pour faciliter la version céphalique des fœtus en siège à la fin de la grossesse. Malgré ce manque d'efficacité, les femmes ne regrettaient pas d'avoir tenté cette intervention, ce qui suggère qu'elles sont très motivées pour éviter l'accouchement d'un fœtus en siège.

## PREVALENCE, STAGING DE LA MALADIE ET RISQUE DE TRANSMISSION PAR VOIE SANGUINE DE LA MALADIE DE CHAGAS CHEZ LES MIGRANTS LATINO-AMERICAINS A GENEVE, SUISSE

*Yves Jackson<sup>1</sup>, Laurent Gétaz<sup>1</sup>, Hans Wolff<sup>1</sup>, Marylise Holst<sup>1</sup>, Anne Mauris<sup>2</sup>, Aglaé Tardin<sup>3</sup>, Juan Sztajzel<sup>4</sup>, Valérie Besse<sup>5</sup>, Louis Loutan<sup>3</sup>, Jean-Michel Gaspoz<sup>1</sup>, Jean Jannin<sup>6</sup>, Pedro Albajar-Vinas<sup>6</sup>, Alejandro Luquetti<sup>7</sup> et François Chappuis<sup>3</sup>*

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**Introduction:** La migration de personnes latino-américaines (LA) vers l'Amérique du Nord et l'Europe a modifié la distribution de la maladie de Chagas (MC). Or, les données sur les cas importés sont rares. Nos objectifs consistent à évaluer la prévalence et les facteurs associés à la MC à Genève, le stade clinique et les attitudes envers le don de sang et d'organe parmi les migrants.

**Méthode:** Cette étude transversale inclut consécutivement tous les migrants LA consultant à l'UMSCO et fréquentant deux églises locales. Les participants ont rempli un questionnaire et furent dépistés par deux tests sérologiques. Les sujets infectés ont bénéficié d'un bilan médical extensif. Les facteurs prédictifs d'infection furent analysés en méthode univariée et par analyse de régression logistique multivariée

**Résultat:** 1012 personnes (femmes 83%, âge moyen 37.2 (DS 11.3) ans, boliviens 48%, sans-papiers 96%) furent recrutées. La MC fut diagnostiquée chez 130 sujets (12.8%; IC95% 10.8-14.9) dont 127 boliviens (26.2%; IC95% 22.3-30.1). Tous les patients étaient en phase chronique, dont 11.3% avec une atteinte cardiaque et 0.8% digestive. Les facteurs prédictifs étaient l'origine bolivienne (OR 33.2; 95%CI 7.5-147.5), une infection rapportée chez la mère (OR 6.9; 95%CI 1.9-24.3) et un âge supérieur à 35 ans (OR 6.7 ; 95%CI 2.4-18.8. Alors que 22 (16.9%) patients avec la MC avaient déjà donné leur sang, 24 (18.5%) et 34 (26.2%) envisageaient de donner du sang ou un organe hors d'Amérique Latine.

**Conclusion:** La MC est hautement prévalente parmi les migrants Boliviens en Suisse. Il existe un taux substantiel de complications cardiaques et le risque de transmission locale par voie sanguine ou de transplantation est important. Le dépistage de la MC en zone non-endémique est recommandé et devrait inclure les migrants sans-papier.

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**PROSTATE CANCER PATIENTS OF LOW SOCIOECONOMIC STATUS HAVE DELAYED DIAGNOSIS, POOR TUMOR ASSESSMENT, AND LESS AGGRESSIVE TREATMENTS WITH IMPORTANT DISEASE OVERMORTALITY AS A CONSEQUENCE**

*Gerald Fioretta, Charles-Henri Rapin, **Elisabetta Rapiti**, Helena Marieke Verkooijen, Franz Schmidlin, Raymond Miralbell, Roberto Zanetti, Christine Bouchardy*

Registre Genevois des Tumeurs

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**Introduction:** The causes and the impact of socioeconomic disparities on prostate cancer presentation, treatment and prognosis are far from being established. This study aims to evaluate such disparities in Geneva, Switzerland, where healthcare costs, medical coverage and life expectancy are among the highest in the world.

**Méthode:** This population-based study included all patients diagnosed with invasive prostate cancer among the resident population between 1995-2005. Patients were divided in four socioeconomic groups according to their last known occupation. We used chi square test of heterogeneity to compare patient and tumor characteristics, and treatment patterns between socioeconomic groups. We performed Cox multivariate regression analyses to assess and explain the socioeconomic inequalities in prostate cancer mortality.

**Résultat:** Compared to patients of high social class, those of low social class were more often foreigners, had less frequently screen-detected cancer, lower diagnostic assessment, and more advanced stage at diagnosis. These patients had less often prostatectomy and more frequently watchful waiting surveillance. The risk (Hazard Ratio) of dying of prostate cancer (Hazard Ratio [HR]) in patients with low vs. high socioeconomic status was 1.9 -fold increased (95% Confidence Interval [IC]: 1.5-2.6,  $p=0.0001$ ) respectively. When adjusting for differences in patient and tumor characteristics and treatment, the risk of mortality by prostate cancer decreased to 1.3 and was no more significant (95%CI: 1.0-1.8,  $p=0.211$ ).

**Conclusion:** Patients of low social class are at increased risk of dying of prostate cancer. This overmortality is for the most part explained by delayed diagnosis, poor tumor assessment, and less invasive treatments.

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**GENETIC POLYMORPHISM AND DRUG INTERACTIONS MODULATING CYP2D6 AND CYP3A ACTIVITIES HAVE A MAJOR IMPACT ON OXYCODONE ANALGESIC EFFICACY, SAFETY AND PHARMACOKINETICS**

*Caroline Samer, Youssef Daali, Michel Wagner, Gérard Hopfgartner, Chin Eap, Michela Rebsamen, Michel Rossier, Denis Hochstrasser, Pierre Dayer, Jules Desmeules*

Service de Pharmacologie et Toxicologie Cliniques, HUG

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**Introduction:** Cytochrome P450 (CYP) 2D6 and 3A are the central drug-metabolizing enzymes responsible for the oxidation of oxycodone. Genetic polymorphisms and/or drug-drug interactions explain their high interindividual variability, whose impact on the pharmacokinetics and pharmacodynamics of oxycodone remains poorly explored.

**Méthode:** We conducted a randomized crossover (5-arm) double-blind placebo-controlled study in 10 healthy volunteers genotyped for CYP2D6. Oral oxycodone 0,2mg/kg was given alone or after CYP2D6 and/or CYP3A inhibition (quinidine and/or ketoconazole). Experimental pain (cold pressor, electrical stimulation, thermode), pupil size, psychomotor effects and toxicity were assessed. Plasma samples of oxycodone and metabolites were collected for 24h. CYP2D6 (dextromethorphan) and CYP3A (midazolam) phenotypes were assessed at each session.

**Résultat:** CYP2D6 activity was correlated with oxymorphone and noroxymorphone PK ( $-0.71 < \rho < -0.92$ ,  $p < 0.05$ ). Blocking CYP2D6 reduced oxymorphone and noroxymorphone C<sub>max</sub> (40%-80%) and increased (70%) noroxycodone AUC<sub>∞</sub>. Blocking CYP3A4 tripled oxymorphone AUC<sub>∞</sub> and reduced (80%) noroxycodone and noroxymorphone AUCs. Shunt to CYP2D6 pathway was observed after CYP3A4 inhibition. CYP2D6 activity correlated with oxycodone antinociceptive and pharmacodynamic effects. Cold pressor and pupil size were unchanged in CYP2D6 poor metabolizers whereas CYP2D6 ultrarapid metabolizers experienced increased effects. CYP2D6 blockade reduced oxycodone subjective pain threshold SPT (30%). CYP3A4 blockade had a major impact on all pharmacodynamic assessments. Oxymorphone C<sub>max</sub> correlated with pharmacodynamics ( $\rho = 0.7$ ,  $p < 0.05$ ) and was the only independent positive predictor of SPT. Side-effects were observed after CYP3A4 blockade or in ultrarapid metabolizers.

**Conclusion:** In conclusion, modulations of CYP2D6 and CYP3A activities have a dramatic impact on oxycodone pharmacokinetics and pharmacodynamics; and the effect is dependent on CYP2 D6 genetic polymorphism.

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## ELECTRICAL SOURCE IMAGING FOR PRESURGICAL FOCUS LOCALIZATION IN EPILEPSY PATIENTS WITH NORMAL MRI

*Verena Brodbeck, Agustina Lascano, Claudio Pollo, Karl Schaller, Maria I. Vargas, Mickaël Wissmeyer, Christoph M. Michel, Margitta Seeck, **Laurent Spinelli**.*

Service de Neurologie, Service de Neurochirurgie, Département de Radiologie

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**Introduction:** Patients with magnetic resonance (MR)–negative focal epilepsy (MRN-E) have less favorable surgical outcomes (between 40% and 70%) compared to those in whom an MRI lesion guides the site of surgical intervention (60–90%). Patients with extratemporal MRN-E have the worst outcome (around 50% chance of seizure freedom). We studied whether electroencephalography (EEG) source imaging (ESI) of interictal epileptic activity can contribute to the identification of the epileptic focus in patients with normal MRI.

**Méthode:** We carried out ESI in 10 operated patients with nonlesional MRI and a postsurgical follow-up of at least 1 year. Five of the 10 patients had extratemporal lobe epilepsy. Evaluation comprised surface and intracranial EEG monitoring of ictal and interictal events, structural MRI, [18F]fluorodeoxyglucose positron emission tomography (FDG-PET), ictal and interictal perfusion single photon emission computed tomography (SPECT) scans. Eight of the 10 patients also underwent intracranial monitoring.

**Résultat:** ESI correctly localized the epileptic focus within the resection margins in 8 of 10 patients, 9 of whom experienced favorable postsurgical outcomes.

**Conclusion:** The results highlight the diagnostic value of ESI and encourage broadening its application to patients with MRN-E. If the surface EEG contains fairly localized spikes, ESI contributes to the presurgical decision process.

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## MUSIC-BASED MULTITASK TRAINING (JAQUES-DALCROZE EURHYTHMICS) IMPROVES GAIT, BALANCE AND REDUCES FALL RISK IN THE ELDERLY: A RANDOMIZED CONTROLLED TRIAL

*Andrea Trombetti<sup>1</sup>, Mélanie Hars<sup>1</sup>, Silvia Del Bianco<sup>2</sup>, François Herrmann<sup>1</sup>, Reto Kressig<sup>3</sup>, Serge Ferrari<sup>1</sup>, René Rizzoli<sup>1</sup>*

<sup>1</sup>Service of Bone Diseases, Department of Rehabilitation and Geriatrics, University Hospitals and Faculty of Medicine of Geneva, Geneva <sup>2</sup>Jaques-Dalcroze Institute, Geneva <sup>3</sup>Department of Acute Geriatrics, Basel University Hospital, Basel

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**Introduction:** Falls rank among the most common and devastating concern facing elderly people. We assessed the effects of a 6-month music-based multitask training program (Jaques-Dalcroze eurhythmics) on gait, balance, and fall risk in community-dwelling elderly people at increased risk of falling.

**Méthode:** We randomized 134 community-dwellers (76±7 years) to either a 1-hour weekly Jaques-Dalcroze eurhythmics program (n=66) or a wait-list/delayed intervention control group (n=68) for 6 months. Participants were followed for 12 months. The intervention consisted of multitask exercises performed to the rhythm of improvised piano music. The primary outcome measure was the change in gait variability as assessed by quantitative gait analysis using an electronic walkway. Secondary outcome measures included changes in quantitative balance measures, functional tests performances and falls. Analysis was by intention-to-treat.

**Résultat:** At the end of the 6-month program, intervention group participants exhibited significant improvements in gait as compared with the controls, with an increase in usual gait speed and a reduction in step and stride length variability under dual-task performance. One-legged balance (i.e., duration and mediolateral trunk sway) and functional tests performances were also significantly improved in this group, compared with the control group. During the 6-month intervention-controlled period, there were fewer falls in the intervention group (IRR: 0.46, p! =0.005) and a reduction in the risk of falling (RR=0.61, p=0.03). Benefits of intervention were retained 6 months after the program has ended.

**Conclusion:** The findings of this randomized controlled trial in community-dwelling elderly, indicate that a music-based multitask training program improves gait performance under single and dual-task conditions, and balance, as well as reduces both rate of falls and the risk of falling.



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## COOPERATION AND VIRULENCE OF CLINICAL PSEUDOMONAS AERUGINOSA POPULATIONS

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**Introduction:** Bacteria communicate and cooperate to perform a wide range of social behaviors including production of extracellular products (public goods) that are crucial for growth and virulence. Their expression may be switched on by the detection of threshold densities of diffusible signals (Quorum-Sensing; QS). Studies using the opportunistic pathogen *Pseudomonas aeruginosa* suggest that QS 'cheats' – individuals that don't respond to the QS-signal, but are still able to use public goods produced by others – have a selective advantage in the presence of QS-responders. It is however unclear whether this type of social exploitation is relevant in clinical contexts

**Méthode:** We prospectively collected daily tracheal aspirates and one *P. aeruginosa* isolate from 31 colonized intubated patients until extubation or pneumonia. All isolates were genotyped and the QS-phenotype determined by exoproduct assays. We assessed population dynamics by qRT-PCR of genomic DNA preparations.

**Résultat:** We collected a total of 364 isolates. We observed a large diversity of QS-phenotypes among initial colonizing isolates. This diversity decreased over a matter of days, concomitant with a gradual increase in the proportion of QS-cheating mutants (*lasR* mutants), which were found in 80% of the patients after nine days of colonization. These mutants often evolved from initial wild type genotypes. The fitness advantage of the *lasR* mutants is certainly due to social exploitation, because this advantage was only apparent in the presence of QS-wild type cells. Crucially, ventilator-associated pneumonia occurred significantly earlier in patients predominantly colonized by QS-wild type populations, highlighting the importance of QS in this clinical situation.

**Conclusion:** These results demonstrate that social interactions can shape the short-term evolution and virulence of bacterial pathogens in humans, providing novel opportunities for therapy.



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**DIFFUSION TENSOR IMAGING (DTI) AND TRACTOGRAPHY OF THE BRACHIAL PLEXUS: FEASIBILITY AND INITIAL EXPERIENCE IN NEOPLASTIC CONDITIONS.**

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**Introduction:** The objective of this study was to assess the feasibility and potential clinical applications of diffusion tensor imaging (DTI) and tractography in the normal and pathologic brachial plexus prospectively.

**Méthode:** Six asymptomatic volunteers and 12 patients with symptoms related to the brachial plexus underwent DTI on a 1.5T system in addition to the routine anatomic plexus imaging protocol. Maps of the apparent diffusion coefficient (ADC) and of fractional anisotropy (FA), as well as tractography of the brachial plexus were obtained. Images were evaluated by two experienced neuroradiologists in a prospective fashion. Three patients underwent surgery, and nine patients underwent conservative medical treatment.

**Résultat:** Reconstructed DTI (17/18) were of good quality (one case could not be reconstructed due to artifacts). In all volunteers and in 11 patients, the roots and the trunks were clearly delineated with tractography. Mean FA and mean ADC values were as follows:  $0.30 \pm 0.079$  and  $1.70 \pm 0.35$  mm<sup>2</sup>/s in normal fibers,  $0.22 \pm 0.04$  and  $1.49 \pm 0.49$  mm<sup>2</sup>/s in benign neurogenic tumors, and  $0.24 \pm 0.08$  and  $1.51 \pm 0.52$  mm<sup>2</sup>/s in malignant tumors, respectively. Although there was no statistically significant difference in FA and ADC values of normal fibers and fibers at the level of pathology, tractography revealed major differences regarding fiber architecture. In benign neurogenic tumors (n=4), tractography revealed fiber displacement alone (n=2) or fiber displacement and encasement by the tumor (n=2), whereas in the malignant tumors, either fiber disruption/destruction with complete disorganization (n=6) or fiber displacement (n=1) were seen. In patients with fiber displacement alone, surgery confirmed the tractography findings, and excision was successful without sequelae.

**Conclusion:** Our preliminary data suggest that DTI with tractography is feasible in a clinical routine setting. DTI may demonstrate normal tracts, tract displacement, deformation, infiltration, disruption, and disorganization of fibers due to tumors located within or along the brachial plexus, therefore, yielding additional information to the current standard anatomic imaging protocols.

# PRESENTATIONS POSTERS

EN ORDRE ALPHABETIQUE SELON LE NOM DU 1<sup>ER</sup> AUTEUR

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**P1****DEMENCE ET TROUBLES DE LA MARCHÉ : FOCUS SUR LA DEMENCE FRONTOTEMPORALE**

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**Introduction:** La marche et la cognition sont des fonctions intimement liées, mais dont la relation est souvent méconnue. Par exemple, les principaux critères diagnostiques de la démence frontotemporale (DFT) reposent sur des troubles comportementaux et une atteinte des fonctions exécutives. Bien que le lien entre troubles de la marche et atteinte des fonctions exécutives soit bien établi, il n'est fait aucune mention d'une atteinte de la marche dans la DFT. Le but de cette étude est de quantifier et de comparer les paramètres de marche de patients avec DFT, patients avec maladie d'Alzheimer (MA) et sujets sains contrôles.

**Méthode:** 60 sujets ont été inclus dans cette étude (19 DFT, 19 MA et 22 contrôles). Le coefficient de variation du temps du cycle de marche (CV) a été quantifié en condition de marche standard et de marche avec décompte envers (double tâche).

**Résultat:** Après ajustement sur l'âge, le niveau d'atteinte cognitive, la prise de psychotropes, le genre et la chute, seul le groupe de patients avec DFT était associé avec une augmentation du CV du temps de cycle de marche en condition de marche standard et de double tâche ( $P < 0.001$ ).

**Conclusion:** Ces résultats suggèrent que la présence de troubles de la marche chez un patient avec démence pourrait représenter un argument en faveur du diagnostic de démence frontotemporale. De plus, cette étude confirme le lien étroit entre trouble de la marche et démence et plus particulièrement dans les formes de démences avec atteinte des fonctions exécutives.

**P2****POLYMORPHISMS IN MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 4 GENE ARE ASSOCIATED WITH OUTCOME IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA**

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**Introduction:** Methotrexate (MTX) is used in the treatment of acute lymphoblastic leukemia (ALL). Inter-individual differences in response to this drug may cause treatment failures and adverse drug reactions. Multidrug resistance-related proteins (MRP) are involved in the efflux of MTX and its elimination may be a major determinant of chemoresistance. The polymorphisms in MRP genes may explain differences in expression and thereby the inter-individual differences in clinical outcome for ALL.

**Méthode:** 272 ALL children were genotype by allele-specific oligonucleotide and variants sufficient to infer most common haplotypes analyzed.

**Résultat:** Individuals with the AG -genotype of the A -1393G polymorphism localised in the regulatory region of the MRP4 gene had better event free survival (EFS) (95% vs. 77%,  $p=0.02$ ) compared to patients with the AA genotypes (Hazard ratio, HR= 0.1(95% CI=0.02-0.9). Children with the CA genotype of A934C polymorphism localised in exon 8 and leading to Lys304Asn amino-acid substitution, had worse EFS (67% vs.81%,  $p=0.02$ ) compared to those with the CC genotype (HR=2.2 CI 95% :1.1-4.1 ). When a genotypic association between MRP4 A-1393G and A934C polymorphism was performed, three genotype groups could have been distinguished according to the risk of the relapse (AG, AA/CC and AA/AC) with EFS decreasing from 95% to 80% and then 61%, respectively ( $p=0.002$ ). Increasing risk of grade 3-4 haematological toxicity and higher MTX plasma level detectable for a longer period of time was noted across these genotypes groups ( $p=0.008$  and 0.02, respectively).

**Conclusion:** The variants MRP4 A-1393G and A934C have an impact on the treatment response in ALL children.

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**P3****EVOLUTION INHABITUELLE D'UNE ENDOCARDITE GRAM NEGATIVE NON HACEK, CHEZ UNE PATIENTE ATTEINTE D'UN SYNDROME DE TURNER***C. Bech-Stapfer, J-J Perrenoud*Département de Réhabilitation et Gériatrie, HUG

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**Introduction:** Une patiente de 72 ans, atteinte d'un syndrome de Turner a été hospitalisée en raison d'une toux avec dyspnée. Le bilan a mis en évidence une végétation de la valve tricuspide ainsi que deux paires d'hémocultures positives pour *Salmonella enterica* serovar enteritidis.

**Méthode:** Le diagnostic d'endocardite est posé sur les critères de Duke's, un majeur et trois mineurs: échocardiographie positive, fièvre, pathologie cardiaque prédisposante, microbiologie. L'évolution sous antibiothérapie est favorable

**Résultat:** Durant des années, les endocardites à bactéries Gram négative non HACEK ont été principalement rapportées à l'usage de drogues. Les cas récents sont associés aux contacts rapprochés avec des milieux de soin et aux valves prothétiques. Il n'est pas rare que la bactériémie ne soit pas précédée de symptômes gastro-intestinaux. A l'exception de son âge, notre patiente ne présente pas de facteurs de risque pour une bactériémie à *Salmonelle* tels que diabète, immunosuppresseurs, HIV ou cancer. La localisation droite de la végétation et l'absence de valve prothétique permet probablement d'expliquer la bonne évolution clinique

**Conclusion:** L'endocardite à bacille Gram négative peut être difficile à diagnostiquer et son pronostic est sombre. Cette maladie n'est pas limitée aux classiques groupes à risque. En l'absence d'immunosuppression ou de matériel prothétique, l'introduction rapide d'une antibiothérapie adéquate peut mener à une guérison.

**P4****LE PROFIL D'EXPRESSION DE GENES DANS LES CELLULES SANGUINES PERIPHERIQUES PERMET LA DETECTION DES ANEURISMES INTRACRANIENS**

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**Introduction:** Deux à six pourcent de la population portent un anévrisme intracrânien qui reste le plus souvent asymptomatique. Toutefois la rupture de la lésion est un risque majeur d'handicap ou de décès. La détection est le plus souvent fortuite et l'évaluation est dirigée par l'imagerie. L'objectif de l'étude est d'identifier des biomarqueurs sanguins permettant d'identifier la population à risque et de mieux comprendre la physiopathologie de la maladie.

**Méthode:** Le sang de 267 patients et 154 volontaires sains a été collecté dans des tubes PAXgene. Trois groupes homogènes ont été formés par sélection de participants sur la base de l'âge, du sexe, du tabagisme et de l'hypertension. L'expression de gènes dans le sang de 93 patients ayant souffert une rupture d'anévrisme(R), 68 patients porteurs d'anévrisme non rompu(A) et 99 volontaires sains(V) a été mesuré par des puces à billes Illumina HT-12v3. La sélection de gènes différemment exprimés a été obtenue par l'application d'un modèle linéaire sur une succession de rééchantillonnages (bootstrapping).

**Résultat:** En comparant les trois groupes, 207 gènes sont exprimés différemment entre V-R, 67 entre R-A et 43 entre V-A. En utilisant 28 gènes, un profil propre aux trois groupes a été établi sur un échantillon d'apprentissage. L'utilisation des profils avec un échantillon test a permis la classification avec une précision de 85%, en sensibilité de 81.25% et une spécificité de 87%.

**Conclusion:** Cette étude identifie pour la première fois une signature sanguine permettant d'identifier des patients porteurs d'anévrismes intracrâniens dans la population.

**P4a****MESURE DE LA PRESSION DE PERFUSION OPTIMALE CHEZ LES PATIENTS SOUFFRANT GRAVEMENT D'UNE HEMORRAGIE SOUS-ARACHNOÏDIENNE SECONDAIRE A LA RUPTURE D'UN ANEURISME INTRACRANIEN.**

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**Introduction:** La perfusion cérébrale est maintenue constante dans un domaine de pression artérielle grâce à la réactivité cérébrovasculaire et assure un approvisionnement suffisant de l'encéphale mis en danger par le vasospasme. Cette réactivité peut-être mesurée par un index (Index de Pression-Reactivité :PRx). La mesure du PRx permet d'identifier une pression de perfusion optimale (PPopt) correspondant à la pression de perfusion cérébrale minimale pour obtenir une réactivité maximale. L'objectif de l'étude est de mesurer les changements de pression de perfusion optimale chez les patients souffrant de vasospasme secondaire à une hémorragie sous-arachnoïdienne.

**Méthode:** Les mesures de pression intracrânienne et de pression artérielle ainsi que les mesures de vitesse sanguine dans les artères cérébrales moyennes ont été obtenues chez 42 patients souffrant d'hémorragies sous-arachnoïdiennes graves (WFNS 4 et 5). L'index PRx a été calculé sur des intervalles de 3 minutes durant les première 24 heures pour 25 cas, durant les 3 premiers jours dans 29 cas. Des enregistrements couvrant 20 jours ont été obtenus pour 23 patients.

**Résultat:** Un PRx inférieur à 0 durant les 48 premières heures présente une valeur prédictive de survie de 87.5%. La valeur de PPopt croît avec le vasospasme ( $78 \pm 3$  mmHg avant vasospasme, N=29 ;  $98 \pm 4$  mmHg durant le vasospasme, N=17 ;  $p < 0.0001$ )

**Conclusion:** L'index PR x mesuré durant les premières 48h permet d'évaluer les chances de survie. La mesure de la PPopt est un outil potentiel de surveillance du vasospasme au lit du patient. L'impact sur le pronostic clinique de l'application d'une stratégie d'hypertension artérielle contrôlée visant la PPopt reste à être mesuré.



## P4b

**UNE ETUDE PANGENOMIQUE DECOUVRE 3 NOUVEAUX LOCI ASSOCIES AVEC LA FORMATION D'ANEVRISMES INTRACRANIENS**

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**Suite P4b**

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**Introduction:** Les anévrismes intracrâniens sont des bulles qui se forment sur les parois des artères intracrâniennes et menacent de se rompre. Les saignements sont à l'origine de séquelles neurologiques fréquentes et souvent de décès. Cette étude fait suite à une première étude qui avait identifié 3 loci associés avec la formation d'anévrismes intracrâniens. Elle confirme 2 loci précédemment décrits et en découvre 3 nouveaux.

**Méthode:** La cohorte comprend 5891 patients d'Europe et du Japon ainsi que 14181 sujets sains. Le génotypage couvre le génome entier avec ~832000 SNPs.

**Résultat:** Trois nouveaux loci sont associés avec évidence à la maladie, à proximité du gène RBBP8 en position 18q11.2, STARD13-KCL en position 13q13.1 et une région riche en gènes en 10q24.32. Les loci à proximité de SOX17 en 8q11.23-q12.1 et CDKN2A et CDKN2B en 9p21.3. Plusieurs gènes de risque jouent un rôle dans la progression du cycle cellulaire pouvant affecter la prolifération et la sénescence des populations de cellules progénitrices participant à la formation et réparation de la paroi vasculaire.

**Conclusion:** Quand combinée avec des facteurs de risque traditionnels comme le sexe, l'hypertension artérielle et le tabagisme, la découverte des facteurs de risques génétiques forme la base de futurs travaux visant à identifier les individus à risques de former des anévrismes et de souffrir d'une rupture.

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**P5****THROMBOPROPHYLAXIS WITH LOW-MOLECULAR-WEIGHT HEPARIN AFTER CESAREAN DELIVERY**

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**Introduction:** Although venous thromboembolism (VTE) is the leading cause of maternal mortality in developed countries, the usefulness of preventive low-molecular-weight heparin (LMWH) after cesarean delivery remains a matter of controversy. It was the objective of this study to evaluate the usefulness of thromboprophylaxis with LMWH after cesarean delivery.

**Méthode:** A decision model was constructed to evaluate the risks and benefits associated with a seven-day LMWH prophylaxis, compared with none. All probabilities were obtained from literature according to the highest level of evidence. We performed our analysis on two different sets of outcomes (utilities and disutilities), to calculate the quality-adjusted life expectancy at three months. Finally, we calculated the outcomes for four hypothetical cases with different risk.

**Résultat:** Prophylaxis with LMWH yielded the highest quality-adjusted life expectancy, with a net gain of 1.5-2.8 quality-adjusted days. Sensitivity analyses showed the incidence of VTE after cesarean delivery and the haemorrhagic risk related to LMWH to be critical, at threshold values of 0.15-0.22% and 0.23-0.35%, respectively. In the hypothetical cases, LMWH was safe but only marginally more effective in women with no risk factors. In case of an emergency procedure, a body-mass index >25kg/m<sup>2</sup>, tobacco smoking, or any combination of these, reductions in VTE greatly outnumbered the increase in major haemorrhages, with a modest benefit on mortality.

**Conclusion:** Our decision analysis suggests that the benefits of LMWH after cesarean delivery exceed the risks. This benefit is; however, very low in women with no risk factors.

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**P6****DEPRESSION RELAPSE PROPHYLAXIS WITH MINDFULNESS-BASED COGNITIVE THERAPY: REPLICATION AND EXTENSION IN THE SWISS HEALTH CARE SYSTEM**

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Service de Psychiatrie Adulte

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**Introduction:** Mindfulness-Based Cognitive Therapy (MBCT) is a group intervention that integrates elements of Cognitive Behavioural Therapy (CBT) with components of mindfulness training to prevent depressive relapse. The efficacy of MBCT compared to Treatment As Usual (TAU), shown in two randomized controlled trials indicates a significant decrease in 1-year relapse rates for patients with at least three past depressive episodes. The present study is the first independent replication trial comparing MBCT+TAU to TAU alone across both language and culture (Swiss health care system).

**Méthode:** Sixty unmedicated patients in remission from recurrent depression ( $\geq 3$  episodes) were randomly assigned to MBCT+TAU or TAU. Relapse rate and time to relapse were measured over a 60 week observation period. The frequency of mindfulness practices during the study was also evaluated.

**Résultat:** Over a 14-month prospective follow-up period, time to relapse was significantly longer with MBCT+TAU than TAU alone (median 204 and 69 days, respectively), although both groups relapsed at similar rates. Analyses of homework adherence revealed that following treatment termination, the frequency of brief and informal mindfulness practice remained unchanged over 14 months, whereas the use of longer formal meditation decreased over time.

**Conclusion:** Relapse monitoring was 14 months in duration and prospective reporting of mindfulness practice would have yielded more precise frequency estimates compared to the retrospective methods we utilized. Further studies are required to determine which patient characteristics, beyond the number of past depressive episodes, may predict differential benefits from this therapeutic approach.

**P7****MICROBIOLOGICAL TESTING AND OUTCOMES OF FULL-MOUTH SCALING AND ROOT PLANING WITH OR WITHOUT AMOXICILLIN/METRONIDAZOLE IN CHRONIC PERIODONTITIS**

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**Introduction:** The purpose of this study was to assess whether microbiological testing was of value in predicting which patients would specifically benefit from amoxicillin and metronidazole adjunctive to non-surgical mechanical treatment of chronic periodontitis.

**Méthode:** Single centre, double blind, placebo controlled, randomized longitudinal study of 6 months. 51 patients received full-mouth periodontal debridement, performed within 48 hours. 25 subjects then received 500 mg metronidazole and 375 mg amoxicillin 3/d for 7 days, and 26 received a placebo. Before and 6 month after treatment microbiological samples were taken from the deepest pocket in each quadrant. Six periodontal pathogens (*Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum* ssp., *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema. denticola*, *Tannerella forsythia*) were quantified by real-time PCR.

**Résultat:** 47 patients could be followed up to month 6. After treatment, test subjects had a substantially lower mean number of persisting sites with pocket probing depth >4 mm and bleeding on probing than control subjects (0.4 vs. 3.0,  $p=0.005$ , month 6). In the antibiotic group, *A. actinomycetemcomitans* could no longer be detected after treatment and significantly lower frequencies were noted for *P. gingivalis* ( $p=0.013$ ), and *T. forsythia* ( $p=0.007$ ). However, presence of 6 putative periodontal pathogens quantified prior to therapy was not correlated to the clinical outcome.

**Conclusion:** Systemic metronidazole and amoxicillin significantly improved the 6 months clinical outcomes, hereby significantly reducing the need for additional therapy. Better results in the antibiotics group were obtained irrespective of the detection or non-detection of 6 classical periodontal microorganisms prior to treatment

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**P8****ATTEINTES ARTICULAIRES INFLAMMATOIRES CHEZ LES PATIENTS AVEC UNE MALADIE INFLAMMATOIRE CHRONIQUE DE L'INTESTIN (MICI): UNE ETUDE DE COHORTE SUISSE**

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**Introduction:** L'atteinte articulaire inflammatoire (AAI) est la manifestation extra-digestive la plus commune des patients avec une MICI. Notre objectif était d'identifier et caractériser les AAI dans une cohorte de patients avec MICI.

**Méthode:** Il s'agit d'une étude de cohorte multicentrique. Analyse de questionnaires remplis à l'inclusion (juillet 2006 à juillet 2009) par les patients et leur gastro-entérologues. Puis, une analyse univariée entre diverses caractéristiques cliniques de la maladie intestinale et la présence d'une AAI est réalisée. Finalement, une régression logistique multivariée est effectuée pour déterminer quelles variables sont associées de façon indépendante à une AAI.

**Résultat:** 1118 patients inclus (668 avec maladie de Crohn (MC) et 450 avec colite ulcéreuse (CU)). 49% des patients remplissaient les critères d'AAI. Ces patients ont plus fréquemment une MC qu'une CU (prévalence 67% versus 33%) et sont plus souvent fumeurs (prévalence 52% versus 48%). Dans notre cohorte, seuls 28% des patients avec AAI a été vu par un rhumatologue. L'analyse logistique multivariée montre une association entre la présence d'AAI et le sexe féminin (O R pour le sexe masculin entre 0.54 et 0.6), la MC (OR 1.83), le tabagisme chez les patients avec MC (OR 1.4), ainsi qu'avec un âge avancé (OR >50 ans entre 1.87 et 2.25)

**Conclusion:** Les AAI sont très fréquentes (49%) chez les patients avec MICI. Cependant, seuls 28% ont consultés un rhumatologue pour ce problème, indiquant que la prise en charge des AAI n'est pas optimale. L'AAI est plus fortement associée à la MC qu'à la CU. En présence d'une MICI, les facteurs de risques pour des AAI sont le sexe féminin, l'âge avancé et le tabagisme lors de MC.

**P9****RIGHT VENTRICULAR SYSTOLIC FUNCTION IN RIGHT VENTRICULAR PACING: A LONG-TERM EVALUATION.**

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**Introduction:** If chronic right ventricular (RV) pacing is known to impair left ventricular function, its effects on the right ventricle has not been well established, partly due to the difficulty in assessing RV systolic function in device patients (pts). Radionuclide ventriculography allows accurate quantification of right and left ventricular ejection fraction (RVEF and LVEF) in these pts.

**Méthode:** A total of 47 pts (38 males, age  $77\pm 6$  years) requiring ventricular pacing were evaluated. Radionuclide ventriculography was performed at baseline, at about 1 year, and at long-term follow-up (f-up) to assess RVEF and LVEF.

**Résultat:** After a median of 1.1 years (range 0.5-1.7) of pacing, there was a significant reduction in LVEF from baseline to f-up ( $54\pm 11\%$  and  $50\pm 13\%$  respectively,  $p = 0.007$ ), whereas RVEF was not significantly impaired ( $45\pm 7\%$  at baseline and  $44\pm 6\%$  at f-up,  $p = 0.26$ ). A total of 33 pts completed long-term f-up (6 pts died, 8 pts dropped-out). LVEF was significantly reduced at long-term f-up compared to baseline ( $-4\pm 10\%$  in absolute terms,  $p = 0.038$ ), whereas RVEF was not affected ( $+1\pm 5\%$  in absolute terms,  $p = 0.27$ ). Pacing site, either apical (16/33 pts) or septal (17/33 pts), did not influence RVEF at long-term f-up.

**Conclusion:** Contrary to a significant reduction in LVEF, RV pacing does not result in impairment in RVEF at mid- and at long-term f-up.

**P10****CHEMOATTRACTANT SIGNALS AND ADHESION MOLECULES PROMOTING HUMAN REGULATORY T-CELL RECRUITMENT TO PORCINE ENDOTHELIUM**

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**Introduction:** Cellular rejection of xenografts mediated by CD4+T cells represents one of the obstacles for the clinical implementation of xenotransplantation. Recently, human CD4+ T cell-mediated anti-pig xenogeneic responses in vitro. Although the mechanisms by which huTregs mediated their suppressive function have been elucidated, the chemotactic factors responsible for huTregs recruitment and the receptors involved in their adhesion to and transmigration through porcine endothelial cells (pEC) are unknown.

**Méthode:** The present study investigated the role of human beta2 integrins, their porcine ligands and the chemoattractant factors that promote the recruitment of huTregs to pEC using ex vivo expanded huTregs and immortalized pEC lines, blocking antibodies in static chemotaxis assays, flow-based adhesion and transmigration assays.

**Résultat:** We demonstrate that TNF $\alpha$ -activated pEC release factors that induce huTregs chemotaxis. This effect was inhibited by blocking human CXCR3. Under static conditions the migration of huTregs across pEC was inhibited by masking huCD18, porcine VCAM -1 and ICAM-2. When the effect of immobilized chemokines on huTregs transmigration was analysed under physiological shear stress, exposure of CCR4+ huTregs to human recombinant CCL17 immobilized on pEC significantly increased their transmigration. Finally, the suppressive function of huTregs was analysed showing inhibition of allogeneic T-cell proliferation and xenogeneic NK cell cytotoxicity mediated by freshly isolated human NK cells.

**Conclusion:** we identified several factors involved in the recruitment of functionally active huTregs to the porcine endothelium in a model of pig-to-human xenotransplantation. Ongoing studies will further explore the specificity of these factors for huTregs and the potential inhibitory effect of huTregs on pEC and the other human cellular subsets involved in xenograft rejection. The knowledge of these mechanisms may lead to the development of new strategies to protect xenografts from cell-mediated rejection.

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**P11****GENOME-WIDE ASSOCIATION STUDY OF BLOOD PRESSURE AND HYPERTENSION**

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**Introduction:** Blood pressure is a major cardiovascular disease risk factor. To date, few genetic variants associated with interindividual blood pressure variation have been identified and replicated.

**Méthode:** Here we report results of a genome-wide association study of systolic (SBP) and diastolic (DBP) blood pressure and hypertension in the CHARGE Consortium (n=29,136).

**Résultat:** We identify 13 SNPs for SBP, 20 for DBP and 10 for hypertension at P.

**Conclusion:** Identifying genes associated with blood pressure advances our understanding of blood pressure regulation and highlights potential drug targets for the prevention or treatment of hypertension.



**P12****RECRUITMENT APPROACHES FOR A NOVEL SCREENING STRATEGY FOR RHEUMATOID ARTHRITIS**

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**Introduction:** Rheumatoid arthritis (RA) was once viewed as an inexorably progressive disease, but has become a potentially curable disease with very early use of disease-modifying antirheumatic therapy. Therefore, diagnosing RA early and identifying pre-clinical RA as accurately as possible has become a high-stakes undertaking. The contemporary view of its pathophysiology is a process that starts with a pathologic activation of the adaptive immune system (or 'immune onset of the disease'), followed by an asymptomatic period (or 'preclinical phase'), which eventually leads to the 'clinical onset of the disease'. During the preclinical phase of RA, auto-antibodies are often already present and synovitis can be demonstrated on histology in clinically uninfamed joints. Biomarkers and clinical risk factors of pre-symptomatic disease exist and suggest that screening at risk populations for early detection of RA and treatment are not out of the realm of the possible. The objective of this project is thus to develop and evaluate a screening strategy for the development of RA in first degree relatives of patients with RA.

**Méthode:** We are assembling a cohort of individuals at increased risk of RA, namely first-degree relatives of patients with RA. Participants will have risk factors for RA determined and be tested for biomarkers of RA susceptibility and followed prospectively until they develop RA.

**Résultat:** Recruitments strategies of healthy first-degree relatives for this cohort will be achieved via their diseased parent. Patients with RA will be informed of the possibility of a free screening test of RA susceptibility for their unaffected family members via regional RA patient associations, at patient conferences, through advertisement in patient journals, via their treating rheumatologists and on patient websites. We also plan to create internet links to our screening program using sponsored links to 'Google.ch' key-words searches. In addition, we will also contact patients from the Swiss RA cohort (SCQM-RA) that have expressed willingness to participate in additional studies and ask them to inform their relatives.

**Conclusion:** The screening study will establish the diagnostic accuracy of clinical risk factors and biomarkers of RA susceptibility in family members of RA patients. Ultimately this study aims at testing whether an early detection of pre-clinical RA is feasible and whether a screening strategy can be implemented in a high risk population for RA.

## P13

**EFFICACY OF METHOTREXATE IN THE MANAGEMENT OF CHRONIC CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) ARTHROPATHY: AN INTERIM ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL**

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**Introduction:** Calcium pyrophosphate dihydrate (CPPD) deposition may cause severe arthropathy and major joint destruction. There is currently no specific treatment to prevent CPPD deposition and the therapy of chronic or recurrent CPPD arthropathies can be problematic. We are conducting a randomized controlled trial (RCT) to test the efficacy of methotrexate (MTX) versus placebo (PBO) on symptoms and signs of chronic or recurrent CPPD arthropathy. We present here an interim analysis of the first 21 patients, which was performed by an external reviewer. Objectives: To assess the tolerance and efficacy of MTX in CPPD arthropathy and to validate the ethics and the rationale underlying this ongoing RCT.

**Méthode:** This is a double-blind, crossover RCT, with a 2 month “wash-out” between the 3 month treatment periods. Patients with CPPD arthropathy are randomized to receive either weekly subcutaneous injections of 15 mg/week of MTX or similar injections of PBO. Inclusion criteria comprise definite CPPD deposition disease (McCarty diagnostic criteria), recurrent mono- or oligo-arthritis (“pseudogout”) or persistent polyarthritis, and an insufficient response to NSAIDs, glucocorticoids or colchicine. Exclusion criteria are a positive rheumatoid factor or anti-CPP antibodies and contraindication to MTX therapy. Concomitant analgesic medication and additional glucocorticoids are allowed and number of pills assessed. The evaluation is performed in a double-blind manner at 0, 1, 2, 3 months and at 5, 6, 7, 8 months. The primary outcome is a reduction in arthritis pain level (VAS), and improvement in the DAS44 for polyarticular presentations or in number of flares for the pseudogout presentations. The analysis was performed on an intent-to-treat basis, using simple descriptive statistics, without significance testing.

**Résultat:** 21 patients from 5 centers were randomized and 16 patients completed all follow-up assessments. Baseline characteristics were balanced between the groups. During the study follow-up, 21 adverse events (AE) were reported, but no serious AE (hospitalization or permanent damage) occurred. Overall minor AE occurred more commonly on MTX (55% of patients) than on PBO (35% of patients). Patient’s pain levels improved minimally in both groups (median VAS-pain decreased from 5 to 4.5 on MTX and from 6 to 5 on PBO). DAS44 levels did not vary substantially over time in either group (mean DAS44 decreased from 2.5 to 2.3 on MTX and from 2.7 to 2.2 on PBO). Forty percent of patients presented with pseudogout flares at baseline, after 3 months the proportion decreased to 17% in patients receiving MTX and to 24% in patients receiving PBO. A larger proportion of patients on MTX than on PBO was able to reduce analgesic or anti-inflammatory medications (40% versus 25%).

**Conclusion:** In this elderly population with chronic or recurrent CPPD arthropathy, minor AEs appear to be more frequent in patients receiving MTX than in those receiving PBO. In this interim analysis, no strong signal emerged in favour of MTX, warranting the continuation of the trial.

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**P14****CHARACTERISTICS OF PLATELET FUNCTION IN STABLE ASPIRIN-TREATED CARDIOVASCULAR PATIENTS**

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**Introduction:** In healthy subjects, platelet reactivity is a global phenomenon – as opposed to agonist specific – and a subgroup with relative platelet hyperreactivity can be identified. Whether platelet reactivity in stable aspirin-treated cardiovascular patients follows the same pattern is unknown.

**Méthode:** Platelet function with various agonists was assessed twice, two weeks apart, in 110 stable cardiovascular patients treated with aspirin 100 mg/d as their sole antiplatelet drug. Drug compliance was evaluated with serum thromboxane B2. Factorial analysis was performed to determine whether the different platelet function tests could be summarized in one single axis allowing the construction of a composite “platelet reactivity” variable. Multivariate regression analysis was performed to explore determinants of “platelet reactivity”.

**Résultat:** Factorial analysis showed that the platelet function tests can be summarized in a single variable (“platelet reactivity”) that contained 60% of the information. Results obtained at the first visit were consistent with those obtained at the second visit. Univariate analysis that included more than 25 relevant biological and clinical parameters and subsequent multivariate regression analysis did not identify any variable associated with platelet reactivity.

**Conclusion:** Similarly to what has been demonstrated in healthy subjects, platelet reactivity is a global phenomenon in aspirin-treated stable cardiovascular patients. The variability of platelet reactivity is not explained by several biological and clinical parameters pointing out genetic factors at the forefront to regulate platelet reactivity in cardiovascular patients. A proteomics analysis of selected patients of this study is underway.

**P15****PHYSICIANS AND ADVANCE DIRECTIVES IN PATIENTS PLANNED FOR HEART SURGERY**

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**Introduction:** In Switzerland, the extent of Advance Directives (AD) is unknown, whereas a federal law is in preparation. The literature reports their importance, but also their complexity for health and public policies.

**Méthode:** Investigation of what general practitioners+specialists involved in planned heart surgery think about AD by mailed self-administered questionnaires

**Résultat:** 409 questionnaires, 164(40) fulfilled. Men:116(71). Specialities:General Practitioners:50(31);Internists:73(45);Intensivists:22(13);Cardiologists:18(11). Private activity:121(73). 22/164(13)physicians did not know AD, especially men( $p=.006$ ). 67/154(42) physicians learned about AD in post-graduate courses. Physicians with >20y. of practice did learn more through literature( $p=.01$ ). More "private" physicians had heard about it from patients than institutional physicians( $p=.02$ ). 93(57)physicians thought that AD should be written when the patient is severely ill. 68(41)thought they should be written the soonest possible, 69(42)before a major surgery and 41(25)when patients are >55yo. 138/162(85)physicians thought AD useful. 123/162(76)are ready to help a patient planned for heart surgery to write AD in order to respect the patient's autonomy{118/130(92)}, to enhance reassurance{110/130(86)}, to avoid his feeling of being a burden{102/130(80)}. Cardiologists were the least prone to help writing( $p=.002$ ). The reasons for refraining help were that the topic can induce fear {24/43(56)}, discomfort{17/43(40)}, lack of knowhow{15/43(35)}.

**Conclusion:** 13% of physicians did not know AD. More than 3/4 thought AD useful. More than 2/3 would propose their help in the writing for respecting the patient's autonomy. A minority did not encourage AD, since the topic could induce fear and could be harmful. 1/3 lacked the knowledge for helping. Comparison with what patients think is awaited. This study is sustained by the FNRS (CR31I3\_127135/1).

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**P16****SIMULTANEOUS EEG AND FUNCTIONAL MRI IN PRESURGICAL EPILEPSY EVALUATION**

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**Introduction:** Simultaneous EEG and fMRI (EEG-fMRI) is a helpful tool for the non-invasive localisation of epileptic networks. However, only 30% of the exams are conclusive. The reasons are twofold: first, recent findings have suggested that the hemodynamic properties of epileptic brain could differ significantly from physiological responses. Second, in up to 40% of patients, absence of Interictal Epileptiform Discharges (IEDs) precludes statistical analysis. In order to overcome these obstacles, we developed two methods to increase the yield of this exam.

**Méthode:** During their presurgical workup, 25 epileptic patients had a continuous and simultaneous 20-minute EEG-fMRI recording. We developed a deformable model-based analysis to estimate the Hemodynamic Response Function (HRF) at the single subject level, to localize hemodynamic changes correlated with epileptic activity. Epileptic scalp topographies computed from IEDs obtained during long-term clinical EEG recordings, were also fitted into the EEG recorded during fMRI and the time-course of the correlation coefficient quantifying the presence of this epileptic state was used for the fMRI analysis. The correctness of the results was estimated on the basis of other cerebral imaging (MRI, PET, SPECT, etc), intracerebral or per-operative recordings.

**Résultat:** After characterizing HRF individually, 95% of patients with IEDs had concordant activations. Fitting of the epileptic maps allowed the identification of the epileptic network even in the 40% of patients without IEDs during the exam

**Conclusion:** Using these methods we drastically increased the yield of EEG-fMRI from 30% up to 90%. This study demonstrates that EEG-fMRI is a promising method for the non-invasive presurgical localisation of epileptic networks.

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**P17****A SIX MONTHS FOLLOW UP STUDY AFTER 10 DAYS TOPICAL MUPIROCINE APPLICATION ON INTRA NASAL STAPHYLOCOCCUS AUREUS CARRIAGE**

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**Introduction:** Intranasal *Staphylococcus aureus* (SA) carriage has been suspected to be responsible for community- and hospital-acquired infections. Healthy intra nasal carriers of methicilin resistant *Staphylococcus aureus* (mrsa) have frequently received topical mupirocine as preventive treatment of nosocomial infections. The aim of this study was to evaluate the outcome, 6 months after 10 days topical mupirocine intranasal treatment, on the SA nasal carriage.

**Méthode:** 36 patients, with positive SA culture from intranasal swabs and/or nasal mucosa biopsies, were treated by topical mupirocine (Bactroban®) bid for 10 days; swabs were taken again after treatment as well as 6 months later. Rapid genotyping was performed on the stems to investigate their characteristics.

**Résultat:** Six (16 %) positive *Staphylococcus aureus* carriers were not available for the 6 months control and were excluded. After treatment, no SA could be found in 14 patients (36 %). 19 (63 %) were still SA carriers after 10 days of treatment. 20 were found SA carriers 6 months later. 6 patients were re-colonised 6 months after primary sterilisation, while 14 remained persistent carriers. In this last group of patients, 12 were carrying monoclonal SA stems during the 6 months study

**Conclusion:** Intranasal SA carriage seems to be poorly influenced after topical mupirocine treatment. Several mechanisms could be involved in this observation including SA intracellular residency and/or biofilms.

**P18****INCIDENCE OF NEUROLOGIC LESIONS AFTER TOTAL SHOULDER ARTHROPLASTY**

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Chirurgie orthopédique et traumatologie de l'appareil moteur

**Introduction:** Clinically evident neurological injury on the operated limb after total shoulder arthroplasty (TSA) is not uncommon. Subclinical incidence is unknown. The purpose of this prospective study was to determine the incidence of neurological lesions after reverse shoulder arthroplasty (RSA) and anatomic shoulder arthroplasty (ASA) (group control), and to correlate its occurrence to postoperative lengthening of the arm.

**Méthode:** We included all patients undergoing either a RSA or an ASA. This study focused on the clinical, radiological and pre- and postoperative EMG evaluation, with a measure of arm lengthening in case of RSA.

**Résultat:** Between November 2007 and February 2009, 41 patients were included, 19 reverse and 23 anatomic primary shoulder arthroplasties. The two groups were similar with respect to sex ratio, preoperative neurological lesions and Constant score. Control EMG realized at a mean of 3.6 weeks postoperatively in the RSA group showed nerve lesions in 9 patients (47% of cases) involving mainly the axillary nerve; 8 were regressive in less than 6 months. In ASA group, we noticed, one plexus lesion. The incidence of acute intra-operative nerve injury was significantly more frequent in the RSA group ( $p=0.002$ ) with a risk 10.9 times higher (95% CI 1.5, 78.5). Mean lengthening of the arm after RSA was  $2.7\pm 1.8$  cm (range 0 to 5.9) compared to the normal contra-lateral side. In the RSA group, three of four patients (75%) with a mean arm lengthening of 4 cm or more and six of fifteen patients (40%) with a mean arm lengthening of less than 4 cm developed a neurological lesion postoperatively.

**Conclusion:** The occurrence of peripheral neurological lesions following RSA seems to be frequent but mainly transient. Lengthening of the arm is considered as one major factor responsible for this neurologic damage.



**P18a****INFLUENCE OF ARM LENGTHENING IN REVERSE SHOULDER ARTHROPLASTY**

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Chirurgie orthopédique et traumatologie de l'appareil moteur

**Introduction:** Reverse shoulder arthroplasty (RSA) can improve anterior active elevation (AAE) in cases of deficient rotator cuff by lengthening of the deltoid and hence increasing its lever arm. However, evaluations of functional outcomes of RSA have revealed variable improvements in the range of motion. The aim of our study was to correlate humerus and arm lengthening to postoperative AAE.

**Méthode:** 183 RSA were reviewed with a minimum follow-up of one year. Lengthening of the humerus and the arm was evaluated either in relation to the contra-lateral side.

**Résultat:** We observed an average humeral lengthening of  $0.2 \pm 1.4$  cm (range, -4.7 to +5.2 cm) and arm lengthening of  $1.6 \pm 1.9$  cm (range -5.1 to +5.4 cm). Postoperative AAE was  $141 \pm 27^\circ$  (range, 30 to  $180^\circ$ ). We found no correlation between lengthening or shortening of the humerus and AAE ( $p=0,169$ ). Shortening of the arm lead to a mean AAE of  $121^\circ$ ; lengthening between 0 and 1 cm to a mean AAE of  $140^\circ$ ; lengthening of 1 to 2.5 cm resulted in a mean AAE of  $144^\circ$  and  $147^\circ$  beyond 2.5 cm. The difference of AAE was statistically significant ( $p$

**Conclusion:** This study shows that there is a negative statistical correlation between shortening of the arm and AAE. We have not noted any lengthening threshold at which the AAE decreased. On objective assessment of deltoid lengthening is possible pre-, intra- and postoperatively and this measure may be correlated to the functional outcome.



**P18b****MID TO LONG-TERM CLINICAL, ISOKINETIC AND RADIOLOGICAL RESULTS OF TYPE III TO V ACROMIOCLAVICULAR JOINT RECONSTRUCTION USING CERCLAGE AUGMENTATION**

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Chirurgie orthopédique et chirurgie de l'appareil moteur

**Introduction:** Only few data are available on mid- to long-term results of different stabilisation methods of acute acromioclavicular (AC) injuries. Moreover, there is, to our knowledge, no study analysing isometric performance of the shoulder after AC stabilisation. The objective of this retrospective study was thus to present functional, including isokinetic testing, outcomes and radiographic features of patients treated with stabilisation of AC joint dislocations using cerclage augmentation.

**Méthode:** Thirty-seven patients (19 type V, 12 type IV and 6 type III) with acute AC joint disruption underwent stabilization. The surgical technique consisted of open coracoclavicular (CC) and AC stabilization with non-absorbable sutures. Constant Score, DASH Score and Pain Score were assessed. Radiographs of shoulder girdle were performed in the order to measure AC reduction and CC distance and to note the emergence of degenerative changes, calcification or distal clavicular osteonecrosis. Isokinetic evaluation testing was also proposed. Data were compared for the operated and the non-operated shoulders.

**Résultat:** Clinical scores were excellent with a mean CS of 95.7 points, a median DASH Score of 7 points and an average Pain Score of 1.8. Overall, 89% patients were very satisfied with results and cosmetic appearance. All patients returned to their work within a median of 4 months after operation and 81% returned to their preinjury level of sports. Two patients need further operations: one suffered from a skin irritation by sutures knots and the other developed a transitory postoperative plexus lesion. Radiographically, 72% showed a difference of CC distance in comparison to the contralateral side of <5 mm and 28% of 5–10 mm. Quality of AC reduction and symmetric CC distance affect ultimate outcome in a statistically significant manner. Signs of osteoarthritis were present in 7 operated shoulders and CC calcifications were seen in 13. However, none of these latter abnormalities neither the type of AC dislocation had any influence on the clinical result. When compared with the contralateral limb, limited deficits relative to PT, PT/BW, AP and TW existed for (range 3 to 6.8%) and both internal and external rotation (range 0.3 to 3.6%).

**Conclusion:** Considering good to excellent results without the need to remove implant, complications linked to implants and graft source morbidity, this technique of cerclage augmentation offers an attractive alternative in AC joint stabilization.

**P18c****INFLUENCE OF SURGICAL APPROACHES IN REVERSE SHOULDER ARTHROPLASTY SURGERY**

*Alexandre Lädermann, Panayiotis Christofilopoulos, Gilles Walch*

Chirurgie orthopédique et traumatologie de l'appareil moteur

**Introduction:** Reverse shoulder arthroplasty can be performed using different surgical approaches. The purpose of this retrospective multicentric study is to compare the results concerning arm and humeral length as well as overall shoulder function using either the deltopectoral (DP) or the trans-deltoid (TD) approach.

**Méthode:** Between 2003 and 2008, 183 prostheses (180 patients) were enrolled in this clinical and radiological study with a minimum follow-up of 1 year. Lengthening of the arm (distance elbow-acromion) and the humerus (distance elbow-top of the head) was calculated on plain x-rays using a previously validated protocol. Postoperative function was evaluated by determining anterior active elevation.

**Résultat:** 146 reverse shoulder arthroplasty were implanted by a delto-pectoral approach (group a) and 37 through a trans-deltoid approach (group b). The average lengthening of the humerus compared to the contro-lateral side was 0.4 cm  $\pm$  1.4 for group a compared to a shortening of -0.5 cm  $\pm$  1 for group b (p

**Conclusion:** Reverse shoulder arthroplasty can improve anterior active elevation through the restoration of deltoid muscle tension and by increasing the humeral lever arm. The evaluation of deltoid tensioning to date was based on subjective intraoperative elements. By using objective pre-and postoperative measures of lengthening of the arm and overall humeral length, we could highlight a difference between the DP and TD approaches. The humeral bone cut in the TD approach is statistically more important. There is no difference in term of function between the two approaches.

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**P19****INCREASING THE DIAGNOSTIC VALUE OF EVOKED POTENTIALS IN MULTIPLE SCLEROSIS BY QUANTITATIVE TOPOGRAPHIC ANALYSIS OF MULTICHANNEL RECORDINGS**

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**Introduction:** This study presents a method to record and analyze multichannel visual-evoked potential (VEP) and somatosensory-evoked potential (SEP) in an objective, automatic, and quantitative manner. The intention of this study was to assess their diagnostic value in multiple sclerosis (MS).

**Méthode:** A 256- channel VEP and SEP were recorded in 44 healthy subjects, 26 patients with MS, and 20 patients with other neurologic diseases. Topographic pattern recognition methods were applied and a normative database was established. Z-score statistics allowed identifying the number of subjects with significant abnormal values in each group. These values were compared with conventional single-channel waveform analysis.

**Résultat:** The diagnostic value of the new measures for MS reached a sensitivity of 72% and a specificity of 100% for the VEP, which was significantly higher than the conventional analysis. For the SEP, the specificity was also high (93%) but the sensitivity remained low as in the conventional analysis (30%).

**Conclusion:** The quantitative topographic analysis of multichannel VEP revealed high-diagnostic sensitivity and specificity for MS. Moreover, the method reliably identified the most dominant VEP and SEP components in the healthy subject group. The results indicate that objective topographic analysis of multichannel recordings increase the value of VEP as surrogate marker for MS.

**P20****DECREASED BONE TURNOVER IN CHILDREN AND ADOLESCENTS WITH WELL CONTROLLED TYPE 1 DIABETES**

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**Introduction:** Osteoporosis is a common long-term complication of type 1 diabetes (T1DM). We aimed to determine whether bone mineral density (BMD) and turnover are already altered during childhood.

**Méthode:** We recruited 27 T1DM children and 32 controls (age  $10.5 \pm 2.5$  yr.) and measured BMD (dual-energy x-ray absorptiometry); bone biomarkers levels (osteocalcin: OC; procollagen type 1 propeptides aminoterminal: PINP; crosslinking telopeptides of type 1 collagen C-terminal: CTX), glycated hemoglobin (HbA1c), dietary intake and physical activity.

**Résultat:** Patients with T1DM had lower levels of OC ( $70.3 \pm 3.3$  vs  $105.3 \pm 6.8$ ), PINP ( $556.4 \pm 47.6$  vs  $716.3 \pm 53.8$ ), CTX ( $0.97 \pm 0.07$  vs  $1.20 \pm 0.08$ ), physical activity, and calcium intake. Biomarkers were negatively correlated with HbA1c. Though, BMD was similar among groups and not related to HbA1c, disease duration, physical activity or dietary intakes.

**Conclusion:** Bone turnover is altered in T1DM children, whereas BMD remains normal during growth. Physical activity and optimal calcium intakes may improve bone metabolism and delay osteoporosis.

**P21****DEMOGRAPHICS AND OUTCOMES OF SEVERE HERPES SIMPLEX VIRUS HEPATITIS: A SRTR REGISTRY-BASED STUDY**

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**Introduction:** Herpes simplex virus (HSV) hepatitis is a rare, but severe disease, thus far only documented by case reports and short series.

**Méthode:** The present study was based on the SRTR registry, a large nation-wide US registry (including all listed and/or transplanted patients in the US). All patients listed for liver transplantation for HSV hepatitis from December 1985 to January 2009 were included. We assessed demographics and outcome of all listed patients, and further conducted a case-control study, matching each transplanted patient with 10 controls was further performed. Matching criteria included: transplant status (according to UNOS classification), Model for End-Stage Liver Disease score  $\pm 5$ , transplant date  $\pm 6$  months and age at transplant  $\pm 5$  years. During the study period, 30 patients were listed for HSV hepatitis. Patients were distributed into two groups, young children (with most of them  $\leq 5$  months) and adults. Twelve listed patients were not transplanted, including seven spontaneous recoveries and five deaths. The chance of recovery was significantly higher in children than in adults (7/9 vs. 0/11,  $p=0.02$ ). Ten children and eight adults were transplanted. Most transplants (15/18) were performed on an emergency basis, with a mean MELD score of  $28\pm 13$ .

**Résultat:** The overall 5-year post-transplant survival was 53%. In children, survival was similar between the HSV patients and the matched controls (5-year survival: 69 vs. 64%, log-rank  $p=0.89$ ). Conversely, survival was poor in adult HSV recipients (5-year survival: 38 vs. 65%, log-rank  $p=0.006$ ), with 62% of them dying within the first 12 months. In addition, all three reported post-transplant deaths in children were independent from HSV, while 4/7 adults deaths were infection-related.

**Conclusion:** Children listed for HSV hepatitis have a significantly better survival than adults both prior and after liver transplantation. While HSV fulminant hepatitis is an appropriate indication for liver transplantation in children, it should only be performed in selected adult patients in otherwise good condition.

**P22****RECONSTRUCTION ORBITAIRE POST-TRAUMATIQUE PAR GRILLES EN TITANE PREFORMEES ET NON PREFORMEES**

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**Introduction:** Le but de notre étude est de comparer cliniquement et radiologiquement par une analyse volumétrique assistée par ordinateur la précision et la fiabilité de deux types de grilles en titane soit non préformées (GNP) soit préformées industriellement dans les trois axes (GP), utilisées pour les reconstructions orbitaires.

**Méthode:** Deux groupes constitués respectivement de 15 patients traités soit par plaques préformées soit non préformées ont été établis. Sur des coupes coronales de Ct scan, les volumes orbitaires des deux groupes du côté sain et du côté opéré ont été calculés grâce au logiciel d'analyse d'image OsiriX Medical Image software (version 3.5, [www.osirix-viewer.com](http://www.osirix-viewer.com)) Le sexe, l'âge, la distribution des fractures, l'existence de diplopie et/ou d'enophtalmie, et les volumes ont été analysés rétrospectivement.

**Résultat:** On ne retrouve pas de différence statistique significative du volume moyen ( $P > 0.05$ ) entre les deux orbites, traités par GNP (20.27 cm<sup>3</sup>), ou GP (21.75 cm<sup>3</sup>) pour les côtés reconstruits en comparaison avec le côté non atteint pour les deux groupes, 20.62 cm<sup>3</sup> (GP) et 21.75 cm<sup>3</sup> (GNP). Il n'y a pas de différence statistique ( $P > 0.05$ ) dans la comparaison des volumes orbitaires entre les deux côtés reconstruits 20.27 cm<sup>3</sup> pour GP et 21.75 cm<sup>3</sup> pour GNP.

**Conclusion:** Cette étude démontre qu'il n'existe pas de différence significative dans les volumes orbitaires post opératoires après une reconstruction orbitaire par grilles en titane préformées industriellement ou non. Les deux approches semblent être efficaces dans la restitution du volume orbitaire reconstruit.

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**P23****SYSTEMIC AND INTRAPLAQUE INFLAMMATION IS INCREASED IN PATIENTS SYMPTOMATIC FOR ISCHEMIC STROKE**

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**Introduction:** The concept of “vulnerable plaque” has been extended to the more recent definition of “cardiovascular vulnerable patient”, in which “intraplaque” and “systemic” factors contribute to the cumulative risk of acute cardiovascular events. Thus, we investigated the possible role of systemic and intraplaque inflammation in patients asymptomatic vs. symptomatic for ischemic stroke.

**Méthode:** Regions upstream and downstream the blood flow were isolated from internal carotid plaques of patients asymptomatic (n=63) or symptomatic (n=18) for ischemic stroke. Specimens were analyzed for lipid, collagen, macrophage, lymphocyte, neutrophil, mast cell and smooth muscle cell (SMC) content and chemokine and cytokine mRNA expression. Chemokine receptors and adhesion molecules were assessed on circulating leukocytes by flow cytometry. Systemic inflammatory markers and biochemical parameters were measured on total blood, plasma and serum.

**Résultat:** TNF-alpha and CCL5 serum levels as well as ICAM-1 expression on circulating neutrophils were increased in symptomatic as compared to asymptomatic patients. Collagen content and SMC infiltration were decreased in symptomatic plaques. In upstream regions of symptomatic plaques, lipid content and lymphocyte infiltration were increased. In downstream regions of symptomatic plaques, macrophage, neutrophil, mast cell infiltration were increased. Intraplaque collagen content was positively correlated with SMC infiltration, and inversely correlated with macrophages, neutrophils or serum TNF-alpha. Collagen reduction in downstream regions and serum TNF-alpha were independently associated with the likelihood to be symptomatic.

**Conclusion:** Inflammatory mediators are increased in ischemic stroke. Despite statistically significant, correlation between TNF-alpha serum level and intraplaque vulnerability was weak and probably of limited biological importance.

**P24****HIV-1 ACTIVATES CDC42 AND INDUCES FILOPODIA IN IMMATURE DENDRITIC CELLS TO FACILITATE CELL-TO-CELL VIRUS PROPAGATION**

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**Introduction:** Dendritic cells (DC), due to their unique localization at mucosal surfaces, coupled with their known proficiency in capturing antigens, are among the first potential targets for HIV-1 during transmission. One of the limiting steps for HIV-1 propagation is the transfer of virus at an infectious synapse (IS) between DC and CD4+ T cells. Bacterial pathogens can hijack the host actin cytoskeleton to facilitate invasion and propagation.

**Méthode:** Dendritic cells-T lymphocytes infectious synapses were analyzed by confocal microscopy, electron microscopy, live imaging and 3D-electron microscopy.

**Résultat:** We report here the first evidence that a virus, HIV-1, induces the formation of filopodia in DC through activation of the Rho GTPase Cdc42. We provide direct evidence that filopodia are obligate components of the HIV-1 induced DC-T cell infectious synapse and required for transfer of HIV-1 infection to target CD4+ T cells. HIV-1 at the surface and near the tip of filopodia was observed by confocal microscopy, electron microscopy, live imaging and 3D-EM. Silencing of Cdc42 in dendritic cells dramatically reduced number of filopodia and decreased HIV-1 transfer via dendritic cell-T lymphocyte infectious synapses. Transfection of dominant-negative or constitutively active mutants of Cdc42 in dendritic cells decreased or increased HIV-1 transfer, respectively. Finally, we show that filopodia play an essential role in the transfer of virus when a low number of DC are co-cultured with T cells, a situation that mimics DC-T cell ratios in mucosal tissues or lymph nodes.

**Conclusion:** In conclusion we identify a critical role for Cdc42-dependent filopodia induction by HIV-1 in the transfer of HIV-1 from DC to T cells thereby identifying a novel pathway for HIV-1 cell-to-cell propagation.



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**P25****ECSTATIC EPILEPTIC SEIZURES: A POTENTIAL WINDOW ON THE NEURAL BASIS FOR HUMAN SELF-AWARENESS***F. Picard 1, A.D. Craig 2*

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**Introduction:** The purpose of this study was to better understand the anatomical correlate of epileptic seizures with ecstatic auras, which has not been established yet.

**Méthode:** We document precise descriptions of the ecstatic seizures experienced by five patients. In addition to neuroradiological and EEG data, an ictal SPECT was performed in one patient.

**Résultat:** All patients' descriptions of ecstatic seizures encompassed an emotional dimension of bliss, a physical dimension of enhanced well-being and a heightened awareness of all feelings and of the self. Among these five patients, three suffered from a cerebral lesion located in the anterior part of the temporal lobe. Interictal or ictal scalp EEGs showed anterior temporal abnormalities. An ictal SPECT showed increased blood flow maximal in the right anterior insula.

**Conclusion:** It has recently been proposed that the anterior insular cortex has a fundamental role in the feeling of well-being and in self-awareness. We propose here that the descriptions by these patients, together with the neurophysiological and neuroradiological evidence, support a theoretical framework for understanding ecstatic states based on hyperactivation of the anterior insula, rather than the temporal lobe.

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**P26****NEURAL SUBSTRATES OF THE TENDENCY TO RUMINATE***Camille Piguet, Martin Desseilles, Virginie Sterpenich, Yann Cojan, Gilles Bertschy, Patrik Vuilleumier*Neurosciences Fondamentales, Faculté de Médecine Psychiatrie Adulte, HUG Psychiatrie, Hôpitaux Universitaires de Strasbourg

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**Introduction:** During depression, patients frequently report that their thoughts are dominated by a few repetitive ideas, usually negative, which cannot be suppressed or escaped. This tendency to ruminate is classically quantified by a clinical scale, the Ruminative Response Scale (RRS). Everyone in condition of low mood may experience ruminative style of thinking. We hypothesized that this tendency to ruminate might be associated with a specific pattern of spontaneous brain activity, at rest and/or during a concurrent cognitive task.

**Méthode:** We used functional magnetic resonance imaging (fMRI) in volunteers recruited among the general population in these two conditions: during a resting state session and during a face categorization task with different levels of cognitive demands (easy or difficult conditions). We then correlated our measure for the tendency to ruminate (RRS), with whole-brain fMRI data during the rest and the cognitive categorization task.

**Résultat:** Our results reveal that the more subjects have the tendency to ruminate, the more they activate the left entorhinal and hippocampal region, both during rest and during the easiest condition of the active cognitive task. On the other hand, the less the tendency to ruminate, the more some visual areas were activated, again during both the rest and active task conditions.

**Conclusion:** These results indicate that people prone to ruminate in condition of low mood may display a particular biomarker corresponding to increased spontaneous activity in memory-related areas (i.e. hippocampus), and thus exhibit more internally-driven trains of thoughts. Conversely, people not prone to ruminate show increases in sensory visual areas and more externally-driven activity.

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**P27****DERMATOSCOPIE: VALEUR DIAGNOSTIQUE DU RESEAU INVERSE DANS LE DEPISTAGE DU MELANOME.**

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**Introduction:** En raison de l'absence de traitement efficace du mélanome avancé, la détection précoce et l'excision des mélanomes débutants sont impératives. L'objectif de cette étude est d'établir la valeur diagnostique du réseau inversé (RI) - réseau réticulé non pigmenté, plus ou moins étendu, sur fond brun ou rouge - dans le dépistage dermatoscopique du mélanome.

**Méthode:** Les photographies numériques des lésions pigmentées proviennent de patients vus à la consultation de dépistage et de suivi du mélanome des HUG. Nous avons revu toutes les lésions pigmentées (n=25000 lésions) de notre base de données dermatoscopiques (Fotofinder) pour ressortir celles (n=81) présentant le signe recherché (RI) indépendamment de la présence des autres signes d'atypies.

**Résultat:** La VPP du RI pour le diagnostic de mélanome est de 47.5 %, pour les naevus dysplasiques avec atypies sévères 16.3 %, marquées 18.8%, modérées 13.8 % et pour les naevus sans atypies 3.8 %. La sensibilité et la spécificité sont de 38.8% et 96.5 % respectivement, le Breslow médian de 0,35 mm. Le Positive likelihood ratio du RI pour le mélanome est > 11.0 et negative likelihood ratio < 0.6.

**Conclusion:** L'importance dermatoscopique du RI est confirmée. En effet, dans au moins 63.8 % des cas l'excision est impérative puisqu'il s'agit de mélanome ou de naevus dysplasiques avec atypies sévères. Cette étude permet également de clarifier la signification histologique du RI. Celui-ci ne correspond pas à la fibroplasie papillaire comme initialement décrit mais à une inversion de la répartition habituelle du pigment dermo-épidermique. En pratique courante, au cours d'un examen dermatoscopique classique non numérisé, la présence du Réseau Inversé, justifie donc l'excision de la lésion.

**P28****IMPACT OF OBESITY OF DIAGNOSIS AND TREATMENT OF BREAST CANCER**

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Registre Genevois des Tumeurs

**Introduction:** In this population-based study we evaluated the impact of obesity on presentation, diagnosis and treatment of breast cancer, to better understand the mechanism through which obese women experience worst outcome.

**Méthode:** We identified all 1110 women diagnosed with invasive breast cancer in the canton Geneva (Switzerland) between 2003-2005. By multivariate logistic regression, we compared tumour, diagnostic and treatment characteristics between obese (BMI $\geq$ 30 kg/m<sup>2</sup>, n=86) and lean women (BMI<25 kg/m<sup>2</sup>, n=252).

**Résultat:** Obese women presented significantly more often with stage III-IV disease (Adjusted Odds Ratio [ORadj] 1.8, 95%CI: 1.0-3.3). Tumours  $\geq$ 1cm and pN2-N3 lymph nodes were significantly more often palpable in obese than in normal/underweight patients (ORadj 2.4 [1.1-5.3] and ORadj 5.1 [1.0-25.4] respectively). Obese women were less likely to have undergone ultrasound (ORadj 0.5, [0.3-0.9]) and MRI (ORadj 0.3, [0.1-0.6]) and were at increased risk of prolonged hospital stay (ORadj 4.7, [2.0-10.9]).

**Conclusion:** Since the observed differences in diagnosis and treatment associated with obesity may impair prognosis of obese women with breast cancer, specific strategies are needed to optimise the care of obese women with or at risk of breast cancer.

**P28a****EXCESS OF CARDIOVASCULAR MORTALITY AMONG NODE-NEGATIVE BREAST CANCER PATIENTS IRRADIATED FOR INNER QUADRANT TUMORS**

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Registre Genevois des Tumeurs

**Introduction:** Radiotherapy of the left breast is associated with higher cardiovascular mortality linked to cardiotoxic effect of irradiation. Radiotherapy of inner breast quadrants can also be associated with greater irradiation to the heart, but no study has evaluated the effect of inner quadrant irradiation on cardiovascular mortality.

**Méthode:** For 1,245 women irradiated for primary node-negative breast cancer between 1980-2004, registered at the Geneva Cancer Registry, we compared breast cancer-specific and cardiovascular mortality between inner (n=393) vs. outer quadrant tumors (n=852) by multivariate Cox regression analysis.

**Résultat:** After a mean follow-up of 7.7 years, 28 women died from cardiovascular disease and 91 from breast cancer. Patients with inner quadrant tumors had a more than doubled risk of cardiovascular mortality compared with patients with outer quadrant tumors (adjusted Hazard Ratio: 2.3, 95% Confidence Interval: 1.1-5.1). This mortality excess concerned the period 1990-2004. Patients with left-sided breast cancer had no excess of cardiovascular mortality compared with patients with right-sided tumors.

**Conclusion:** Radiotherapy of inner quadrant breast cancer is associated with an important increase of cardiovascular mortality, a possible result of higher radiation exposure to the heart. Patients with inner quadrant tumors should be proposed radioprotection of the heart.

**P28b****THE LYMPH NODE RATIO AS AN ALTERNATIVE TO PN-STAGING IN NODE POSITIVE BREAST CANCER**

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Registre Genevois des Tumeurs

**Introduction:** In the current pTNM classification system, nodal status of breast cancer is based on the number of involved lymph nodes and does not account for the total number of lymph nodes removed. In this study we assessed the prognostic value of the lymph node ratio (i.e. ratio of positive over excised lymph nodes, LNR) as compared to pN staging and determined its optimal cut-off points.

**Méthode:** From the Geneva Cancer Registry we identified all women diagnosed with node-positive breast cancer between 1980 and 2004 (n=1829). The prognostic value of LNRs was calculated for values ranging from 0.05 to 0.95 by Cox regression analysis and validated by bootstrapping. Based on maximum likelihood, we identified cut-off points classifying women into low-, intermediate-, and high-risk LNRs.

**Résultat:** Optimal cut-off points classified patients into low (0.20 and 0.65) LNRs, corresponding to 10-year disease-specific survival rates of 10-years of 75%, 63%, and 40%, and adjusted mortality risks of 1 (reference), 1.78 [95% confidence interval = 1.46-2.18], and 3.21 [2.5! 4-4.06], respectively. In contrast to LNR risk categories, survival curves of pN2 and pN3 crossed after 15 years, and their adjusted mortality risks showed overlapping confidence intervals, 2.07 [1.69-2.53] and 2.84 [2.23-3.61], respectively.

**Conclusion:** LNR predicts survival after breast cancer more accurately than pN classification and should be considered as an alternative to pN-staging.

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**P29****CLINICAL PREDICTORS OF DUAL ASPIRIN AND CLOPIDOGREL RESISTANCE IN STABLE CARDIOVASCULAR PATIENTS FROM THE ADRIE STUDY**

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**Introduction:** Resistance to both aspirin and clopidogrel (dual resistance) is a major risk factor for recurrent ischemic events. The aim of this study was to identify factors associated with dual resistance and derive a predictive clinical score

**Méthode:** We studied 771 consecutive stable cardiovascular patients treated with aspirin (n=223), clopidogrel (n=111) or both drugs (n=437). Aspirin responsiveness was evaluated by serum thromboxane (Tx) A2 assay, and clopidogrel responsiveness by calculating the platelet reactivity index (PRI) based on the phosphorylation status of the vasodilator phosphoprotein. The primary analysis focused on patients treated with both drugs, and on independent predictors of dual resistance

**Résultat:** Among patients on dual therapy there was no relevant correlation between Tx<sub>B2</sub> levels and PRI values (r=0.11). Sixty-seven patients (15.4%) had dual resistance. Diabetes (OR=1.89, 95%CI [1.06-3.39], high body weight (>86Kg versus 160mg, OR=0.12, 95%CI [0.09-0.93], and high C-reactive protein (CRP, >1.6mg/l versus

**Conclusion:** Diabetes, body weight, the aspirin dose and CRP levels are readily available independent predictors of dual resistance, and some are potential targets for reducing its prevalence. Drug adjustment strategies may be beneficial in the population with dual resistance.

**P30****HYPERAMMONIEMIE CAPILLAIRE PROVOQUEE PAR VOIE ORALE ET ENCEPHALOPATHIE HEPATIQUE (EH) LORS DE CIRRHOSE : UNE ETUDE PROSPECTIVE CHEZ 57 PATIENTS**

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**Introduction:** L'EH est une complication grave dont le diagnostic est soit grossier (astérisis), soit compliqué (neuropsychologie), soit imprécis (ammoniémie (NH<sub>3</sub>) veineuse). Un dosage de NH<sub>3</sub> dans le sang capillaire après une charge protéique permettrait d'améliorer le diagnostic.

**Méthode:** 57 patients (âge : 56 ans, MELD : 13.5 [7-12], Child A/B/C : 10/33/14) et 13 contrôles (âge : 54 ans) ont été inclus. Après une mini-batterie de tests neuropsychologiques (Trail tests A, B, Pegboard) et un dosage du NH<sub>3</sub> capillaire (lobe oreille, Blood Ammonia Checker Arkray), le patient ingérait 20 gr de glutamine/50 ml d'eau. Le NH<sub>3</sub> capillaire était dosé à 30' et 60', et les tests neuropsychs répétés à 60'. L'incidence d'EH/événements hépatiques était étudiée au cours du suivi.

**Résultat:** 1. Tolérance : bonne : nausée (n=1), étourdissement (n=1). 2. NH<sub>3</sub> capillaire : les valeurs étaient plus élevées chez les patients que chez les sujets sains [0', 30', 60' : 75.2, 117, 169 vs 52, 59, 78 umol/l, p<0.05]. 3. Diagnostic d'EH : à T0', 25 patients présentaient une EH (neuropsych), alors qu'à T60', 38 patients avaient une EH (chi<sup>2</sup> : p<0.001). 4. Performance de NH<sub>3</sub> capillaire pour le diagnostic d'EH : à T0', la courbe ROC montrait une valeur de 0.541, qui augmentait à T60' avec une valeur de 0.727. 5. Suivi à 365 jours : 34.5% des patients ont développé une EH/événement hépatique. L'analyse multivariée montrait que le MELD (1.122 [1.018-1.236]), et les antécédents d'EH (3.2 [1.069-9.58]), mais pas le NH<sub>3</sub>, étaient des prédicteurs indépendants.

**Conclusion:** Le test d'hyperammoniémie capillaire provoqué est bien supporté et apporte un bénéfice diagnostique pour l'EH par rapport à l'ammoniémie basale.



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**P31****REASSESSING SELECTION CRITERIA PRIOR TO LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA UTILIZING THE SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS DATABASE**

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**Introduction:** The current model of liver graft allocation in place in the United States favors transplantation of patients with small hepatocellular carcinomas (HCCs) within the Milan criteria (a single tumor up to 5 cm in diameter or up to three lesions, none larger than 3 cm). Although several reports have suggested that these criteria could be extended, there is currently no agreement on new selection tools.

**Méthode:** In this study, we performed an overview of 6478 adult recipients of an isolated first liver transplant registered in the Scientific Registry of Transplant Recipients (SRTR) database.

**Résultat:** From March 2002 to January 2008, increasing numbers of patients outside Milan criteria ( $P < 0.001$ ) have been registered for a transplant, but they still represent less than 5% of the transplants performed for HCC. Of all the tested variables (tumor number, largest tumor size, and Milan and University of California San Francisco criteria), only total tumor volume (TTV;  $P > 115 \text{ cm}^3$  or an AFP  $> 400 \text{ ng/mL}$  being outside criteria. The combined TTV/AFP score efficiently predicted posttransplant survival (hazard ratio=2, 95% confidence interval=1.7-2.4,  $P$

**Conclusion:** According to the present SRTR data, Milan criteria are too restrictive, and patients with larger TTV can enjoy satisfactory posttransplant survivals. A composite patient selection score combining TTV and AFP was the most effective of all tested staging criteria for the prediction of posttransplant patient survival for candidates with HCC.

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**P32****SIROLIMUS-BASED IMMUNOSUPPRESSION IS ASSOCIATED WITH INCREASED SURVIVAL AFTER LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA***Shaheed Merani David L. Bigam A.M. James Shapiro Norman M. Kneteman C. Toso*Services de chirurgie viscérale et transplantation

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**Introduction:** Liver transplantation is an important treatment option for selected patients with nonresectable hepatocellular carcinoma (HCC). Several reports have suggested a lower risk of posttransplant tumor recurrence with the use of sirolimus and a higher one with calcineurin inhibitors, but the selection of an ideal immunosuppression protocol is still a matter of debate. The aim of this study was to define the immunosuppression associated with the best survival after liver transplantation for HCC.

**Méthode:** The study was based on the Scientific Registry of Transplant Recipients and included 2,491 adult recipients of isolated liver transplantation for HCC and 12,167 for non-HCC diagnoses between March 2002 and March 2009. All patients remained on stable maintenance immunosuppression protocols for at least 6 months posttransplant.

**Résultat:** In a multivariate analysis, only anti-CD25 antibody induction and sirolimus-based maintenance therapy were associated with improved survivals after transplantation for HCC (hazard ratio [HR] 0.64, 95% confidence interval [CI]: 0.45-0.9, P

**Conclusion:** According to these data, sirolimus-based immunosuppression has unique posttransplant effects on HCC patients that lead to improved survival.

**P33****EFFECT OF TOPICAL MORPHINE (MOUTHWASH) ON ORAL PAIN DUE TO CHEMO- AND/OR RADIOTHERAPY INDUCED MUCOSITIS: A RANDOMIZED DOUBLE-BLIND STUDY**

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**Introduction:** The objective of the study was to determine if mouthwashes with a morphine containing solution decrease oral pain associated with radio- and/or chemo-therapy induced oral mucositis (OM).

**Méthode:** Randomized double-blind cross-over study to evaluate the effect of topical oral application of 2‰ morphine solution in patients suffering from radio- and/or chemotherapy induced OM. Participants assigned to either the morphine solution or a placebo mouthwash received one of the solutions days 1-3 and were then switched over to the other treatment for days 4-6.

**Résultat:** 9 patients were randomized in both groups. All the patients (mean age 55.1±3.0) but one had head and neck cancers. Mean intensity of pain associated with mucosal injury (WHO mucositis ≥2) was on a 10 points visual analog scale: 6.0± 2.7). The ANOVA model that included morphine or placebo, day and time of mouthwash and mouthwash effect shows that pain alleviation one hour after mouthwash was significantly influenced by the gesture of the mouthwash ( $P < 0.001$  with either morphine or placebo) and almost by the efficiency of morphine ( $P = 0.020$ ). Duration of pain relief was 123.7 (SD ±98.2) minutes for morphine. Most other reported symptoms were present at the baseline and were probably associated with the main disease and not secondary to the morphine mouthwash.

**Conclusion:** Our results suggest a possible analgesic effect of topical morphine in line with previous studies. However more efforts must be made for the adjustment of systemic analgesics and the development of new alternatives to treat locally OM-associated pain.

**P34****PATIENT–VENTILATOR ASYNCHRONY DURING NON-INVASIVE VENTILATION FOR ACUTE RESPIRATORY FAILURE: A MULTICENTER STUDY**

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**Introduction:** The objective of the study was to determine the prevalence of patient–ventilator asynchrony in patients receiving noninvasive ventilation (NIV) for acute respiratory failure (ARF)

**Méthode:** It was a prospective multicenter observation study, performed in three university hospitals intensive care units. Patients consecutively admitted to ICU and receiving NIV for ARF were included. NIV, performed with an ICU ventilator, was set by the clinician. Airway pressure, flow, and surface diaphragmatic electromyography were recorded continuously for 30 min. Asynchrony events and the asynchrony index (AI) were determined from visual inspection of the recordings.

**Résultat:** A total of 60 patients were included, 55% of whom were hypercapnic. Auto-triggering was present in 8 (13%) patients, double triggering in 9 (15%), ineffective breaths in 8 (13%), premature cycling 7 (12%) and late cycling in 14 (23%). An AI  $\geq 10\%$ , indicating severe asynchrony, was present in 26 patients (43%), whose median (25–75 IQR) AI was 26 (15–54%). A significant correlation was found between the magnitude of leaks and the number of ineffective breaths and severity of delayed cycling. Multivariate analysis indicated that the level of pressure support and the magnitude of leaks were weakly, albeit significantly, associated with an AI  $\geq 10\%$ . Patient comfort scale was higher in pts with an AI  $\geq 10\%$ .

**Conclusion:** Patient–ventilator asynchrony is common in patients receiving NIV for acute respiratory failure. Our results suggest that leaks play a major role in generating patient–ventilator asynchrony and discomfort, and point the way to further research to determine if ventilator functions designed to cope with leaks can reduce asynchrony in the clinical setting.

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**P35****EVALUATION OF THE USER-FRIENDLINESS OF SEVEN NEW GENERATION INTENSIVE CARE VENTILATORS***Laurence Vignaux Didier Tassaux Philippe Jolliet*Research laboratory in mechanical ventilation, Intensive care unit, university hospital of Geneva

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**Introduction:** The objective was to explore the user-friendliness and ergonomics of seven new generation intensive care ventilators

**Méthode:** This prospective task-performing study was performed in our intensive care research laboratory. Ten physicians experienced in mechanical ventilation, without prior knowledge of the ventilators, were asked to perform eight specific tasks (turning the ventilator on; recognizing mode and parameters; recognizing and setting alarms; mode change; finding and activating the pre-oxygenation function; pressure support setting; stand-by; finding and activating non-invasive ventilation (NIV) mode). The time needed for each task was compared to a reference time (by trained physiotherapist familiar with the devices). A time >180 s was considered a task failure.

**Résultat:** For each test on the ventilators, all physicians' times were significantly higher than the reference time ( $P < 0.001$ ). A mean of  $13 \pm 8$  task failures (16%) was observed by ventilator. The most frequently failed tasks were mode and parameter recognition, starting pressure support and finding the NIV mode. Least often failed tasks were turning on the pre-oxygenation function and alarm recognition and management. Overall, there was substantial heterogeneity between machines, some exhibiting better user-friendliness than others for certain tasks, but no ventilator was clearly better than the others on all points tested.

**Conclusion:** The present study adds to the available literature outlining the ergonomic shortcomings of mechanical ventilators. These results suggest that closer ties between end-users and manufacturers should be promoted, at an early development phase of these machines, based on the scientific evaluation of the cognitive processes involved by users in the clinical setting.

## P36

**ANTI-APOLIPOPROTEIN A-1 IGG AS AN INDEPENDENT CARDIOVASCULAR PROGNOSTIC MARKER AFFECTING BASAL HEART RATE IN MYOCARDIAL INFARCTION**

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**Introduction:** to assess the prognostic value of anti-apolipoprotein A-1 (anti-apoA-1) IgG after myocardial infarction (MI) and its association with major cardiovascular events (MACE) at 12 months and to determine their association with resting heart rate (RHR), a well established prognostic feature after MI. Anti-apoA-1 IgG have been reported in MI without autoimmune disease, but their clinical significance remains undetermined.

**Méthode:** 221 consecutive patients with MI were prospectively included and all completed a 12-months follow-up. MACE consisted in death, MI, stroke or hospitalization either for an acute coronary syndrome or heart failure. RHR was obtained on Holter the day before discharge under the same medical treatment. Neonate rat ventricular cardiomyocytes (NRVC) were used in vitro to assess the direct anti-apoA-1 IgG effect on RHR.

**Résultat:** During follow-up, 13% of patients presented a MACE. Anti-apoA-1 IgG positivity was 9% and was associated with a higher RHR ( $p=0.0005$ ) and higher MACE rate (adjusted OR:4.3; 95%CI:1.46-12.6;  $p=0.007$ ). Survival models confirmed the significant nature of this association. Patients with MACE had higher median anti-apoA-1 IgG values at admission than patients without ( $p=0.007$ ). On NRVC, plasma from MI patients and monoclonal anti-apoA-1 IgG induced an aldosterone and dose-dependent positive chronotropic effect, abrogated by apoA-1 and therapeutic immunoglobulin (IVIg) pre-incubation.

**Conclusion:** In MI patients, anti-apoA-1 IgG is independently associated to MACE at 1-year, interfering with a currently unknown aldosterone-dependent RHR determinant. Knowing whether anti-apoA-1 IgG assessment could be of interest to identify a MI patient subset susceptible to benefit from apoA-1/IVIg therapy remains to be demonstrated.

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**P37****CONTINUOUS EEG SOURCE IMAGING ENHANCES THE ANALYSIS OF EEG-FMRI IN PATIENTS WITH FOCAL EPILEPSY**

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**Introduction:** In 25-30% of patients with epilepsy, the seizures are not controlled by antiepileptic drugs. An in-depth diagnostic work-up is recommended to localise the epileptic focus and determine if these patients could be candidates for resective surgery. Simultaneous EEG-fMRI is a new non-invasive imaging technique that maps regions where haemodynamic changes are correlated to Interictal Epileptic Discharges (IED). Methodological improvements are needed to increase sensitivity and specificity for localising the epileptogenic zone. We investigated whether using the EEG source activity estimated non-invasively by EEG source imaging could improve the yield of EEG-fMRI studies.

**Méthode:** Ten patients with pharmaco-resistant focal epilepsy underwent EEG-fMRI. EEG Source Imaging (ESI) was performed on averaged IED recorded in the MR scanner. The continuous activity of the estimated IED (cESI) was used for fMRI analysis (cESI model). These maps of haemodynamic changes were compared to results of the conventional model (haemodynamic changes related to individual IED).

**Résultat:** ESI was concordant with non-invasive data in 13/15 different types of IED. In 10/15 IED, the cESI model explained additional variance of the fMRI signal compared to IED alone. These changes occurred in regions concordant with video-EEG, structural MRI or, when available, intracranial EEG. In 4 IED types, the results showed a diffuse pattern suggestive of artefact contamination. In one type of IED, there was no significant haemodynamic change with either model.

**Conclusion:** Continuous EEG source imaging can improve the analysis of EEG-fMRI studies. This may enhance the non-invasive localisation of the epileptic focus and have important consequences for epilepsy surgery.

**P38****PREDICTED RISK OF RADIATION-INDUCED CANCERS AFTER INVOLVED FIELD- AND INVOLVED-NODE RADIOTHERAPY WITH OR WITHOUT INTENSITY MODULATION FOR EARLY STAGE HODGKIN LYMPHOMA IN FEMALE PATIENTS**

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**Introduction:** To assess the excess relative risk (ERR) of radiation-induced cancers (RIC) in Hodgkin lymphoma (HL) female patients treated with 3D conformal (3DCRT), intensity modulated (IMRT) or volumetric modulated arc (RA) radiation therapy.

**Méthode:** Plans for 10 early stage HL female patients were computed for 3DCRT, IMRT and RA with involved-field (IFRT) and involved-node (INRT) radiation fields. The organ at risk's (OAR) Dose-Volume Histograms (DVHs) were computed and inter-compared for IFRT vs. INRT and 3DCRT vs. IMRT/RA, respectively. The excessive relative risk (ERR) for cancer induction in breasts, lungs and thyroid was estimated, using both linear and non-linear-models.

**Résultat:** The mean estimated ERR for breast, lung and thyroid were significantly ( $p < 0.01$ ) lower with INRT than with IFRT planning, regardless of the radiation technique delivery used, assuming a linear dose-risk relationship. Using the non-linear model, mean ERR were significantly ( $p < 0.01$ ) increased with IMRT or RA when compared to 3DCRT planning for the breast, lung and thyroid using an IFRT paradigm. After INRT planning, IMRT or RA increased the risk of RIC for lung and thyroid only.

**Conclusion:** In this comparative planning study, using a non-linear dose-risk model, IMRT or RA increased the estimated risk of RIC for breast, lung and thyroid for HL female patients. This study also suggests that INRT, when compared to IFRT planning, may reduce the ERR of RIC, when risk is predicted using a linear model. Observing the opposite effect, with a non-linear model, questions however the validity of these biologically parameterized models.



## P39

**ALTERATIONS OF BONE MICROARCHITECTURE IN YOUNG PATIENTS WITH INFLAMMATORY BOWEL DISEASES ARE ASSOCIATED WITH FRACTURE RISK DURING GROWTH**

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**Introduction:** Inflammatory bowel diseases (IBD) appearing during childhood and adolescence compromise peak bone mass acquisition and increase fracture risk. The structural determinants of bone fragility in IBD however remain unknown.

**Méthode:** We investigated volumetric bone mineral density (vBMD), trabecular and cortical bone microstructure at distal radius and tibia by high-resolution pQCT (XtremeCT, Scanco, Switzerland), aBMD at distal radius, hip and spine and vertebral fracture assessment (VFA) by DXA in 107 young patients (62 females and 45 males; mean age 22.8 yrs, range 12.2-33.7 yrs) with Crohn's disease (n=75), ulcerative colitis (n=25), undetermined colitis (n=2), or no definitive diagnosis (n=5), and in 389 healthy young individuals.

**Résultat:** Mean disease duration was 6.1 yrs, 89/107 IBD patients received corticosteroids, 83 other immunomodulators, and 59 vitamin D. Clinical fractures were reported by 38 patients (mean age at 1st fracture, 12.6 yrs), the vast majority of the forearm, arm or hand; 5 had vertebral crush fractures (Grade 1 or 2) and 11 had multiple fractures. As compared to healthy controls (matched 2:1 for age, sex, height and fracture history), the 102 patients with established IBD had similar weight but significantly lower aBMD at all sites, lower trabecular (Tb) BV/TV and number, and greater Tb separation and inhomogeneous Tb distribution (1/SD TbN) at both distal radius and tibia, lower tibia cortical thickness (CTh), but no differences in cortical vBMD nor bone perimeter. Among IBD's, aBMD was not associated with fractures (by logistic regression adjusted for age, age square, sex, height, weight and protein intake). However, radius and tibia Tb BV/TV, thickness and SD 1/TbN, as well as radius Tb separation and perimeter, were significantly associated with fracture risk (fully adjusted as above), whereas cortical vBMD and CTh were not. After adjustment for aBMD at radius, respectively at femur neck, radius SD 1/TbN and tibia BV/TV, TbTh and perimeter remained independently associated with fracture risk.

**Conclusion:** Young subjects with IBD have low bone mass and poor bone microarchitecture compared to healthy controls. Alterations of bone microarchitecture, particularly in the trabecular bone compartment, are specifically associated with increased fracture risk during growth.