

2^{ème} Journée et Prix de la Recherche Clinique

Vendredi 29 mai 2009
13h30 – 18h00

HUG – Site Cluse-Roseraie
Salle Opéra, niveau 0



**Programme final
et
Recueil des résumés**

MOT DE BIENVENUE

Cher(e) Collègue,

Vous la croisez dans le couloir, vous lui dites bonjour, mais savez-vous vraiment ce qu'elle fait? Peut-être a-t-elle la solution au problème qui vous réveille la nuit, ou plus prosaïquement, déjà rempli le formulaire qui vous confond...

Faire connaissance, instruire, informer, faciliter: voici les buts de cette deuxième demi-journée de recherche clinique. La première fut organisée il y a une année par Thomas Perneger et Sandrine Rudaz. Il faut croire que l'initiative était bonne car l'intérêt va en grandissant: 73 contributions ont été soumises en 2009, comparé à 36 en 2008. Un jury, présidé par Thierry Berney, a sélectionné celles qui seront présentées oralement, et celle qui recevra le prix 2009 de la recherche clinique, à la fin de cette journée.

Le présent fascicule contient le programme de la journée, les résumés de toutes les présentations, et en annexe, le 3^{ème} bulletin du CRC.

Un grand merci à tous ceux qui ont facilité l'organisation de cette manifestation, en premier lieu Corinne Chaudet, assistante administrative du Centre de recherche clinique et la Direction médicale des HUG, qui sponsorise croissants, canapés, et Prix.

Soyez donc les bienvenus, et revenez, toujours plus nombreux, le 28 mai 2010 pour la troisième édition de la Journée de la recherche clinique !



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.

75 recherches provenant de services très variés ont été soumises pour cette deuxième 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, médecine

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.

A vos agendas :

3^{ème} Journée de la recherche clinique: le 28 mai 2010

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

PROGRAMME

13h30 Allocutions d'ouverture

M. Bernard Gruson, directeur général des HUG
La recherche clinique dans le plan stratégique des HUG

Pr. Bernard Hirschel, président du comité de gestion du CRC
Centre de recherche clinique, état à mi-2009

13h50 Présentations orales – Partie I (9 minutes de présentation, suivie de 3 minutes de discussion) Modérateur: Pierre Dayer, directeur médical des HUG

- 13h50 Dr Patrice Lalive: **Glatiramer acetate increases IL-1 receptor antagonist but decreases T cell-induced IL-1beta in human monocytes and multiple sclerosis**
- 14h02 Dr Nader Perroud: **L'association entre abus sexuel et tentatives de suicide violentes est modulé par le gène BDNF**
- 14h14 Dre Sabine Yerly: **The impact of transmission clusters on primary drug resistance in newly diagnosed HIV-1 infection**
- 14h26 Dr Laurent Spahr: **Stimuler la régénération hépatique en mobilisant des cellules souches hématopoïétiques chez des patients atteints de stéatohépatite alcoolique : une étude randomisée**
- 14h38 Dr J.-F Etter: **Pre-cessation treatment with the nicotine gum for smoking cessation: a randomized trial**
- 14h50 Dr Giorgio La Scala : **Développement d'un score pour prédire l'absence de lésion d'organe lors de traumatisme abdominal fermé chez l'enfant**

15h05 Visite des posters Une cinquantaine de posters seront exposés Café et douceurs à disposition

16h30 Présentations orales – Partie II Modérateur: Denis Hochstrasser, vice-doyen de la Faculté de médecine

- 16h30 Dr Domizio Suva: **Influence of preoperative patient education on the risk of dislocation after primary total hip arthroplasty**
- 16h42 Dr Pietro Majno: **Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis**
- 16h54 Dr Omar Kherad: **The role of respiratory viruses and biomarkers in chronic obstructive pulmonary disease exacerbations**
- 17h06 Dr Thomas Matthes: **GDF15 production is erythropoietin-dependent and highly increased in erythroblasts of patients with refractory anemia with ring-sideroblasts (RARS)**
- 17h18 Dr N. Vuilleumier: **Cardiac biomarkers for risk stratification in non massive pulmonary embolism: a multicenter prospective study**

17h30 Conférence par le Dr Hans-Beat Jenny de Swissmedic *Swissmedic et la qualité de la recherche clinique en Suisse*

18h10 Remise du Prix par le jury (président: Pr Thierry Berney) Clôture de la journée par le Pr Pierre Dayer, directeur médical des HUG

18h20 Apéritif

RECUEIL DES RESUMES

PRESENTATIONS ORALES

ORDRE SELON LE PROGRAMME

GLATIRAMER ACETATE INCREASES IL-1 RECEPTOR ANTAGONIST BUT DECREASES T CELL-INDUCED IL-1BETA IN HUMAN MONOCYTES AND MULTIPLE SCLEROSIS

Danielle Burger¹, Nicolas Molnarfi^{1,2}, Martin S. Weber^{2,3}, Karim J. Brandt¹, Mahdia Benkhoucha⁴, Lyssia Gruaz¹, Michel Chofflon⁵, Scott S. Zamvil², and Patrice H. Lalive^{4,5,6}

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Introduction : Mechanisms of action as well as cellular targets of glatiramer acetate (GA) in multiple sclerosis (MS) are still not entirely understood. IL-1beta is present in CNS-infiltrating macrophages and microglial cells and is an important mediator of inflammation in experimental autoimmune encephalitis (EAE), the MS animal model. A natural inhibitor of IL-1beta, the secreted form of IL-1 receptor antagonist (sIL-1Ra) improves EAE disease course.

Méthode: In this study we examined the effects of GA on IL-1 system in vitro, ex-vivo and in the MS animal model (EAE).

Résultats: In vivo, GA-treatment enhanced sIL-1Ra blood levels in both EAE mice and MS patients, whilst IL-1beta levels remained undetectable. In vitro, GA per se induced the transcription and production of sIL-1Ra in isolated human monocytes. Furthermore, in T cell contact-activated monocytes, a mechanism relevant to chronic inflammation, GA strongly diminished the expression of IL-1beta and enhanced that of sIL-1Ra. This contrasts with the effect of GA in monocytes activated upon acute inflammatory conditions. Indeed, in LPS-activated monocytes, both IL-1beta and sIL-1Ra production was increased in the presence of GA.

Conclusion: These results demonstrate that upon chronic inflammatory conditions GA enhances circulating sIL-1Ra levels and directly affects monocytes by triggering a bias towards a less inflammatory profile, increasing sIL-1Ra whilst diminishing IL-1beta production. This study sheds light on a new mechanism that is likely to participate in the therapeutic effects of GA in MS.

L'ASSOCIATION ENTRE ABUS SEXUEL ET TENTATIVES DE SUICIDE VIOLENTES EST MODULE PAR LE GENE BDNF

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Introduction: Les conduites suicidaires sont d'étiologie complexe. Les gènes impliqués dans la transmission sérotoninergique et les abus sexuels ont été plus particulièrement étudiés. Le Brain-Derived Neurotrophic Factor (BDNF) joue un rôle fondamental dans la neurogénèse sérotoninergique et est ainsi un candidat majeur. Nous nous proposons ici d'investiguer si le polymorphisme fonctionnel Val66Met de ce gène module l'effet de la maltraitance dans l'enfance sur l'âge de début, le nombre et la violence des tentatives de suicide (TS).

Méthode: 813 sujets ayant commis une TS, génotypés pour Val66Met, ont remplis un auto-questionnaire d'évaluation de la maltraitance dans l'enfance couvrant les domaines suivants : l'abus sexuel, l'abus physique, l'abus affectif, la négligence physique et la négligence affective. L'intoxication médicamenteuse et les coupures superficielles ont été considérées comme des TS non violentes, les autres formes de TS comme violentes. Une régression logistique a été utilisée pour l'analyse des interactions.

Résultats: Une interaction entre abus sexuel dans l'enfance et Val66Met modifie le risque de TS violente. L'abus sexuel n'est associé aux TS violentes que chez les individus porteurs du génotype Val/Val et non chez ceux porteurs d'un allèle Met.

Conclusion: Des modifications épigénétiques spécifiques au variant Val66 du gène BDNF pourraient être impliquées dans la vulnérabilité aux TS violentes augmentées par l'abus sexuel. Ce résultat pourrait offrir au clinicien un outil précieux dans la mise en évidence des sujets à risque de TS violentes et donc à haut risque de suicide.

THE IMPACT OF TRANSMISSION CLUSTERS ON PRIMARY DRUG RESISTANCE IN NEWLY DIAGNOSED HIV-1 INFECTION

Sabine Yerly, Thomas Junier, Angèle Gayet-Ageron, Emmanuelle Boffi El Amari, Viktor von Wyl, Huldrych F. Günthard, Bernard Hirschel, Evgeny Zdobnov, Laurent Kaiser and the Swiss HIV Cohort Study

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Department of Genetic Medicine and Development, University of Geneva Medical School AIDS Unit,
Division of Infectious Diseases, Geneva's University Hospitals Division of Infectious Diseases and
Hospital Epidemiology, Zurich University Hospital

Introduction: To monitor HIV-1 transmitted drug resistance (TDR) in a well defined urban area with large access to antiretroviral therapy and to assess the potential source of infection of newly diagnosed HIV individuals.

Méthode: All individuals resident in Geneva, Switzerland, with a newly diagnosed HIV infection between 2000 and 2008 were screened for HIV resistance. An infection was considered as recent when the positive test followed a negative screening test within less than 1 year. Phylogenetic analyses were performed by using the maximum likelihood method on pol sequences including 1058 individuals with chronic infection living in Geneva.

Résultats: Of 637 individuals with newly diagnosed HIV infection, 20% had a recent infection. Mutations associated with resistance to at least one drug class were detected in 8.5% (NRTIs, 6.3%; NNRTIs, 3.5%; PIs, 1.9%). TDR (P-trend=0.015) and, in particular, NNRTI resistance (P=0.002) increased from 2000 to 2008. Phylogenetic analyses revealed that 34.9% of newly diagnosed individuals, and 52.7% of those with recent infection were linked to transmission clusters. Clusters were more frequent in individuals with TDR than in those with sensitive strains (59.3% vs. 32.6%, respectively; P<0.0001). Moreover, 84% of newly diagnosed individuals with TDR were part of clusters composed of only newly diagnosed subjects.

Conclusions: Reconstruction of the HIV transmission networks using phylogenetic analysis shows that newly diagnosed HIV infections are a significant source of onward transmission, particularly of resistant strains, thus suggesting an important self-fuelling mechanism for TDR.

STIMULER LA REGENERATION HEPATIQUE EN MOBILISANT DES CELLULES SOUCHES HEMATOPOIETIQUES CHEZ DES PATIENTS ATTEINTS DE STEATOHEPATITE ALCOOLIQUE : UNE ETUDE RANDOMISEE

Laurent Spahr, Jean-François Lambert, Laura Rubbia-Brandt, Yves Chalandon, Jean-Louis Frossard, Emiliano Giostra, Antoine Hadengue

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Introduction: Chez des patients atteints de stéatohépatite alcoolique (SHA) grave, une infiltration neutrophilique et une leucocytose prononcées sont associées à un meilleur pronostic (Gastroenterology 1996). Chez l'animal, la mobilisation par du G-CSF (granulocyte colony stimulating factor) de cellules souches hématopoïétiques issues de la moelle osseuse améliore les lésions histologiques et la survie (Exp Hematology 2005 ; Dig Dis Sci 2003). But : étudier l'effet du G-CSF sur la régénération hépatique et les lésions histologiques chez des patients atteints de SHA

Méthode: sur une période de 12 mois, 24 patients avec SHA (biopsie), sélectionnés (Maddrey 20 à 70 ; leucocytes < 15000/mm³ ; pas d'infection ni hémorragie récente ; pas de HBV ni HCV), ont reçu soit un traitement standard seul, ou g/kg 2x/j scut). La randomisation associée à 5 jours de G-CSF (Neupogen, 10 été effectuée avec stratification en fonction de la gravité de la SHA. Une corticothérapie était prescrite lors de forme grave de SHA. Les lésions histologiques (score semi-quantitatif), un immunomarquage pour le MIB-1 (marqueur de prolifération cellulaire), le taux de cellules souches hématopoïétiques CD34 (cytométrie de flux) ont été mesurés à J0 et à J7. Les concentrations sériques d'alpha-fœtoprotéine (AFP) et d'hepatocyte growth factor (HGF) ont été dosées à J0, J7 et J28.

Résultats: 13 patients (âge 53 ans ; Maddrey 34 [25-60] ; stéroïdes n=5 ; MELD 15.5 ; neutrophiles 5100/mm³) ont reçu le G-CSF, et 11 patients (54 ans ; Maddrey 38 [21-59] ; stéroïdes n=7 ; MELD 16.1 ; neutrophiles 6100/mm³) le traitement standard seul. La tolérance au G-CSF était excellente. L'évolution du MELD à J28 n'était pas différente dans les 2 groupes. Les lésions histologiques restaient stables à J7 dans les 2 groupes. Par contre, dans le groupe G-CSF, on observait une mobilisation plus importante des cellules CD34 circulantes à J7 (+379% vs -40%, p < 0.003), ainsi qu'un immunomarquage MIB-1 plus intense sur la biopsie à J7 (+35% vs -36%, p < 0.007). L'augmentation du taux sérique d'AFP était significative dans les 2 groupes à J7, sans différence à J28 (G-CSF : +60% vs traitement standard : +26%, p=0.7). Dans le groupe G-CSF, l'augmentation de l'HGF était marquée à J7 (+60% vs -21%, p < 0.003), mais non significative à J28 (-1% vs -45%, p = 0.06).

Conclusion: Le G-CSF est bien toléré chez des patients atteints de SHA avec insuffisance hépatocellulaire. Il induit une mobilisation de cellules souches hématopoïétiques circulantes ainsi qu'une augmentation de l'activité proliférative cellulaire dans le foie. Sur de faibles effectifs et une période d'observation de 28 jours, cet effet n'est pas associé à un bénéfice de fonction hépatique.

PRE-CESSATION TREATMENT WITH THE NICOTINE GUM FOR SMOKING CESSATION: A RANDOMIZED TRIAL

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Introduction: There is a need to explore new ways of improving the efficacy of nicotine replacement therapy. We tested whether starting a nicotine gum treatment 4 weeks before the quit date improved smoking abstinence rates, compared with starting the treatment on the quit date.

Méthode: An open randomized trial in 314 daily smokers (mean 23.7 cigarettes/day) enrolled through the internet and by physicians in Switzerland in 2005-2007. In the pre-cessation treatment condition, participants received nicotine gums (4 mg, unflavored) by mail during 4 weeks before and 8 weeks after their target quit date, and they were instructed to decrease their cigarette consumption by half before quitting. In the usual care condition, participants received the same nicotine gums during 8 weeks after their quit date and were instructed to quit abruptly. Instructions were limited to a booklet sent by mail and to access to a smoking cessation website. We report self-reported abstinence rates at the end of treatment, and biochemically verified smoking abstinence (cotinine plus carbon monoxide) after 12 months.

Résultats : Eight weeks after the target quit date, self-reported 4-week abstinence rates were 41.6% in the pre-cessation condition and 44.4% in the usual care condition ($p=0.61$). One year after the target quit date, biochemically verified 4-week smoking abstinence rates were 20.8% in the pre-cessation condition and 19.4% in the usual care condition ($p=0.76$).

Conclusion: Starting the nicotine gum treatment 4 weeks before the target quit date was no more effective than starting the treatment on the quit date. Registered in Controlled trials.com (ISRCTN60585119).

DEVELOPPEMENT D'UN SCORE POUR PREDIRE L'ABSENCE DE LESION D'ORGANE LORS DE TRAUMATISME ABDOMINAL FERME CHEZ L'ENFANT

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Introduction: Les traumatismes abdominaux fermés (TAF) sont fréquents chez l'enfant et peuvent engager le pronostic vital. L'objectif de cette étude était de créer un score permettant d'exclure une lésion significative d'organe intra-abdominal chez ces patients.

Méthode: Récolte prospective de données sur 30 mois. Analyse de la valeur statistique des différents paramètres (mécanisme du traumatisme, examen clinique, résultats de laboratoire et échographie) par rapport aux lésions intra-abdominales. Définition de valeurs-seuil des examens de laboratoire par courbes ROC (Receiver Operating Characteristic). Choix des paramètres avec les valeurs prédictives négatives (VPN) plus élevées, calcul du risque relatif pour chacun d'eux. Elaboration d'un score (Blunt Abdominal Trauma in Children: BATiC), testé sur notre population.

Résultats: 147 enfants pris en charge pour TAF. Sur 31 paramètres évalués, dix différaient significativement entre les patients avec/sans lésion d'organe : douleurs abdominales, péritonisme, instabilité hémodynamique, leucocytes, LDH, ASAT, ALAT, lipase, créatinine et US abdominal anormal. Pour les examens de laboratoire les valeurs-seuil étaient: leucocytes >9.5G/L, LDH >330IU/L, ASAT >60IU/L, ALAT >25IU/L, lipase >30IU/L, créatinine >50µg/L. Des points ont été attribués en considérant le risque relatif de lésion d'organe pour chaque paramètre: US abdominal anormal (4), douleur abdominale (2), péritonisme (2), instabilité hémodynamique (2), ASAT >60IU/L(2), ALAT >25IU/L(2), LDH >330IU/L(1), leucocytes >9.5G/L(1), lipase >30IU/L(1), créatinine >50µg/L(1). Un score ≤7 a un VPN de 97% et représente 67% du collectif étudié.

Conclusion: Chez un patient avec TAF, hémodynamiquement stable avec US abdominal normal et score BATiC ≤7, la probabilité d'une lésion d'organe intra abdominale est très faible, et un CT scan systématique ou une hospitalisation pourrait être évité.

INFLUENCE OF PREOPERATIVE PATIENT EDUCATION ON THE RISK OF DISLOCATION AFTER PRIMARY TOTAL HIP ARTHROPLASTY

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Introduction: Dislocation is a well-known complication after total hip arthroplasty (THA), and is the second-highest cause of revision surgery. Our objective was to assess the effect of preoperative patient education on the occurrence of hip dislocation within 6 months after primary THA.

Méthode: Between 1998 and 2007, we conducted a prospective cohort study at the Geneva University Hospital Department of Orthopaedic Surgery, including all primary THAs performed via an anterolateral transgluteal approach with the use of a 28-mm diameter head. The preoperative education session was introduced in June 2002 and included advice on muscle strengthening exercises and postoperative restrictions of range of motion as a means of preventing dislocation. The main outcome was the incidence of dislocation within 6 months of surgery.

Résultats: A total of 597 patients who underwent 656 THAs between June 2002 and June 2007 participated in the education session, whereas 1,641 patients who underwent 1,945 procedures did not. Forty-six dislocations occurred over the study period, 5 (0.8%) in participants and 41 (2.1%) in nonparticipants (absolute risk reduction 1.3%; 95% confidence interval [95% CI] 0.4, 2.3), with the time interval between surgery and dislocation being significantly shorter among participants (0.2 versus 1.2 months). Nonparticipants had a 2.8 times higher risk of dislocation than participants (unadjusted odds ratio [OR] 2.80; 95% CI 1.10, 7.13). Adjustment for age, sex, comorbidities, and prior surgery did not change the results (adjusted OR 2.79; 95% CI 1.09, 7.15).

Conclusion: Our findings suggest that participation in a preoperative patient education session may reduce the risk of dislocation within 6 months after THA.

PREDICTING SURVIVAL AFTER LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA BEYOND THE MILAN CRITERIA: A RETROSPECTIVE, EXPLORATORY ANALYSIS

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Introduction: Patients undergoing liver transplantation for hepatocellular carcinoma within the Milan criteria (single tumour ≤ 5 cm in size or ≤ 3 tumours each ≤ 3 cm in size, and no macrovascular invasion) have an excellent outcome. However, survival for patients with cancers that exceed these criteria remains unpredictable and access to transplantation is a balance of maximising patients' chances of cure and organ availability. The aim of this study was to explore the survival of patients with tumours that exceed the Milan criteria, to assess whether the criteria could be less restrictive, enabling more patients to qualify as transplant candidates, and to derive a prognostic model based on objective tumour characteristics, to see whether the Milan criteria could be expanded.

Méthode: Data on patients who underwent transplantation for hepatocellular carcinoma despite exceeding Milan criteria at different centres were recorded via a web-based survey completed by specialists from each centre. The survival of these patients was correlated retrospectively with the size of the largest tumour nodule, number of nodules, and presence or absence of microvascular invasion detected at pathology. Contoured multivariable regression Cox models produced survival estimates by means of different combinations of the covariates. The primary aim of this study was to derive a prognostic model of overall survival based on tumour characteristics, according to the main parameters used in the Tumour Node Metastasis classification. The secondary aim was the identification of a subgroup of patients with hepatocellular carcinoma exceeding the Milan criteria, who achieved a 5-year overall survival of at least 70%—ie, similar to the outcome expected for patients who meet the Milan criteria.

Résultats: Over a 10-month period, between June 25, 2006, and April 3, 2007, data for 1556 patients who underwent transplantation for hepatocellular carcinoma were entered on the database by 36 centres. 1112 patients had hepatocellular carcinoma exceeding Milan criteria and 444 patients had hepatocellular carcinoma shown not to exceed Milan criteria at post-transplant pathology review. In the group of patients with hepatocellular carcinomas exceeding the criteria, the median size of the largest nodule was 40 mm (range 4–200) and the median number of nodules was four (1–20). 454 of 1112 patients (41%) had microvascular invasion and, for those transplanted outside the Milan criteria, 5-year overall survival was 53.6% (95% CI 50.1–57.0), compared with 73.3% (68.2–77.7) for those that met the criteria. Hazard ratios (HR) associated with increasing values of size and number were 1.34 (1.25–1.44) and 1.51 (1.21–1.88), respectively. The effect was linear for size, whereas for number of tumours, the effect tended to plateau above three tumours. The effect of tumour size and number on survival was mediated by recurrence ($b=0.08$, $SE=0.12$, $p=0.476$). The presence of microvascular invasion doubled HRs in all scenarios. The 283 patients without microvascular invasion, but who fell within the Up-to-seven criteria (hepatocellular carcinomas with seven as the sum of the size of the largest tumour [in cm] and the number of tumours) achieved a 5-year overall survival of 71.2% (64.3–77.0).

Conclusion: More patients with hepatocellular carcinoma could be candidates for transplantation if the current dual (yes/no) approach to candidacy, based on the strict Milan criteria, were replaced with a more precise estimation of survival contouring individual tumour characteristics and use of the up-to-seven criteria.

THE ROLE OF RESPIRATORY VIRUSES AND BIOMARKERS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS

Omar Kherad¹, Laurent Kaiser², Pierre-Olivier Bridevaux³, Francois Sarasin⁴, Yves Thomas², Jean-Paul Janssens³, Olivier Rutschmann⁴

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Introduction: Respiratory viruses are frequently associated with COPD exacerbations, but their role as contributing pathogens remains unclear. The usefulness of biomarkers, such as procalcitonin and C-reactive protein, to identify viral diseases in this setting also needs to be evaluated.

Méthode: Prospective cohort study of COPD patients admitted to the emergency ward for acute exacerbation. Reverse transcriptase (RT) PCR for 14 respiratory viruses was performed on nasopharyngeal swabs collected at admission and during a clinically stable period within four months following acute exacerbation. This study is registered with ClinicalTrials.gov, number NCT00448604.

Résultats: Of 86 patients (mean age, 72 y, male, 64%) enrolled, the following viruses were identified in 44 (51%) during exacerbations: picornavirus (n=22); metapneumovirus (n=7); coronavirus (n=8); influenza A/B (n=2); parainfluenza (n=2); and respiratory syncytial virus (n=3). A dual infection was present in three patients. During the clinically stable period, viruses were detected in only 8 of 71 (11%) patients ($p=0.0002$ compared to baseline data). In five of these patients, no virus had been identified during the initial exacerbation, thus suggesting a new viral infection acquired during follow-up. During exacerbations, procalcitonin and C-reactive protein levels did not differ significantly between patients with or without viral infection. Clinical features and outcome were not statistically different, except for upper respiratory tract symptoms that were more frequent in the presence of a viral infection.

Conclusion: Our results suggest that COPD exacerbations are frequently triggered by acute viral infections. Clinical features and available biomarkers are unlikely to identify viral associated exacerbations.

GDF15 PRODUCTION IS ERYTHROPOIETIN-DEPENDENT AND HIGHLY INCREASED IN ERYTHROBLASTS OF PATIENTS WITH REFRACTORY ANEMIA WITH RING-SIDEROBLASTS (RARS)

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Introduction: The myelodysplastic syndromes (MDSs) are a heterogeneous group of preleukemic hematological diseases, characterized by a disturbed hematopoiesis. The classification of MDSs is largely based on morphologic criteria (FAB classification, 1982; WHO classification, 1997) and distinguishes two risk groups, depending on survival rates and evolution into acute leukemia. Refractory anemia with ring-sideroblasts (RARS) is part of the low risk MDSs. In addition to abnormal proliferation/apoptosis of hematopoietic precursors, patients with RARS present the particularity of a disturbed iron metabolism in erythroid precursors, leading to the characteristic appearance of “ring-sideroblasts” in the bone marrow.

Méthode: To gain insight into these pathophysiologic mechanisms we compared the gene expression profile (GEP) of erythroid precursors from 11 patients with RARS to the GEP of normal erythroid precursors

Résultats: 364 probe sets were found unregulated (e.g.: TRIB3, TP53, GDF15..) and 253 probe sets were found down-regulated (e.g.: ACSL6, MBNL3, CTSE, ..) in RARS cells. Most interestingly, Growth Differentiation factor 15 (GDF15), a cytokine from the TGF β family with a pro-apoptotic function in solid tumors, was dramatically upregulated in all RARS patients. Measurement of GDF15 protein in the sera from twenty RARS patients as well as from patients with other forms of ineffective erythropoiesis showed significantly increased GDF15 levels (7.2-fold). To test the erythroid specific expression of GDF15 mRNA, we performed in vitro experiments in which we differentiated CD34+ cord blood cells into erythroid or myeloid lineage cells. Whereas GDF15 mRNA and secreted protein became detectable in erythroid cultures at day five and increased with ongoing erythroid differentiation, myeloid cultures did not show any detectable GDF15 mRNA or protein production. Subsequently, we studied various cytokines stimulating GDF15 production in short-term cultures of erythroid progenitors: only erythropoietin was found to lead to any significant increase in GDF15 mRNA and protein (9-fold). In parallel experiments we found that apoptotic stimuli (e.g.: arsenic) increased GDF15 production in a similar way (3-fold). Finally, we could show in CD34+ cultures that inhibition of endogenous GDF15 production by specific siRNAs results in inhibition of erythroid differentiation (2-fold).

Conclusion: In summary, our findings indicate that high GDF15 serum levels in RARS patients originate from erythroid precursors and may be the result of a combination of high erythropoietin levels and apoptotic stimuli. We show moreover that GDF15 is necessary for normal erythroid differentiation. Therefore, we propose that high GDF15 levels in RARS patients probably constitute a compensatory mechanism to counter regulate ineffective erythropoiesis.

CARDIAC BIOMARKERS FOR RISK STRATIFICATION IN NON MASSIVE PULMONARY EMBOLISM: A MULTICENTER PROSPECTIVE STUDY

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Introduction: Troponins (cTnI and cTnT), N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), myoglobin, heart-type fatty acid-binding protein (H-FABP), and fibrin D-Dimer are emergent candidates for risk stratification in pulmonary embolism (PE). We compared the respective prognostic values of biomarker in patients with non-massive PE to predict an adverse outcome at 3 months.

Méthode: 146 consecutive patients with non-massive PE were included in this multicenter prospective study. The combined outcome consisted in need for intensive care monitoring on admission, death, or hospitalisation attributable either to PE-related complication (defined by PE/DVT relapse or major bleeding under anticoagulation) or to dyspnoea with or without chest pain during follow-up.

Résultats: The outcome was met in 12% of patients. In univariate analysis, NT-proBNP level above 300pg/ml was the strongest predictor of unfavourable outcome with an odds ratio of 15.8 (95%CI: 2.05-122). Odds ratios for the other variables were: 8.0 for D-dimer > 2000ng/ml (95%CI:1.1-64), 4.7 for H-FABP > 6ng/ml (95%CI:1.5-14.8), 3.5 for cTnI >0.09ng/ml (95%CI:1.2-9.7), 3.4 for myoglobin >70ng/ml (95%CI:0.9-12.2). ROC curve analysis indicated that NT-proBNP was the best predictor (AUC 0.84; 95%CI: 0.76-0.92; p<0.0001) with a negative predictive value of 100% (95%CI: 91-100) at 300 pg/ml. At that cut-off, the true negative rate for NT-proBNP was 40%. In multivariate analysis, NT-proBNP was the only significant independent predictor.

Conclusions: NT-proBNP appears to be a good risk stratification marker to identify low-risk patients with non-massive PE who could be treated in an outpatient setting.

PRESENTATIONS POSTERS

EN ORDRE ALPHABETIQUE SELON LE NOM DU 1^{ER} AUTEUR

P1**IMPACT DES FONCTIONS EXECUTIVES SUR LE CONTROLE DE LA MARCHÉ**

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Introduction : Les fonctions exécutives semblent contribuer au contrôle de la marche des sujets âgés. Les modifications de la marche en condition de double tâche dépendent en partie de la capacité à allouer l'attention entre 2 tâches réalisées simultanément et sont sous le contrôle des fonctions exécutives. Le but de cette étude est de décrire l'impact des fonctions exécutives sur le contrôle de la marche chez des sujets âgés avec démence en utilisant la double tâche.

Méthode : La valeur moyenne et le coefficient de variation du temps du cycle de marche durant les conditions de marche seule et de marche avec décompte envers (double tâche) ont été mesurés par le système GAITRite® chez 18 sujets avec démence et atteinte sévère des fonctions exécutives, 16 sujets avec démence et atteinte légère des fonctions exécutives et 22 sujets non-déments.

Résultat : Le temps du cycle de marche et plus particulièrement sa variabilité augmentait de façon significative lors de la double tâche ($p < 0.05$). L'atteinte des fonctions exécutives était associée aussi bien en condition de marche seule que de double tâche avec une augmentation de la valeur moyenne du temps du cycle de marche et sa variabilité.

Conclusion : Cette étude confirme le rôle des fonctions exécutives lors de la réalisation d'une double tâche en condition de marche et suggère leur importance pour la stabilité de la marche.

P2**GAIT ALTERATIONS OF DIABETIC PATIENTS WHILE WALKING ON DIFFERENT SURFACES**

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Introduction: Patients with diabetes have been shown to suffer from increased fall risk. However, authors disagree as to whether only diabetic patients with neuropathy, or also those without neuropathy, present gait alterations. Existing studies evaluate gait indoors, i.e. in specialized gait laboratories. This study evaluates gait parameters in diabetic patients under various real life conditions and compares them to those recorded for healthy controls.

Méthode: We conducted a clinical observation study. 45 subjects' gait was assessed on three different surfaces (tar, grass and stones) with a Physilog® system (BioAGM, CH), consisting of accelerometers and gyroscopes. Temporal and spatial gait parameters as well as stride-to-stride variability of 30 patients with type 2 diabetes, 15 with and 15 without neuropathy were compared to 15 healthy controls.

Résultats: The three groups were comparable for age, height and body weight ($p > 0.05$). Diabetic patients' gait parameters differed significantly from those of healthy controls. Post hoc analysis revealed a significant difference between healthy individuals and patients with neuropathy, and between healthy individuals and patients without neuropathy. No difference was observed between patients with and without neuropathy. The highest surface effect was found in patients with diabetic neuropathy, followed by patients without neuropathy and healthy controls.

Conclusion: Walking in real life conditions revealed gait difficulties in patients with type 2 diabetes before neuropathy was clinically detectable. Clinicians should be aware that diabetic individuals' gait capacity decreases and fall risk increases at an early stage of the disease.

P3**IDENTIFICATION OF A POTENTIAL MELANOMA TUMOR SUPPRESSOR GENE WITH DIFFERENTIAL ANALYSIS OF TRANSCRIPTS WITH ALTERNATIVE SPLICING TECHNOLOGY**

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Introduction: Melanoma is an aggressive cancer with a propensity to cause widespread metastatic disease. New methods based on the study of global gene expression are needed in order to understand the events underlying melanoma carcinogenesis.

Méthode: Alternative splicing events in benign nevus and metastatic melanomas were studied using a new global gene profiling technology: Differential Analysis of Transcripts with Alternative Splicing (DATAS). This genomic analysis confirmed by quantitative PCR assays revealed that the expression of BCSC-1 was consistently down regulated in patients with metastatic melanoma. The analysis of BCSC-1 expression in a cohort of 70 skin biopsies from patients with benign nevus, atypical nevus, primary melanoma or metastatic melanoma revealed that BCSC-1 expression was decreased in melanoma patients in comparison with healthy donors. Comparable results were obtained in melanoma cell lines.

Résultats: Ectopic expression of BCSC-1 in several human melanoma cell lines decreases their proliferation and induces a block in the G2/M phase of the cell cycle. Microarray analysis confirmed the involvement of BCSC-1 on the expression of several cell cycle proteins and showed that BCSC-1 might be also involved in the cell adhesion. Invasion assays are ongoing to establish if BCSC-1 regulates only proliferation or affects also invasion potential. Using immunofluorescence analysis, BCSC-1 appears to be predominantly a cytosolic protein. Experiments in the B16 murine melanoma model demonstrate that the ectopic expression of BCSC-1 decreases metastasis in vivo.

Conclusion: We conclude that BCSC-1 is down regulated in metastatic melanoma and may have a role in the pathogenesis of melanoma.

P4**GSTA1 AND M1 GENE POLYMORPHISMS INFLUENCE BUSULFAN PHARMACOKINETICS IN CHILDREN.**

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Introduction: Busulfan is a key compound in the conditioning myeloablative regimens of children undergoing hematopoietic stem cell transplantation (HSCT). Inter-individual differences in busulfan levels may cause treatment failure and adverse drug reactions such as hepatic veno-occlusive disease and graft rejection. Since busulfan is mainly eliminated by glutathione S-transferase (GST)-catalyzed conjugation with glutathione, it is hypothesized that functional polymorphisms in GST genes may underlie, at least in part, variability in busulfan pharmacokinetics.

Méthode: We analyzed polymorphisms in GSTA1 (C-69T, A-513G, G-631T, G-1142C), GSTM1, (deletion-null genotype) and GSTP1 gene (A578G, C2293T). Genotyping was performed retrospectively in 28 children that underwent HSCT at CHU Ste-Justine with individualized busulfan dosing based on monitoring first dose pharmacokinetics following intravenous administration. Cumulative drug dose and pharmacokinetic data were correlated with genotypes.

Résultats: Haplotype analysis in GSTA1 gene revealed the existence of six haplotypes; five were previously defined as A1, *A2, *A3, *B1 and *B2, whereas newly defined *B1a differed from *B1 by the presence of G-513 allele. The carriers of the *B2 haplotype (11%) had higher cumulative busulfan doses ($p=0.05$), lower area under the curve ($pAUC=0.03$) and maximum plasma concentration ($pC_{max}=0.03$), and higher clearance ($p=0.02$). GSTM1 null individuals (50%) received lower cumulative doses ($p=0.02$), had higher drug plasma concentrations ($pC_{max}=0.003$ and $pAUC=0.008$), and lower clearance ($p<0.001$). No significant association was found with GSTP1 variants.

Conclusion: GSTA1 and GSTM1 polymorphisms seem to have an impact on the busulfan pharmacokinetics in children following intravenous administration. A prospective study is needed to confirm these results and to evaluate if the optimal dose of busulfan can be determined according to the GST genotypes.

P5**SINGLE PORT ACCESS LAPAROSCOPIC CHOLECYSTECTOMY (WITH VIDEO)**

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Introduction: Background Single port access (SPA) surgery is a rapidly evolving field due to the complexity of NOTES (natural orifice transluminal endoscopic surgery). SPA combines the cosmetic advantage of NOTES and possibility to perform surgical procedure with standard laparoscopic instruments. We report a technique of umbilical SPA cholecystectomy using standard laparoscopic instruments and complying with conventional surgical principle and technique of minimally invasive cholecystectomy.

Méthode: Methods Preliminary, prospective experience of SPA cholecystectomy in 11 patients (median age, 46 (range, 27– 63) years) scheduled for cholecystectomy was evaluated. Diagnoses for cholecystectomy were: symptomatic gallbladder lithiasis (n = 7), previous acute cholecystitis (n = 3), and biliary pancreatitis (n = 1).

Résultats: Results SPA cholecystectomy was feasible in all patients (median body mass index, 24 (range, 20–34) kg/m²) who were scheduled for preliminary experience using conventional laparoscopic instruments. Median operative time was 52 (range, 40–77) minutes. Intraoperative cholangiography was performed in all patients, except one, and was considered normal. No peroperative or postoperative complications were recorded. Median hospital stay was less than 24 h.

Conclusion: Conclusions SPA cholecystectomy is feasible and seems to be safe when performed by experienced laparoscopic surgeons using standard laparoscopic instrumentation. SPA cholecystectomy may be safer than the NOTES approach at this time. It has to be determined whether this approach would benefit patients, other than cosmesis, compared with standard laparoscopic cholecystectomy

P6**DIFFERENTIAL REGULATION OF CYTOKINE PRODUCTION BY PI3K δ IN HUMAN MONOCYTES UPON ACUTE AND CHRONIC INFLAMMATORY CONDITIONS AND CHRONIC INFLAMMATORY CONDITIONS**

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Introduction: Imbalance in cytokine homeostasis plays an important part in the pathogenesis of various chronic inflammatory diseases such as multiple sclerosis (MS). We recently demonstrated that the production of the IL-1 inhibitor, IL-1Ra, was increased in MS patients' blood and induced in human monocytes by IFN β and glatiramer acetate (GA), i.e., immunomodulators displaying similar therapeutic efficacy. Because intracellular pathways are potential therapeutic targets, identification of specific kinases downstream both immunomodulators might lead to more specific therapeutic targeting. Consequently, we addressed the question of intracellular pathways used by IFN β and GA to induce sIL-1Ra in human monocytes.

Méthode : Expression of cytokines (protein and mRNA) in human monocytes activated by cellular contact with stimulated T cells (mimicked by CHAPS-solubilized membranes of stimulated T cells, CEsHUT) and LPS; the latter stimuli being relevant to chronic/sterile and acute/infectious inflammation, respectively, in the presence or absence of GA or IFN β , or by immunomodulators alone.

Résultats: PI3K δ was the isoform of PI3K involved in the induction of IL-1Ra by either IFN β or GA in monocytes. Besides this common element, IFN β and GA induced different transduction pathways leading to IL-1Ra production. IFN β required activation of MEK2 but not MEK1 or ERK1/2, whereas GA signaled through MEK1 and MEK2, and GSK3 β . In addition, IFN β and GA differentially regulated IL-1 β and IL-1Ra upon chronic/sterile and acute/infectious inflammatory conditions.

Conclusion: Since PI3K δ is also involved in the differential regulation of pro- and-anti-inflammatory cytokine production in LPS- or CEsHUT-activated monocytes. These studies suggest that PI3K δ might represent a new target in MS therapy.

P7**IMPROVEMENT IN CARDIAC SYMPATHETIC NERVE ACTIVITY IN RESPONDERS TO CARDIAC RESYNCHRONIZATION THERAPY**

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Introduction: Patients with severe heart failure may have an increase in sympathetic tone. Cardiac resynchronization therapy (CRT) has been shown to improve outcome and left ventricular ejection fraction (LVEF) in these patients. Whether CRT also improves cardiac sympathetic activity has not been well studied. ¹²³I-MIBG is a noradrenalin analog, and may be used to assess cardiac adrenergic activity. Our aim was to assess changes in cardiac adrenergic activity with CRT, and to evaluate whether these changes are related to an improvement in LVEF (showing >5% absolute increase in LVEF). Cardiac sympathetic nerve activity was studied by ¹²³I-MIBG scintigraphy.

Méthode : Sixteen patients (13 males, age 66+/- 7 years) were studied at baseline and after > 6 months of CRT (mean follow-up 9.2 +/- 3.2 months). LVEF was assessed by nuclear angiography (with responders defined as patients showing >5% absolute increase in LVEF). Cardiac sympathetic nerve activity was studied by ¹²³I-MIBG scintigraphy.

Résultats: Responders (n=8) showed lower ¹²³I-MIBG washout at follow-up compared to non-responders (P=0.002), indicating lower cardiac sympathetic nerve activity. The decrease in ¹²³I-MIBG washout at follow-up compared to baseline was only seen in the responder group (P=0.036). There was a moderate correlation between increase in LVEF and decrease in ¹²³I-MIBG washout (r=0.52, P=0.04).

Conclusion: CRT induces a reduction in cardiac sympathetic nerve activity in responders. This may contribute to the improvement in outcome and reduction of cardiac arrhythmias observed in these patients.

P8**CLINICAL TRIALS AND DATA SAFETY MONITORING BOARDS**

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Introduction: A Data Safety Monitoring Board (DSMB), also called Data Safety Committee, is a committee of experts, independent from the sponsor and the investigator, which regularly evaluates the safety data of an ongoing clinical trial in order to determine whether the benefit/risk ratio remains adequate. DSMBs are particularly of interest for large clinical trials, multicenter trials, high morbidity and mortality trials, in the early phases of a novel intervention with limited information on safety and for trials testing drugs with a low therapeutic margin. At the University Hospitals of Geneva (HUG), research protocols are submitted for approval to four Departmental Ethics Committees and then centralised in a Central Ethics Committee. Following CIOMS, ICH and GCP recommendations, all drug-related protocols should provide information on how adverse events will be evaluated and reported. The aim of our investigation was therefore to evaluate the management of the safety data that could potentially be produced by all protocols that were submitted to (but not necessarily accepted by) one of the ethics committee of the HUG in 2008.

Méthode: All the clinical trial protocols submitted to the HUG Central Ethics Committee in 2008 were systematically reviewed for safety considerations, specifically for the presence or absence of a DSMB and the description of the assessment and management of adverse events occurring during the trial.

Résultats: Among the 275 submitted protocols, 45 (16%) were retrospective studies and were therefore excluded from the analysis. Among the 230 prospective studies, 68 (30%) were drug-related: 38 were sponsored by the pharmaceutical industry and 30 were investigator-initiated. Based on the WHO recommendations, 30 protocols required a DSMB (26 sponsored and 4 investigator-initiated). Of the sponsored protocols, 38/38 (100%) included a detailed section on measurement and management of safety data and 12/26 (46%) included a DSMB. Of the investigator-initiated protocols, 15/30 (50%) included a detailed section on measurement and management of safety data and 2/4 (50%) included a DSMB. The remaining 162 studies were not directly related to drug efficacy or safety. However, 60 of them included invasive procedures: 11/60 (18%) included safety definitions and/or adverse event reporting procedures.

Conclusion: The continuation of a study should be challenged if the safety/efficacy benefit ratio is altered. In order to evaluate such a concept, a DSMB can be an important approach tool to evaluate such a concept, but only if clear stopping rules and statistics are provided. Analysis of the protocols submitted to the four Ethics Committees of the HUG show that only 50% of the protocols (industry sponsored or investigator-initiated) that required a DSMB had effectively planned one. More alarming is the fact that only 50% of the investigator-initiated protocols included safety definitions and collection and management of adverse event procedures. A special effort is needed to improve the safety monitoring of the drug-related clinical studies that are carried out in our hospital.

P9**REVERSAL OF THE HIP FRACTURE SECULAR TREND IS RELATED TO A DECREASE IN THE INCIDENCE IN INSTITUTION-DWELLING ELDERLY WOMEN**

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Introduction: A decrease in age-adjusted hip fracture incidence has been recently evidenced in some countries. Since a large proportion of hip fractures occurred in nursing homes, we analyzed whether this decreasing trend would be more detectable in institutional-dwelling elderly as compared to community-dwelling elderly.

Méthode: All hip fractured patients aged 60 years and over were identified in a well-defined area. Incidence of hip fracture, age- and sex-adjusted to the 2000 Geneva population, was computed in community- and institutional-dwelling elderly.

Résultats: From 1991 to 2000, 1624 (41%) hip fractures were recorded in institutionalized-dwelling elderly and 2327 (59%) in community-dwelling elderly. The standardized fracture incidence decreased by 1.3% per year in women ($p=0.039$) but remained unchanged in men (+ 0.5%; $p=0.686$). Among institutional-dwelling women, hip fracture incidence fell by 1.9% per year ($p=0.044$) whereas it remained stable among community-dwelling women (+0.0%, $p=0.978$). In men, no significant change in hip fracture incidence occurred among institutional-dwelling or community-dwelling elderly.

Conclusion: The decrease in the standardized hip fracture incidence in institutional-dwelling women is responsible for the reversal in secular trend. To better identify the causes responsible for the trend in hip fracture incidence, future research should include stratification according to the residential status of the fractured patients.

P10**DELETERIOUS EFFECT OF LATE MENARCHE ON DISTAL TIBIA MICROSTRUCTURE IN HEALTHY 20 YEAR OLD AND PREMENOPAUSAL MIDDLE-AGED WOMEN**

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Introduction: Late menarche is a risk factor for fragility fractures. We hypothesized that pubertal timing-dependent alterations in bone structural components would persist from peak bone mass to menopause, independent of premenopausal bone loss.

Méthode: We studied the influence of menarcheal age (MENA) on femoral neck BMD (FN aBMD) by DXA and microstructure of distal tibia by HR-pQCT in healthy young adult (YAD, 20.4±0.6 (±SD) years, n=124) and premenopausal middle-aged (PREMENO, 45.8±3.4 yrs, n=120) women.

Résultats: Median of MENA was 13.0±1.2 and 13.1±1.7 years in YAD and PREMENO, respectively. In YAD and PREMENO (n=244), FN aBMD (R=-0.29, P=0.013), as well as total volumetric bone density (D_{tot}, R=-0.23, P=0.006) and cortical thickness (Ct.Th, R=-0.18, P=0.011) of distal tibia were inversely correlated to MENA. After segregation by the median of MENA in EARLY and LATE subgroups, the significant influences of both MENA (P=0.004) and chronological age (P<0.0001) were observed for FN aBMD and trabecular bone volume fraction of the distal tibia with similar differences in T-scores between LATE and EARLY subgroups in YAD (-0.36 and -0.31 T-scores) and PREMENO (-0.35 and -0.42 T-scores) women. Ct.Th was negatively influenced by MENA, whereas trabecular thickness (Tb.Th) was negatively influenced by chronological age. There was a striking inverse relationship between cross-sectional area and Ct.Th (R=-0.57, P<0.001).

Conclusion: In conclusion, the negative influence of late menarcheal age at weight-bearing sites as observed by the end of skeletal growth remains unattenuated a few years before menopause, and is independent of premenopausal bone loss. Alterations in both bone mineral mass and microstructural components may explain the increased risk of fragility fractures associated with later menarcheal age.

P11**CONTENT-BASED RETRIEVAL AND ANALYSIS OF HRCT IMAGES FROM PATIENTS WITH INTERSTITIAL LUNG DISEASES**

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Introduction: The interpretation of high-resolution computed tomography (HRCT) of the chest from patients with interstitial lung diseases (ILD) is often challenging with numerous differential diagnoses. We developed computer tools and created a database (126 cases representative of the 15 most frequent ILDs) to assist the radiologist in the diagnosis workup of ILDs.

Méthode: Automatic detection and characterization of abnormal pulmonary tissue in HRCT images as well as retrieval of similar cases are implemented based on the visual information contained in the images along with a set of clinical parameters describing the clinical state of the patient. Similar cases are retrieved based on the volumes of abnormal tissues detected as well as subsets of clinical parameters.

Résultats: An automatic detection rate of 78% among five types of lung tissue (including healthy) was obtained using a leave-one-patient-out cross validation of 70 image series from patients affected with ILDs. The recognition rate is obtained with an experimental setup that is faithfully similar to actual clinical situations.

Conclusion: Image-based diagnostic aid tools are available for evaluation to clinicians at the Emergency Radiology Service of the University Hospitals of Geneva. The automatic recognition of abnormal lung tissue provides a draft overview of the image series that constitutes a second opinion with reliability assessment. In addition, image-based retrieval of similar cases enables advanced browsing of large repositories of ILD cases. We plan to integrate content-based access to literature to retrieve state-of-the-art documentation associated with the HRCT image under investigations.

P12**INFLUENCE OF CYP2D6 ACTIVITY ON THE PREEMPTIVE ANALGESIC AND NEUROMODULATORY EFFICACY OF THE N-METHYL-D-ASPARTATE BLOCKER DEXTROMETHORPHAN: A RANDOMIZED CONTROLLED TRIAL ON POST-OPERATIVE PAIN**

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Introduction: There is some evidence that dextromethorphan (DEM) is effective as preemptive analgesic agent and contradictory results on the effectiveness of DEM as preemptive analgesic might be related to genotypic variability. DEM is mainly metabolized by cytochrome 2D6 (CYP2D6). We have made use of a potent inhibitor of CYP2D6, quinidine, to conduct a double blind, randomized, controlled trial on the impact of CYP2D6 phenotype on the preemptive analgesic effectiveness of DEM in acute post-operative pain.

Méthode: We randomized 40 patients to receive one single dose of 50mg of quinidine or placebo. All patients subsequently received one dose of 50mg of DEM. Both medications were given preoperatively to ligament reconstruction of the knee. Principal endpoints were analgesic requirements (non steroidal anti-inflammatory drug (NSAID) and morphine) at 48h after surgery. All patients were genotyped for major CYP2D6 and MDR1 variants and phenotyped for CYP2D6 activity by urine metabolic ratios and plasma pharmacokinetics.

Résultats: NSAID consumption over 48h was reduced by more than half in the quinidine group (mean: 29.6mg vs. 63.6 ketorolac equivalents, $p=0.014$), whereas opioid consumption, side effects, pain scores, and duration of hospitalization were similar. There was no association between NSAID consumption and two variants typed in the MDR-1 gene (rs1045642 and rs2032582).

Conclusion: CYP2D6 phenotype strongly influences the preemptive analgesic effectiveness of DEM in this randomized, controlled trial and suggest that preemptive analgesia by DEM can be modulated by administration of a 2D6 inhibitor, offering an interesting therapeutic option.

P13**DEPENDENCE ON THE NICOTINE GUM IN FORMER SMOKERS***Jean-François ETTER*Institute of Social and Preventive Medicine, Faculty of Medicine, University of Geneva, Switzerland

Introduction: Aim: to assess use of, and dependence on the nicotine gum in former smokers**Méthode:** We conducted an Internet survey in 2004-2007 in 526 daily users of the nicotine gum. We used modified versions of the Nicotine Dependence Syndrome Scale (NDSS-G), the Cigarette Dependence Scale (CDS-G) and the Fagerström Test (FTND-G). After 30 days, 155 participants (29%) indicated their gum use.**Résultats:** Higher dependence on the gum predicted a lower chance of stopping using it at follow-up (odds ratio=0.36 for each standard deviation unit on CDS-G, $p=0.001$). More long-term (>3 months) than short-term (≤ 3 months) users of the gum agreed with: "I use the nicotine gum because I am addicted to it" (83% vs 7%, $p<.001$), and fewer long-term users reported that they used the gum to avoid relapsing to smoking (42% vs 92%, $p<.001$). Long-term users had higher ratings of dependence on the gum than short-term users, as assessed with NDSS-Gum, CDS-Gum and FTND-Gum (all $p<.001$).**Conclusion:** Most long-term users reported symptoms of dependence on the nicotine gum. Lower levels of dependence on the gum predicted cessation of gum use. However, long term use of the nicotine gum has no known serious adverse consequence, and may be beneficial if it prevents late relapse.

P13a**CITATIONS TO TRIALS OF NICOTINE REPLACEMENT THERAPY ARE BIASED TOWARDS POSITIVE RESULTS AND HIGH IMPACT FACTOR JOURNALS***Jean-François ETTER¹, John STAPLETON²*¹Institute of Social and Preventive Medicine, Faculty of Medicine, University of Geneva, Switzerland²Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College, London, UK

Introduction: To study variations in the number of times trials of nicotine replacement therapy (NRT) were cited, and which characteristics of trials predicted the number of citations and the impact factors of journals where articles were published.

Méthode: We used all 105 randomized controlled trials in the Cochrane review of NRT for smoking cessation. We obtained impact factors from the Journal Citation Reports and the number of citations from ISI Web of Knowledge and Google Scholar.

Résultats: Trials were cited from 0 to 632 times (median 23 times). Trials were cited more often when results were statistically significant than when they were not (median=41 vs 17 times, $p<0.001$), and when impact factors were higher (10.2 more citations per impact factor point, $p<0.001$). Patch trials were cited more often than gum trials (median=29 vs 17 times, $p=0.001$), and trials funded by the pharmaceutical industry were cited more often than other trials (median=28 vs 16.5 times, $p=0.001$). Trials with statistically significant results were published in journals with higher impact factors than trials with non-significant results (median impact factor=2.80 vs 1.81, $p=0.011$).

Conclusion: Citations were biased towards trials with positive results and towards trials published in high impact factor journals.

P13b**ACCEPTABILITY AND IMPACT OF A PARTIAL SMOKING BAN FOLLOWED BY A TOTAL SMOKING BAN IN A PSYCHIATRIC HOSPITAL**

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Introduction: Aim: To assess the impact of a partial smoking ban followed by a total smoking ban in a psychiatric hospital in Geneva, Switzerland.

Méthode: In 2003, smoking was allowed everywhere in psychiatric units. In 2004, smoking was prohibited everywhere except in smoking rooms. In 2006, smoking rooms were removed and smoking was totally prohibited indoors. Patients and staff were surveyed in 2003 (n=106), 2004 (n=108), 2005 (n=119) and 2006 (n=134).

Résultats: Exposure to environmental tobacco smoke (ETS) decreased after the partial ban and further decreased after the total ban. Among patients, after the total ban, more smokers attempted to quit smoking (18%) relative to before the total ban (2%, odds ratio=10.1, p=0.01). More smokers said that hospital staff gave them nicotine replacement products after the total ban (52%), compared with before (13%, odds ratio=7.6, p<0.001). Many participants (55%) commented that the total ban was too strict, and most (64%) preferred the partial ban.

Conclusion: The partial ban decreased exposure to ETS and the total ban further improved the situation and increased the proportion of smokers who attempted to quit smoking and received nicotine medications. The total ban was loosely enforced and was overall acceptable, but most participants preferred a partial ban.

P13c**PERCEIVED PRIORITIES FOR PREVENTION: CHANGE BETWEEN 1996 AND 2006 IN A GENERAL POPULATION SURVEY***Jean-François ETTER*Institute of Social and Preventive Medicine, University of Geneva, Switzerland

Introduction: We assessed change between 1996 and 2006 in opinions of the general public on priorities for the prevention of health problems.

Méthode: Postal surveys in 1996 and 2006, in representative samples of the general population of Geneva, Switzerland. Participants indicated, for each of 13 health problems, a priority rating for the spending of prevention resources.

Résultats: There were 742 participants in 1996 (response rate 75%) and 1487 in 2006 (response rate 76%). According to participants, in 2006, resources should be spent in priority for the prevention of sexual abuse on children (67% answered "high priority"), illegal drugs (58%), AIDS (55%), tobacco smoking (45%), road traffic accidents (43%), alcoholism (42%), family violence (42%), suicide in young people (39%), mammography screening for breast cancer (37%), abuse of medications (27%), cannabis use (24%), poor diet (22%) and lack of physical activity (20%). Between 1996 and 2006, the largest change was observed for tobacco smoking (+18.6% answered "high priority"), poor diet (+11.4%), lack of physical activity (+10.8%) and AIDS (-10.8%, $p < .001$ for all change scores).

Conclusion: Smoking, poor diet and lack of physical activity were more likely to be perceived as priorities in 2006 than in 1996, whereas priority ratings decreased for AIDS.

P14**LOW RISK OF ANTI-HLA ANTIBODY SENSITIZATION AFTER COMBINED KIDNEY AND ISLET TRANSPLANTATION**

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Introduction: Anti-HLA antibody could lead to humoral rejection and a decrease in graft survival after kidney transplantation. Reports suggested that islet transplantation alone is associated with a high rate of sensitization. As the specific risk of immunization of multiple islet infusions remains unknown, we studied the immunization rate in our cohort of multiple islet infusions transplant recipients.

Méthode: We analyzed 37 transplantations in 34 patients, and their sera were analyzed for the presence of anti-HLA class I and class II antibodies by solid phase assays ELISA, and all positive results were tested for anti-HLA class I and class II specific antibodies by Luminex single antigen.

Résultats: Four out of 37 patients (10.8%) developed anti-HLA antibodies after transplantation, two patients at 12 months, one at 24 months and the last at 36 months. Sensitization never appeared earlier after the islet transplantation. In all four cases, the islets had class I and class II mismatches with respects to the patients and the kidney HLA typing. Donor-specific antibodies (DSA) directed against HLA antigens of the islets were detected in only two of the four sensitized patients by Luminex.

Conclusion: Our study showed that the rate of sensitization (10.8%) after islet transplantation is similar to the rate of sensitization after kidney transplantation alone and contrasted with a recent report of a large cohort of ITA which has shown a rate of 34 % sensitization. Multiple islet infusions do not represent a specific risk for the development of anti-HLA antibodies after combined kidney-islets transplantation.

P15**USE OF THE PFA-100 CLOSURE TIME TO PREDICT CARDIOVASCULAR EVENTS IN ASPIRIN-TREATED CARDIOVASCULAR PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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Introduction: PFA-100 is a point-of-care assay that evaluates platelet reactivity in high shear stress conditions by measuring the closure time (CT) of a membrane aperture. When determined with a collagen/epinephrine cartridge (CEPI), the CT is usually prolonged by aspirin. Studies of the predictive value of a short PFA-100-CTCEPI for ischemic events in aspirin-treated patients have given variable results.

Méthode: Relevant studies were identified by scanning electronic databases. Studies were selected if they included aspirin-treated patients with symptomatic atherosclerosis, measured the PFA-100-CTCEPI, used a CT cut-off value to define aspirin “responders” and “non-responders” (aR and aNR), and reported ischemic events.

Résultats: We selected seven non-prospective studies (1466 patients) and 8 prospective studies (1227 patients). In non-prospective studies, the PFA-100-CTCEPI was performed after the ischemic clinical endpoint and a publication bias was identified. In prospective studies, the global odds ratio (OR) for the recurrence of an ischemic event in aNR relative to aR was 2.1 (95%CI [1.4-3.4], $p < 0.001$). Pooled analysis with a random effect model revealed no heterogeneity (Q Cochran $p = 0.36$ and $I^2 = 9.4\%$).

Conclusion: CTCEPI is associated with increased recurrence of ischemic™A short PFA-100 events in aspirin-treated cardiovascular patients. This finding needs to be confirmed in stable ischemic patients, and the PFA-100-CTCEPI cut-off. Needs to be refined in these patients.

P16**IL-17 POLARIZATION IN MYCOSIS FUNGOIDES-TYPE CUTANEOUS T-CELL LYMPHOMA ASSOCIATED WITH NEUTROPHILIC INFILTRATION OF THE SKIN**

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Introduction: Mycosis fungoides (MF), the most frequent form of cutaneous T cell lymphoma is characterized by atypical CD4+ lymphocytes infiltrating the skin. MF is generally associated with a TH2 bias and in some instances complicated by a neutrophilic dermatosis that is associated with a poor prognosis. The mechanisms underlying MF with a neutrophilic reaction are unclear. Recently, TH17 cytokines have been implicated in the regulation of autoimmunity or inflammation, and are major regulator of neutrophils. Therefore, we investigated whether TH17 cytokines were implicated in MF with neutrophilic infiltration of the skin.

Méthode: Three MF were investigated by immunohistochemistry and qRT-PCR.

Résultats: Histological skin sections showed exocytosis of CD4 T lymphocyte with spongiosis that was associated in one case with a neutrophilic infiltrate in the superficial dermis and within sub-corneal pustules. qRT-PCR revealed that IL-4, IL-5 were not detected in either the normal skin or the pathological skin whereas IL-13, IL-31 and IL-10 transcript were found in the tested MF. Strikingly, IL-17 transcripts were specifically identified in the MF with were predominantly found in γ , and IFN- β Neutrophilic reaction whereas TNF- typical MF. In the MF with neutrophilic reaction but not in others, the infiltrate contains neutrophils that were IL-17 positive. Double immunofluorescence stainings indicate that CD3 + positive cells were mostly IL-17 negative suggesting that IL-17 positives cells were not T lymphocytes.

Conclusion: In conclusion, we show that MF with neutrophilic infiltration of the skin correlates with the presence of IL-17+ neutrophils along the typical CD4+ lymphocytes. Recently, it has been suggested that TH-17 differentiation is promoted by phagocytosis of apoptotic cells via the release of TH-17 promoting cytokines produced by neutrophils and dendritic cells. Future studies will establish the exact origin of the TH17 polarization in the skin of patients with MF with neutrophilic infiltration and potentially reveal therapeutic opportunities in this subset of MF with poor prognosis.

P17**NATIVE AND RECONSTITUTED HDL PROTECT VENTRICULAR CARDIOMYOCYTES FROM DOXORUBICIN-INDUCED APOPTOSIS: ROLE OF SPHINGOSINE-1-PHOSPHATE, ERK1/2 AND STAT3**

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Introduction: Whilst an effective anti-cancer agent, doxorubicin (DOX) has serious, cardiotoxic side effects. HDL has been shown to protect cardiomyocytes notably against oxidative stress. The aim of this study was to analyze the impact of native and reconstituted HDL (rHDL) on DOX induced cardiomyocyte apoptosis.

Méthode: Cultured rat ventricular cardiomyocytes were subjected to DOX-induced stress, monitored as caspase3 activation and apoptotic DNA fragmentation. The protective effects of HDL and sphingosine-1-phosphate (S1P) were investigated using native HDL, rHDL of varied composition and agonists and antagonists of S1P receptors. Anti-apoptotic signaling pathways were identified with specific inhibitors

Résultats: Native and rHDL significantly decreased DOX-induced cardiomyocyte apoptosis, essentially due to the S1P component of HDL. The latter was mediated by the S1P2 receptor, but not the S1P1 or S1P3 receptors. The ERK1/2 signaling pathway was required for the anti-apoptotic effects of HDL and S1P. The transcription factor, Stat3, also played an important role as inhibition of its activity compromised the protective effects of HDL and S1P on DOX-induced apoptosis.

Conclusion: HDL and its S1P component can protect cardiomyocytes against DOX toxicity and may offer one means of reducing cardiotoxic side effects during DOX therapy. The study identified anti-apoptotic pathways that could be exploited to improve cardiomyocyte survival.

P18**UPPER AND LOWER RESPIRATORY VIRAL INFECTIONS AND ACUTE GRAFT REJECTION IN LUNG TRANSPLANT RECIPIENTS**

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Introduction: Lung transplant recipients are frequently exposed to respiratory viruses and are particularly at risk of severe complications. The goals of the present prospective study were: 1) to detect by RT-PCR a wide panel of respiratory viruses, both in the upper and the lower respiratory tract of adult lung recipients; 2) to assess the possible associations between respectively symptoms, various respiratory conditions, acute rejection and the presence of a proven respiratory viral infection.

Méthode: Over a 27-month period, all lung transplant recipients of our transplantation network who underwent a bronchoscopy with BAL and transbronchial biopsies were eligible. Both upper respiratory specimens and bronchoalveolar fluids were screened by 17 different RT-PCR assays.

Résultats: 343 BAL and 283 nasopharyngeal swabs were performed in 77 lung transplant recipients. The overall viral positivity rate was 29.3% in the upper tract specimens and 17.2% in the BAL samples ($p < 0.001$). We observed a significant association between the presence of any respiratory symptoms and a positive viral detection in the lower respiratory tract ($p=0.012$). On the other hand acute rejection was negatively associated with the presence of a viral infection (OR 0.41 (0.2-0.88)). The recovery of lung function was significantly slower when concurrent acute rejection and viral infection were present.

Conclusion: In lung transplant recipients there is a temporal relationship between acute respiratory symptoms and a positive viral nucleic acid detection in bronchoalveolar fluids. We also provide solid evidences suggesting that per se respiratory viruses do not promote acute graft rejection, at least during the acute phase of the infection.

P19**ETUDE SUR LA VALIDITE DIAGNOSTIQUE DE LA PCR EN TEMPS REEL DANS DIVERS PRELEVEMENTS BIOLOGIQUES DE PATIENTS ATTEINTS DE SYPHILIS**

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Introduction : L'incidence de syphilis a augmenté dans les milieux sexuellement actifs. Son diagnostic repose sur une association clinico-sérologique, mais des présentations atypiques existent chez les patients VIH+. Notre objectif est d'évaluer l'apport diagnostique de la PCR dans différents milieux biologiques et selon le statut VIH.

Méthode : Etude cas-témoins nichée dans une série prospective de cas de syphilis I, II ou latente diagnostiqués sur 2ans dans 3 hôpitaux suisses (Genève, Zürich, Berne). Des échantillons de sang, ulcères muqueux, urine et LCR ont été testés par PCR en temps réel ciblant le gène 47kDa de *Treponema pallidum* (Tp).

Résultats : 126 échantillons de 74 patients, dont 29 VIH+ (41%), atteints de syphilis I (n=26), II (n=40) ou L (n=8). Pour la syphilis I, la sensibilité de la PCR était de 80%(IC95% 44-97%) dans les ulcères, 55%(23-83) dans le sérum, 29%(4-71) dans l'urine et 28%(10-53) dans le sang. Pour la syphilis II, la sensibilité était respectivement de 20%(0,5-72), 47%(21-73), 44%(14-79) et 36%(19-55). Le plasma avait une sensibilité de 100%(16-100) et le LCR 50%(12-88). La sensibilité était nulle dans les échantillons de syphilis L. La spécificité était de 100%(78-100). Le statut VIH ne modifiait pas la sérologie ni la PCR. La concentration de Tp était significativement plus forte dans le sang des patients VIH+ avec syphilis II (p=0,02) et dans les ulcères des syphilis I comparés au sang (p=0,002).

Conclusion : La PCR est plus sensible dans les ulcères que dans le sang des syphilis I /II. Le statut VIH n'affecte pas les résultats. L'association clinico-sérologique reste la référence pour le diagnostic de syphilis.

P20**ICU RESEARCH: WHO SHOULD CONSENT?***Chenaud Catherine, Merlani Paolo, Ricou Bara*

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Introduction: Informed consent (Ic) for research in ICU is controversial, even for conscious patients. Preferences of patients and relatives regarding its modalities were rarely investigated. We sought to explore whether they differed for patients and relatives according to the invasiveness of the study proposed/the consciousness of the patient.

Méthode: Patients/relatives' pairs were randomized to express their opinion about Ic's modalities for non-invasive (NIS, ie retrospective data extraction) or invasive studies (IS, ie prospective drug trial) after ICU discharge. Similar questions were addressed for conscious and unconscious patients.

Résultats: 185(33%) patients (eligible=553) and 125(68%) relatives responded. If conscious, most patients thought they were the person to be asked the Ic {NIS:69/93(74%);IS:64/92(70%)}. For NIS, 7(8%) thought the physicians could consent or that no consent was necessary, 6(7%) that the relatives could consent. If unconscious, the patients wanted the relatives to consent, depending on the invasiveness {NIS:53(57%);IS:48(52%), p=0.01}. ICU doctors were more sought in NIS {10(11%) vs 0} whereas it was the family doctors for IS {13(14%) vs 5(5%)}. 9(10%) for NIS and 8(9%) for IS choose waiving of consent. For conscious patient, most relatives thought patients should consent {NIS:44/64(69%);IS:42/61(69)}. Themselves came in second position {NIS:9 (14%);IS:8(13%)}. For unconscious patients, 2/3 of relatives thought of themselves, and of ICU doctors: NIS:9(14%);IS:8(13%). 1/3 of patients wanted a second person to consent, 48% if unconscious and IS. More relatives wanted a second person to consent for IS than for NIS: for conscious: 3/6(50%) vs 21(33%) (p=0.0012); for unconscious: 37(61%) vs 23(36%) (p=0.0068), respectively. Globally patients-relatives concordances were 64-80%.

Conclusion: Preferences regarding Ic for research were more protective with unconscious patients. For conscious patients, most pairs wanted the patient to consent. For unconscious patients, about half wanted the relatives to decide. The others wanted to defer Ic to physicians. Invasiveness impacted significantly.

P21**LA DEFINITION DE LA REPONSE AU REMPLISSAGE VASCULAIRE PAR LA VARIATION DE LA SCVO2**

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Introduction: Actuellement, seule la mesure de l'index cardiaque (IC) permet de définir la réponse au remplissage vasculaire (RV) (>15% d'augmentation de l'IC). La présente étude évalue la mesure de la saturation veineuse centrale en oxygène (ScvO₂) à un niveau cave supérieure et ses variations après RV comme méthode alternative définissant et classifiant les patients répondeurs (R) et non répondeurs (NR).

Méthode: Nous avons inclus de façon prospective 30 patients de réanimation, équipés d'un cathéter radial et artériel pulmonaire. La mesure de l'IC et de la ScvO₂ étaient réalisées avant et après RV. Les variations de l'IC et de la ScvO₂ étaient ensuite corrélées au moyen d'une régression linéaire. Nous avons ensuite construit des courbes ROC pour les variations de ScvO₂, saturation veineuse mêlée, pression artérielle moyenne et pression veineuse centrale après RV et calculer les aires sous les courbes (ASC) permettant pour chaque paramètre de déterminer leur capacité à discriminer les R des NR.

Résultats: Les variations de ScvO₂ étaient corrélées aux modifications d'IC ($r^2=0.44, p<0.05$). L'ASC de la courbe ROC traduisant la capacité de la ScvO₂ à discriminer les R des NR après RV était de 0.90 ± 0.05 (95%CI;0.79–1.0, $p<0.05$). Une variation de ScvO₂ de 8% après RV permettait de discriminer les R des NR avec une sensibilité de 64%(95%CI;44-80%) et une spécificité de 100%(95%CI;88-100%).

Conclusion: En l'absence de mesure de l'IC, la variation de ScvO₂ après RV pourrait être une méthode alternative permettant de définir les patients R et NR.

P22**CONTROLE D'UNE CHAISE ROULANTE PAR DES SIGNAUX ELECTROPHYSIOLOGIQUES**

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Introduction: Une interface cerveau-machine (ICM) permet au cerveau de communiquer avec le monde extérieur sans passer par les chemins naturels tels que les nerfs ou les muscles. En d'autres termes, l'intention du sujet va produire des signaux électrophysiologiques qui sont décodés par un ordinateur et envoyés sous forme d'ordres ou commandes à une machine externe.

Méthode: Dans cette expérience, nous utilisons un ICM pour piloter un robot mobile dans un espace virtuel et dans un espace réel. Le but de cette étude est de démontrer la possibilité d'atteindre une navigation rapide et précise dans un environnement inconnu (télé-présence) à l'aide des signaux émis par le cerveau.

Résultats: Ce système exploite une propriété bien connue en neurosciences: la stimulation du système visuel par des stimuli périodiques induit une activité neuronale à la même fréquence que celle de présentation des stimuli. Ces fréquences sont aussi présentes dans l'activité neurale (EEG) enregistrée par les électrodes placées sur le cortex occipital. Ces réponses neurales sont fortement modulées par l'attention, même si elles sont automatiques. Ceci permet le développement d'ICO asynchrones dans lesquelles le sujet peut envoyer des commandes quand il le souhaite.

Conclusion: Les potentiels évoqués «steady-state» fournissent un moyen efficace de développement d'Interfaces Cerveau-Ordinateur caractérisés par leur portabilité, un taux de transfert élevé, un entraînement minimal, une grande précision et une facilité d'utilisation. Une telle technique peut offrir une certaine indépendance à des patients lourdement handicapés. Les prochaines étapes de ce travail consisteront à augmenter le nombre de commandes et à tester le système avec des patients.

P23**NATURAL KILLER CELL RECEPTOR REPERTOIRE AND THEIR LIGANDS, AND THE RISK OF CMV INFECTION AFTER KIDNEY TRANSPLANTATION**

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Introduction: Cytomegalovirus (CMV) infection is the most common viral complication after solid organ transplantation (SOT). Whilst current immunosuppression is known to impair antiviral-specific T-cell immunity in SOT, a potential role for natural killer (NK) cells not affected by immunosuppressive therapy remains to be determined.

Méthode: To address this, we compared the genotype of the NK immunoglobulin-like receptor (KIR) genes and their HLA cognate ligands to the rate of CMV infection in 196 kidney transplant recipients.

Résultats: We have shown that the absence of the HLA-C ligand for inhibitory KIR and the presence of activating KIR genes in the recipients were both associated with a lower rate of CMV infection after transplantation. In a cohort of 17 recipients with acute CMV infection, NK cells were phenotyped over a period of time after diagnosis by their expression profile of C-type lectin receptors and capacity to secrete IFN-gamma. The increased expression of the activating C-type lectin receptors NKG2C and NKG2D was paralleled by the decreased IFN-gamma secretion during the early phase of CMV infection.

Conclusion: In conclusion, our findings suggest that KIR/HLA genotype and expression of NKG2C and NKG2D might play a significant role in regulating NK cell function and anti-CMV immunity after kidney transplantation.

P24**THE RESULTS OF SURGERY, WITH OR WITHOUT RADIOTHERAPY, FOR PRIMARY SPINAL MYXOPAPILLARY EPENDYMOMA: A RETROSPECTIVE STUDY FROM THE RARE CANCER NETWORK**

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Introduction: The aim of this study was to assess the outcome of patients with primary spinal myxopapillary ependymoma (MPE).

Méthode: Data from a series of 85 (35 females, 50 males) patients with spinal MPE were collected in this retrospective multicenter study. Thirty-eight (45%) underwent surgery only and 47 (55%) received postoperative radiotherapy (RT). Median administered radiation dose was 50.4 Gy (range, 22.2–59.4). Median follow-up of the surviving patients was 60.0 months (range, 0.2–316.6).

Résultats: The 5-year progression-free survival (PFS) was 50.4% and 74.8% for surgery only and surgery with postoperative low- (<50.4 Gy) or high-dose (≥50.4 Gy) RT, respectively. Treatment failure was observed in 24 (28%) patients. Fifteen patients presented treatment failure at the primary site only, whereas 2 and 1 patients presented with brain and distant spinal failure only. Three and 2 patients with local failure presented with concomitant spinal distant seeding and brain failure, respectively. One patient failed simultaneously in the brain and spine. Age greater than 36 years ($p = 0.01$), absence of neurologic symptoms at diagnosis ($p = 0.01$), tumor size ≥25 mm ($p = 0.04$), and postoperative high-dose RT ($p = 0.05$) were variables predictive of improved PFS on univariate analysis. In multivariate analysis, only postoperative high-dose RT was independent predictors of PFS ($p = 0.04$).

Conclusion: The observed pattern of failure was mainly local, but one fifth of the patients presented with a concomitant spinal or brain component. Postoperative high-dose RT appears to significantly reduce the rate of tumor progression.

P25

SCREENING FOR STAPHYLOCOCCAL SUPERANTIGEN GENES SHOWS NO CORRELATION WITH THE PRESENCE OR THE SEVERITY OF CHRONIC RHINOSINUSITIS AND NASAL POLYPOSIS

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Introduction: Staphylococcus aureus secretes numerous exotoxins able to exert superantigenic properties. Whereas the virulence of several of them is well documented, their exact biological effects are not fully understood. Exotoxins could influence the immune and inflammatory state of various organs, including the nasal mucosa: their possible involvement in chronic rhinosinusitis has been suggested and is the current trend for research. The aim of this study was to investigate whether the presence of any of the 22 currently known staphylococcal exotoxin genes could be correlated with chronic rhinosinusitis.

Méthode: We conducted a prospective, multi-centred European study, analysing 93 Staphylococcus aureus positive swabs taken from the middle meati of patients suffering from chronic rhinosinusitis, with or without nasal polyposis, and controls. Strains were systematically tested for the presence of the 22 currently known exotoxin genes and genotyped according to their agr groups.

Résultats: No direct correlation was observed between chronic rhinosinusitis, with or without nasal polyposis, and either agr groups or the presence of the most studied exotoxin genes (egc, sea, seb, pvl, exfoliatins or tsst-1). However, genes for enterotoxins P and Q were frequently observed in nasal polyposis for the first time, but absent in the control group. The number of exotoxin genes detected was not statistically different among the 3 patient groups.

Conclusion: Unlike many previous studies have been suggesting, we did not find any evident correlation between staphylococcal exotoxin genes and the presence or severity of chronic rhinosinusitis with or without nasal polyposis.

P26**COPING RELIGIEUX CHEZ LES PATIENTS SOUFFRANT DE PSYCHOSE CHRONIQUE : IMPLICATION CLINIQUE**

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Introduction : L'évolution du trouble psychotique est fréquemment compliquée par des problématiques associées telles qu'abus de substances ou tentatives de suicide. Nous avons pu mettre en évidence le rôle important que pouvait jouer la spiritualité et la religion chez ces patients pour faire face à leurs difficultés de vie.

Méthode : Cent-quinze patients ont été sélectionnés pour un entretien semi-structuré portant sur leur coping religieux. D'autres paramètres cliniques ont été relevés, tels que l'usage de substances toxiques ou tentatives de suicide dans le passé.

Résultats : En ce qui concerne les abus de substances, une corrélation inverse a pu être mise en évidence par rapport à l'abus de substances toxiques. L'analyse de contenu montre que la religion a joué un rôle protectif chez 14 % de l'échantillon total, tout particulièrement pour les patients qui avaient présenté dans le passé un tel problème (42 %). Cette analyse montre que la religion fournissait un cadre pour vivre sans substances toxiques, une stratégie de coping alternatif ou même parfois un point d'ancrage pour une complète réorganisation de la vie autour de la spiritualité. La religion jouait un rôle négatif dans 3 % des cas. Il s'agissait de patients utilisant des substances toxiques pour faire face à une détresse spirituelle.

Conclusion : Le rôle favorable de la religion chez les personnes abusant de substances toxiques paraît être également présent chez des patients souffrant de schizophrénie. Les implications cliniques qui en découlent, de même que d'autres recherches en cours portant sur des applications thérapeutiques de ce qui précède seront décrites dans la présentation.

P27**DEEP DISSECTING HEMATOMA: AN EMERGING SEVERE COMPLICATION OF DERMATOPOROSIS***Gürkan Kaya, Felix Jacobs, Christa Prins, Daniela Viero, Aysin Kaya, Jean-Hilaire Saurat*Service de Dermatologie et de Vénérologie, Hôpitaux Universitaires de Genève

Introduction: Skin aging in elderly people may induce a severe cutaneous fragility syndrome, recently coined as dermatoporosis. The most severe complication of dermatoporosis is deep dissecting hematoma (DDH).

Méthode: We performed a retrospective medical record review of 34 patients with DDH hospitalized between 1999 and 2006 at the Department of Dermatology of the University Hospital of Geneva

Résultats: Most frequently, elderly women were affected (mean age, 81.7 years); women outnumbered men by a ratio of 5:1. In all the patients, the leg was the affected part of the body. All the patients, except for the 2 youngest ones, had advanced dermatoporosis, and the most severe form was seen in the older patients who were receiving long-term treatment with systemic corticosteroids. Half of the patients were receiving anticoagulation drugs. The initial symptoms in all the patients were pain and swelling of the leg. Erythema and edema without fever were observed. Skin necrosis developed as a late manifestation. Erysipelas was the initial diagnosis in up to 14 patients who had been treated with antibiotics before admission. The mean delay before hospital referral was 16.4 days. Magnetic resonance imaging and histopathological analysis confirmed deep anatomical location of DDH. Hospital treatment consisted mainly of deep incision and debridement followed by direct closure, skin grafting, or wound healing per secundam. The mean length of hospital stay was 3.5 weeks.

Conclusion: DDH is an emerging clinical entity. Prompt diagnosis and treatment is a major factor for the prognosis. Given the high cost of treatment, preventive measures should be implemented early.

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TUBERCULOSIS SCREENING IN PSORIASIS PATIENTS BEFORE ANTI-TNF THERAPY: COMPARISON OF AN INTERFERON-GAMMA RELEASE ASSAY VERSUS TUBERCULIN SKIN TEST

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Introduction: Anti-TNF treatments may reactivate latent tuberculosis (LTBI). For detecting LTBI, tuberculin skin test (TST) and Interferon gamma release assays (IGRA) are available. We compared TST and T-SPOT.TB IGRA to risk factors of LTBI in psoriasis patients before anti-TNF treatment in two Academic Dermatologic centers (HUG and CHUV).

Méthode: Retrospective study over a 4-year period of psoriasis patients requiring anti-TNF treatment. Association of T-SPOT.TB and TST results with risk factors for LTBI was tested through univariate logistic regression models. Treatment for LTBI was started one month before anti-TNF therapy when indicated.

Résultats: 50 patients were included, 90% had prior vaccination by BCG. T-SPOT.TB was strongly associated with a presumptive diagnosis of LTBI (OR: 7.43; 95% CI 1.38-39.9), which was not the case for the TST. Agreement between T-SPOT.TB = 0.33 (SD: 0.13). LTBI was detected and treated in 20% of patients and TST was poor the patients. In 20% of the cases, LTBI was not retained in spite of a positive TST in front of a negative T-SPOT.TB. All patients received an anti-TNF for a median of 56 weeks (range: 20-188); among patients with TST+/T-SPOT.TB-, no tuberculosis was detected with a median follow-up of 64 weeks (44-188). One case of disseminated TB occurred after 28 weeks of adalimumab in a patient with LTBI in spite of treatment with rifampicine.

Conclusion: This study is the first to underline the frequency of LTBI in psoriasis patients (20%), and to support the use of IGRA instead of TST for its detection. Nevertheless, there is still a risk of tuberculosis under anti-TNF even if LTBI is correctly diagnosed and treated.

P29**PERIPHERAL AUTOIMMUNE NEUROPATHY ASSESSED BY IN VIVO CORNEAL CONFOCAL MICROSCOPY***P.H. Lalive¹, A. Truffert¹, M.R. Magistris¹, T. Landis¹, A. Dosso²*

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Introduction: The cornea is one of the most densely innervated parts of the human body. In vivo confocal microscopy (IVCM) provides the opportunity to examine the living human cornea nerves at the cellular level. The non-invasive nature of IVCM allows performing multiple examinations of the same tissue over time. The objective of this presentation is to describe a case of autoimmune peripheral neuropathy followed up with corneal IVCM.

Méthode: Corneal IVCM was performed using a Heidelberg Retina Tomograph II, Rostock Cornea Module (Heidelberg Engineering GmbH, Dossenheim, Germany). After topical anesthesia (0.4% oxybuprocaine, Novartis Pharma, Bern, Switzerland), Lacryvisc Gel (Alcon Labs, Zug, Switzerland) was applied before aligning the lens. Raw full-screen images were captured throughout the cornea of both eyes at the time of the aggravation. Images are presented without further digital image treatment.

Résultats: Case report: A 56 year-old man presented with peripheral neuropathy diagnosed as anti-myelin associated glycoprotein (MAG) neuropathy. The symptoms initially worsened despite intravenous immunoglobulins and plasma exchange. Evolution was eventually favourable after Rituximab and corticosteroids were initiated. At one year follow up, the clinical recovery was almost complete and the patient was stable on both clinical and electrophysiological assessments. Examination of corneal nerves by IVCM at two different timepoints of his clinical evolution (peak disease and recovery phase) demonstrated histological signs that correlated with both clinical and electrophysiological assessments.

Conclusion: This observation supports the hypothesis that corneal IVCM could be also helpful for early detection or the follow up of autoimmune peripheral neuropathy.

P30**ETUDE PILOTE DE THERAPIE ASSISTEE PAR LE CHIEN AUPRES DE JEUNES PRESENTANT UN TROUBLE ENVAHISSANT DU DEVELOPPEMENT**

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Introduction: L'objectif de la présente étude est d'évaluer dans quelle mesure des séances de thérapie assistée par le chien amènent une baisse des troubles du comportement chez des jeunes présentant un trouble envahissant du développement, un retard mental modéré à profond et des troubles du comportement.

Méthode: Les participants à cette étude sont six jeunes âgés de 16 à 22 ans. Trois d'entre eux sont suivis dans le cadre d'entretiens psychothérapeutiques par une psychologue accompagnée de son chien pendant les 12 premiers mois, et seule pendant les 12 mois suivants. Les trois autres participants voient la psychologue seule les 12 premiers mois et la psychologue accompagnée de son chien les 12 mois suivants. L'homogénéité de notre population est établie avec le Childhood Autism Rating Scale (CARS) en début de recherche. L'évaluation des troubles du comportement est faite par une autre psychologue avec l'Aberrant Behavior Checklist (ABC), qui est passé en début de recherche puis tous les trois mois, en parallèle aux séances de thérapie.

Résultats: Les résultats de l'évaluation ABC devraient objectiver une baisse des troubles du comportement pendant l'année où le chien est présent en thérapie, comparé à l'évaluation des troubles du comportement faite pendant l'année où le chien est absent des séances de thérapie.

Conclusion: Les séances de thérapie assistée par l'animal peuvent amener une baisse dans les troubles du comportement chez de jeunes présentant un trouble envahissant du développement mais sous certaines conditions.

P31**BIATRIAL ANATOMICAL REVERSE REMODELLING AFTER RADIOFREQUENCY CATHETER ABLATION FOR ATRIAL FIBRILLATION: EVIDENCE FROM REAL-TIME 3D ECHOCARDIOGRAPHY**

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Introduction: Reports using 2D echocardiography have indicated that radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) results in a reduction in left atrial (LA) size. Furthermore, the effect of PVI on right atrial (RA) anatomical remodelling has not been studied. 3 D echocardiography allows more precise quantification of atrial volume. Our aim was to assess the effect of PVI on biatrial anatomical remodelling using real-time 3D echocardiography.

Méthode: We prospectively studied 91 patients (age 59±8 years, 79 males) referred for RFCA of paroxysmal (n=79) or chronic (n=19) AF. LA and RA volumes were measured using real-time 3D echocardiography at baseline and after 6 months' follow-up. Data on AF recurrences were also collected.

Résultats: LA volume was significantly reduced at follow-up compared to baseline (51±16ml vs. 60±21ml, p<0.001). The same occurred with RA volume (43±17ml vs. 50±20ml, P=0.001). Reduction in LA volume was more marked in patients with chronic than paroxysmal AF (17±16ml vs. 6±17ml, P=0.017). Patients with AF recurrence (2/ 3%) showed similar atrial volume reduction compared to those who were seemingly cured.

Conclusion: 3D echocardiography shows evidence of biatrial anatomical reverse remodelling after RFCA for atrial fibrillation. Reduction in atrial volume occurs despite recurrence of AF.

P32**HIV-1 INDUCES CDC42-DEPENDENT FILOPODIA FORMATION TO FACILITATE DENDRITIC CELL-T CELL TRANS INFECTION***Damjan S. Nikolic, Martin Lehmann, Eduardo Garcia, Fabien P. Blanchet, Vincent Piguet*Service de Dermatologie et Vénérologie, Hôpitaux Universitaires de Genève

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.

Résultats: 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 support that filopodia are obligate components of the HIV-1 induced DC-T cell infectious synapse and are 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 and live imaging. Silencing of Cdc42, a key controller of filopodia formation, in DC by RNAi dramatically reduced number of filopodia on DC and decreased HIV-1 transfer to CD4+ T lymphocytes but did not alter infectious synapse formation. 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.

P33**PROGRESSION OF RADIOGRAPHIC JOINT DAMAGE IN ALCOHOL DRINKERS VERSUS NON-DRINKERS: SHOULD PATIENTS WITH RHEUMATOID ARTHRITIS CEASE DRINKING?**

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Introduction: Alcohol consumption has recently been found to have a protective effect on the development of rheumatoid arthritis (RA). However, it remains unknown whether RA patients who drink alcohol have less severe disease progression over time than non-drinkers. The aim was to compare the rates of radiographic progression in alcohol drinkers (D) and in non-drinkers (ND) in a large prospective RA cohort.

Méthode: All patients in the Swiss Clinical Quality Management in Rheumatic Diseases RA registry database with sequential X-rays were included. Joint erosions were assessed in 38 joints of hands and feet with a validated scoring method (Ratingen score) by a single experienced reader, blinded to clinical history and expressed as a percentage of the maximum damage score. The rate of erosive progression was analysed using a multivariate longitudinal regression model.

Résultats: 2908 RA patients with a median of 4 sequential X-rays and 4 years of follow-up were included. The 1824 D (62.7%) were more often male, younger, smokers, had shorter disease durations, lower DAS28 and HAQ scores, and consequently had less joint erosions at baseline than the ND. After adjusting for differences in baseline prognostic factors, we found a trend towards a reduced rate of radiographic progression in D compared to ND (0.99 v 1.13, p=0.058). In sub-group analyses, a trend for a more favorable evolution existed in the “occasional” consumers (0.99 v 1.13, p=0.096) and the “daily” consumers (0.92 v 1.13, p=0.087), whereas there was no benefit in the “heavy consumers” (1.29 v 1.13, p=0.511). Male D had significantly reduced progression when compared to male ND (0.86 vs 1.35, p<0.01).

Conclusion: A trend towards reduced radiographic progression was observed in D compared to ND, particularly in occasional and daily alcohol consumers. There was a significant protective effect of alcohol on radiographic progression in male RA patients. The clinical significance of these effects is unknown given the relatively small effect size. While a dose-dependent effect was not observed, it may be that low to moderate alcohol consumption is of benefit, as in cardio-vascular disease.

P34**LONGITUDINAL ANALYSES OF RENAL LESIONS DUE TO ACUTE PYELONEPHRITIS IN CHILDREN AND THEIR IMPACT ON RENAL GROWTH**

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Introduction: Acute pyelonephritis is a common condition in children, and can lead to renal scarring. The aim of this study was to analyze the progression of renal scarring with time and its impact on renal growth.

Méthode: A total of 50 children who had renal scarring on dimercapto-succinic acid scan 6 months after acute pyelonephritis underwent a repeat scan 3 years later. Lesion changes were evaluated by 3 blinded observers, and were classified as no change, partial resolution or complete disappearance. Renal size at time of acute pyelonephritis and after 3 years was obtained by ultrasound, and renal growth was assessed comparing z-score for age between the 2 measures. Robust linear regression was used to identify determinants of renal growth.

Résultats: At 6 months after acute pyelonephritis 88 scars were observed in 100 renal units. No change was observed in 27%, partial resolution in 63% and complete disappearance in 9% of lesions. Overall, 72% of lesions improved. Increased number of scars was associated with high grade vesicoureteral reflux ($p = 0.02$). Multivariate analysis showed that the number of scars was the most important parameter leading to decreased renal growth (CI -1.05 to -0.35 , $p < 0.001$), and with 3 or more scars this finding was highly significant on univariate analysis (-1.59 , CI -2.10 to -1.09 , $p < 0.0001$).

Conclusion: Even 6 months after acute pyelonephritis 72% of dimercapto-succinic acid defects improved, demonstrating that some of the lesions may be not definitive. The number of scars was significantly associated with loss of renal growth at 3 years.

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NEUROPSYCHOLOGICAL DISTURBANCES IN FRONTAL LOBE EPILEPSY DUE TO MUTATED

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Introduction: Mutations in nicotinic receptor subunits have been identified in some families with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Normal intelligence has currently been considered the rule, although anecdotal cases with intellectual disability have been reported.

Méthode: We aimed to evaluate the frequency and degree of neuropsychological disorders in ADNFLE associated with nicotinic receptor mutations by testing 11 subjects from four families with a comprehensive neuropsychological assessment.

Résultats: General intellectual function was below the normal range in 45% of the subjects. All were abnormal in one or more executive task. Memory was either more affected than executive functions or equally affected in two thirds of subjects, suggesting a frontotemporal pattern of cognitive impairment.

Conclusion: Cognitive dysfunction appears to be an integral part of the broad phenotype of ADNFLE with nicotinic receptor mutations, a fact that has been underestimated until now. The cognitive disorder affects executive functions as well as memory in most subjects.

P36**EVALUATION OF A LOW-DOSE CT PROTOCOL WITH ORAL CONTRAST FOR ASSESSMENT OF ACUTE APPENDICITIS**

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Introduction: The aim of this study was to evaluate a low-dose CT with oral contrast medium (LDCT) for the diagnosis of acute appendicitis and compare its performance with standard- dose i.v. contrast-enhanced CT (standard CT) according to patients' BMIs.

Méthode: Eighty-six consecutive patients admitted with suspicion of acute appendicitis underwent LDCT (30 mAs), followed by standard CT (180 mAs). Both examinations were reviewed by two experienced radiologists for direct and indirect signs of appendicitis. Clinical and surgical follow-up was considered as the reference standard.

Résultats: Appendicitis was confirmed by surgery in 37 (43%) of the 86 patients. Twenty-nine (34%) patients eventually had an alternative discharge diagnosis to explain their abdominal pain. Clinical and biological follow-up was uneventful in 20 (23%) patients. LDCT and standard CT had the same sensitivity (100%, 33/33) and specificity (98%, 45/46) to diagnose appendicitis in patients with a body mass index (BMI) ≥ 18.5 . In slim patients (BMI < 18.5), sensitivity to diagnose appendicitis was 50% (2/4) for LDCT and 100% (4/4) for standard CT, while specificity was identical for both techniques (67%, 2/3).

Conclusion: Our data suggest that, in patients with BMI > 18.5 , LDCT may replace standard CT for the initial evaluation of patients with suspected appendicitis. Based on these results, a diagnostic algorithm integrating our LDCT protocol is under further evaluation in our department for patients with clinical suspicion of appendicitis.

P37**NATURAL ORIFICE GASTRIC BYPASS SURGERY: EXPERIMENTAL STUDY ON HUMAN CADAVERS***Pugin François¹, Hagen Monika¹, Bucher Pascal¹, Buchs Nicolas¹, Swain Paul², Fasel Jean³, Morel Philippe¹*¹Chirurgie Viscérale, Hôpitaux Universitaires de Genève²Imperial College, London, UK³Secteur d'Anatomie, Centre Médical Universitaire de Genève

Introduction: The growing obesity epidemic represents a major public health challenge. Bariatric surgery is an effective treatment for improvement or remission of comorbidities, like type 2 diabetes, hypertension, dyslipidemia, thus decreasing mortality. Gastric bypass allows achieving rapid and sustained weight loss. Starting our program of bariatric surgery in 1997 with open procedures (> 500 cases), we move to less invasive surgery [laparoscopy (> 300 cases) and then to robotically-assisted laparoscopy (70 cases)]. Natural orifice transluminal endoscopic surgery (NOTES), an emerging and promising technique, may offer a new option for treating obesity, potentially reducing postoperative risks. The aim of this study was to assess feasibility and limitations of a NOTES gastric bypass.

Méthode: Hybrid NOTES gastric bypass (hNOTES-GB) was attempted in seven human cadavers, using our newly designed surgical and technical approach that we will describe.

Résultats: hNOTES-GB was performed successfully completely in four and partially in one cadaver. Two cadavers were unsuitable due to anatomical abnormalities or advanced decay. Combinations of flexible and rigid visualization and manipulation were helpful, especially for dissection and gastric pouch creation. Stapler manipulation, bowel manipulation and measurement presented the main obstacles.

Conclusion: hNOTES-GB is a very challenging and demanding procedure. Combination of flexible and rigid endoscopic techniques offers specific advantages for dissection. New instrumentation development, probably integrating robotic technology, is required to perform this type of complex surgery. This original initial surgical approach has prompted us to imagine newly designed instruments and techniques profitable for the patients.

P38**IDENTIFICATION BY GENOMIC AND GENETIC ANALYSIS OF TWO NEW GENES PLAYING A KEY ROLE IN GLYCOPEPTIDE INTERMEDIATE RESISTANCE**

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Introduction: Glycopeptide antibiotics are first-line agents for treating methicillin-resistant *Staphylococcus aureus* (MRSA) infections, but there is growing concern about emergence of glycopeptide resistant isolates. The mechanism of resistance observed in GISA isolates is considered as endogenous, resulting from multi-factorial mutations gradually selected by exposure to glycopeptides. However, no global model of the molecular mechanisms of glycopeptide resistance has been provided.

Méthode: Using microarrays, we compared the genomic content of teicoplanin-susceptible and resistant strains. The analysis revealed the specific deletion of a 1.8 kb segment, encompassing two adjacent open reading frames (ORFs) of unknown function, in a teicoplanin-susceptible revertant (strain 14-4rev) compared to its isogenic, teicoplanin-resistant parental strain 14-4. This provocative finding prompted us to perform a detailed genetic analysis of the contribution of this genomic segment to glycopeptide resistance

Résultats: Genetic analysis showed that single or double *trfA* and/or *trfB* mutations abolished te icoplanin resistance in two independent teicoplanin-resistant derivatives. The frequency of teicoplanin-resistant mutants was markedly decreased by the absence of *trfAB* in the teicoplanin-susceptible ISP794 background. Nevertheless, a low rate of teicoplanin-resistant mutants was selected from ISP*trfAB*, thus indicating an additional contribution of *trfAB*-independent pathways in emergence of low-level glycopeptide resistance. Further experiments performed with the clinical GISA isolate NRS3 indicated that *trfAB* mutation could affect not only teicoplanin, but also vancomycin and oxacillin resistance.

Conclusion: In conclusion, our study demonstrates the key role of two novel loci in *S. aureus* endogenous, low-level glycopeptide resistance, whose precise molecular functions warrants further investigation.

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COMPETITIVE WEIGHT-BEARING EXERCISE INCREASES DISTAL TIBIA BONE STRENGTH: A HIGH RESOLUTION PERIPHERAL QCT AND FINITE ELEMENT ANALYSIS*René Rizzoli¹, Xavier Martin², Bert van Rietbergen³, Francois Herrmann¹, Thierry Chevalley¹, Nathalie Farpour-Lambert²*¹Div. of Bone Diseases, Dept. of Rehabilitation & Geriatrics²Div. of Pediatric Specialties, Dept. of Pediatrics, Geneva Univ. Hospitals and Faculty of Medicine, Geneva, Switzerland³Dept. of Biomedical Engineering, Eindhoven Univ. of Technology, Eindhoven, The Netherlands

Introduction: Bone repeated loading is associated with increased bone mineral density. The influence of repeated loading on bone microstructure and bone strength in human is not well established.

Méthode: We investigated femoral neck (FN) and total hip (Hip) areal BMD, using DXA, as well as distal tibia cross-sectional area (CSA), cortical thickness (CTh) and density, relative cancellous bone volume (BV/TV), trabecular number (TbNb), thickness (TbTh) and spacing (TbSp), using high resolution computerized tomography (Xtrem-CT, Scanco, Bruettisellen, Switzerland), and distal tibia predicted failure load, stiffness and apparent modulus, using finite element analysis. We studied long distance runners (n=53), tennis (n=21) and basketball (n= 10) players (> 5 hours per week, confirmed by quantifying accelerometry (MTI/CSA Actigraph)) of both sexes (68% of men) (! mean age: 25.8±4.0 yrs), and 113 sedentary controls (22.6±3.7 yrs). Results are means± SD. Analyses are sex-, age-, height- and weight-adjusted.

Résultats: As compared with sedentary controls, competitive exercisers had higher proximal femur aBMD (FN: 1.011±0.152 vs 0.865±0.128 g/cm², p<0.001; Hip: 1.138±0.162 vs 0.964±0.133 g/cm², p<0.001), higher distal tibia microstructure values (CTh: 1.44±0.30 vs 1.24±0.26 microm, p<0.001; BV/TV: 0.19±0.03 vs 0.16±0.03, p=0.001; TbTh: 86±11 vs 83±14 microm, p<0.02). There was no difference in CSA, cortical density, TbNb, or TbSp after adjustments. Finite element analysis was performed in a subset of 78 competitive exercisers and 35 controls. As compared with the latter, the former had higher predicted failure load (14.7E3±2.8E3 vs 12.9E3±2.9E3 N, p<0.001), stiffness (31.3E4±6.1E4 vs 27.3E4±6.4E4 N/mm, p<0.001), and apparent modulus (2.8E3±0.4E3 vs 2.6E3±0.5E3 MPa, p=0.016).

Conclusion: These results indicate that competitive weight-bearing exercise increases distal tibia bone strength, by influencing bone microstructure.

P40**EFFECTIVENESS OF PROSTATE-SPECIFIC ANTIGEN SCREENING IN A POPULATION-BASED COHORT OF MEN WITH PROSTATE CANCER AFTER ACCOUNTING FOR SELECTION, LEAD-TIME, LENGTH-TIME AND OVER-DIAGNOSIS BIASES**

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Introduction: Evaluation of cancer screening efficacy is impaired by biases of selection, lead-time, length-time and over-diagnosis. Prostate cancer offers a unique opportunity to account for these biases as patients managed by watchful waiting are not treated. In this group, survival advantage linked to prostate-specific antigen (PSA) screening can only be attributed to biases. In this population-based cohort study, we consider all biases to better evaluate PSA screening efficacy on prostate cancer mortality.

Méthode: We identified all prostate cancer patients (n=2295) registered in 1990-2001 at the Geneva Cancer Registry. We compared 10-year prostate cancer-specific mortality between screened versus unscreened patients using Cox models. We adjusted for propensity score of having a PSA screening to account for selection bias. We introduced an interaction term between PSA screening and treatment considering untreated patients as the reference to capture other biases. The considered treatments were prostatectomy, radiotherapy with or without hormonal therapy, watchful waiting and other treatments including palliative surgery with one or more adjuvant treatments.

Résultats: Mortality risk reduction linked to PSA screening was present only in patients with curative treatment (p-interaction: 0.003) with a Hazard ratio of 0.22 (95%CI: 0.10-0.49) in operated patients and 0.42 (95%CI: 0.22-0.81) in irradiated patients.

Conclusion: This innovative approach accounting for screening biases suggests that PSA screening confers substantial reductions in prostate-cancer-specific mortality when a positive screen is followed by surgery or radiotherapy.

P41**PET-MEASURED LONGITUDINAL MYOCARDIAL FLOW GRADIENT DURING VASOMOTOR STRESS IN CORONARY RISK INDIVIDUALS WITH OR WITHOUT EPICARDIAL CALCIFICATION**

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Introduction: We investigated possible differences of a longitudinal myocardial flow gradient during pharmacologically-induced hyperemia, reflecting a non-invasive probe of epicardial vasomotor dysfunction, in coronary risk individuals with or without coronary artery calcification (CAC).

Méthode: Myocardial blood flow (MBF) was measured with ¹³N-ammonia and PET/CT in ml/g/min at rest, and during pharmacologic vasodilation with dipyridamole in healthy controls (CON, n=10) and in individuals with coronary risk factors but without CAC (group1) or with CAC (group 2). MBF was assessed globally as mean MBF, and in the mid and mid-distal myocardium of the left ventricle (LV). A decrease in MBF from mid to mid-distal LV myocardium was defined as longitudinal MBF gradient.

Résultats: Compared with CON, the global hyperemic MBF progressively declined in group 1 and group 2 (2.10 ± 0.60 vs. 1.65 ± 0.30 and 1.45 ± 0.48 ml/g/min, respectively; $p < 0.001$), while it did not differ significantly between group 1 and group 2. Absolute MBFs during pharmacologic vasodilation were significantly lower in the mid-distal than in the mid LV myocardium in group 1 and group 2 (1.45 ± 0.25 vs 1.78 ± 0.23 ml/g/min, and 1.35 ± 0.47 vs 1.58 ± 0.52 ml/g/min, $p < 0.0001$), resulting in a MBF gradient that was significantly higher in group1 than in group 2 (0.32 ± 0.15 vs. 0.23 ± 0.11 ml/g/min, $p < 0.0001$), not observed in CON (0.006 ± 0.05 ml/g/min, $p = \text{NS}$). Notably, the MBF gradient in group 1-2 correlated significantly with the mid LV MBF during pharmacologic vasodilation ($r = 0.42$, $p < 0.05$), implicating the velocity of coronary blood flow as an important determinant of the MBF gradient

Conclusion: As it was observed, the hyperemic MBF gradient was more pronounced in coronary risk individuals without CAC than in those with CAC, while it dependent the velocity of coronary blood flow. These preliminary results further emphasize functional and/or structural alterations of the epicardial vessel as prevalent cause for the longitudinal MBF gradient.

P41a**RELATIONSHIP BETWEEN CORONARY CIRCULATORY DYSFUNCTION IN MORBIDLY OBESE PATIENTS AS DETERMINED BY ¹³N-AMMONIA PET/CT AND DXA-MEASURED BODY FAT CONTENT**

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Introduction: We sought to evaluate effects of body fat content obesity on coronary circulatory dysfunction as early functional precursor of coronary artery disease (CAD) in morbidly obese patients (MOB).

Méthode: Myocardial blood flow (MBF) responses to cold pressor test (CPT) and during pharmacologic vasodilation with dipyridamole was measured with PET/CT and ¹³N-ammonia in ten healthy controls (CON) with body mass index (BMI) <25 kg/m² and in eight MOB (BMI>40 kg/m²) without other traditional cardiovascular risk factors. In MOB patients and CON dual x-ray absorptiometry (DXA) determined the body fat content.

Résultats: MOB patients had a mean body fat content of 62±24 kg reflecting 44±4% of the total body mass content. At rest, MBFs between CON and MOB patients were similar (0.10, p=ns), while the CPT-stimulated MBF was significantly ±(0.98±0.15 vs. 1.00 higher in CON than in MOB (1.34±0.09 vs. 0.94±0.08 ml/g/min, p<0.0001). Thus, the resulting endothelium-related change in MBF from rest to CPT (delta-MBF) was significantly less in MOB than in CON (-0.06±0.10 vs. 0.38±0.15 ml/g/min, p<0.0001). Further, the dipyridamole-induced and predominantly endothelium-independent hyperemic MBF was significantly lower in MOB than in CON (1.53±0.28 vs. 2.11±0.30 ml/g/min, p<0.0001). The body fat content of MOB patients inversely and significantly correlated with delta-MBF to CPT and also with the hyperemic MBF (r=-0.56 and r=-0.37, both p<0.05).

Conclusion: Coronary circulatory function is severely altered in MOB patients that in part are directly related to the body fat content. These observations highlight the effects of adipocytokines from the body fat tissue underlying coronary circulatory dysfunction in MOB patients that warrants further investigations.

P41b**DIAGNOSTIC VALUE OF SEMIQUANTITATIVE AND QUANTITATIVE EVALUATION OF PET/CT-MEASURED MYOCARDIAL PERFUSION FOR THE IDENTIFICATION OF FLOW-LIMITING EPICARDIAL STENOSIS**

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Introduction: We aimed to evaluate the diagnostic value semiquantitative and quantitative evaluation of PET/CT-measured myocardial perfusion for the identification of flow-limiting epicardial stenosis.

Méthode: We evaluated 25 consecutive patients with suspected CAD undergoing stress-rest N-13 ammonia cardiac PET/CT. Myocardial perfusion was assessed visually and myocardial perfusion segments were graded on a semiquantitative 5-point scoring system (0=normal, 1=mildly-, 2= moderately -, and 3=severely reduced- and 4=nearly absent perfusion) to derive the summed stress score (SSS) summed rest score (SRS) and summed difference score (SDS). In addition, regional myocardial blood flow (MBF) was determined with PET and tracer kinetic modeling of N-13 ammonia in ml/g/min at rest, during dipyridamole-stimulated hyperemia, $1.7 \leq$ and the corresponding regional myocardial flow reserve (MFR). A regional MFR was considered abnormal. Coronary angiography was performed within 7 days of the 75% was defined \geq cardiac PET/CT study and any epicardial stenosis morphologically significant.

Résultats: On a vessel based analysis, the semiquantitative visual analysis had a sensitivity, specificity, PPV, NPV and diagnostic accuracy of 64%, 100%, 100%, 85% and 87%, respectively. Calculating the regional MFR with PET yielded a sensitivity, specificity, PPV, NPV and diagnostic accuracy of 100%, 47%, 48%, 100% and 64%, respectively. Combining both parameters resulted in an intermediate sensitivity, specificity, PPV, NPV and diagnostic accuracy of 76%, 77%, 58%, 89% and 77%, respectively.

Conclusion: Combining both semiquantitative and quantitative evaluation of myocardial perfusion with PET/CT may emerge as a new promising analytic approach to further optimize the identification and characterization of flow-limiting CAD burden.

P41c**PREVALENCE OF MYOCARDIAL VIABILITY IN ELDERLY PATIENTS WITHOUT ANGINA PECTORIS BUT WITH ISCHEMIC CARDIOMYOPATHY AS DETERMINED BY 201TI-SPECT AND FDG-PET/CT**

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Introduction: To determine the prevalence of viable myocardium in elderly patients without angina pectoris but with ischemic cardiomyopathy

Méthode: In thirty patients aged >70 years and without chronic angina pectoris but with dyspnea, the combination of perfusion and metabolic imaging with 201thallium (201TI) single-photon emission computed tomography (SPECT) and 2-deoxy-2-[18F] fluoro-D-glucose (FDG) PET/CT determined viability in dysfunctional myocardium. 201TI and FDG uptake defects were graded visually on a four-point scale: 0= normal, 1=mildly reduced, 2= moderately reduced and 3 = severely reduced. A concordant reduction in 201TI and FDG activity scores was classified as a blood flow/metabolism match, subsequently referred to as nonviable myocardium. A reduction in 201TI uptake more severe than the reduction in glucose metabolic activity by >1 point was defined as a blood flow/metabolism mismatch, subsequently referred to as viable myocardium

Résultats: All patients (mean age 76±5, range: 70-84 yrs) were in the NYHA functional class II and III and presented a mean left-ventricular ejection fraction of 38±7%. Thirteen (43%) had a history of myocardial infarction, and 14 (46%) had undergone previous PCI or coronary artery bypass surgery. On standard visual analysis 9 (30%) showed perfusion-metabolic matches (nonviable myocardium), and 21 (70%) had perfusion metabolic mismatches (viable myocardium). Both, mismatches and matches coexisted in 2 patients (6%). 201TI -Tracer uptake as index of myocardial flow was more severely reduced in viable than non-viable myocardium (1.80±0.78 vs. 2.3±0.83, p< 0.0001), while there was a considerable overlap.

Conclusion: Based on the presence of viable dysfunctional myocardium, 70% of elderly patients with ischemic cardiomyopathy may be considered for coronary revascularization. Whether coronary revascularization of viable myocardium in elderly patients also translates into an improvement of symptoms and clinical outcome remains to be investigated.

P42**HIGH EFFICIENCY PRODUCTION AND PURIFICATION OF ⁸⁶Y BASED ON ELECTROCHEMICAL SEPARATION***Dragoljub Lukic^{1,2}, Claire Tamburella², Franz Buchegger², Gerd-Jurgen Beyer², Jozef J. Comor³ Yann Seimbille²*¹Laboratory of Radioisotopes, Vinca Institute of Nuclear Sciences, Belgrade, Serbia²Department of Radiology, University Hospital of Geneva³Laboratory of Physics, Vinca Institute of Nuclear Sciences, Belgrade, Serbia

Introduction: In recent years particular emphasis has been devoted to the long half-life positron emitter ⁸⁶Y (T_{1/2}=14.7 h), which was found to be very important for therapy optimization of ⁹⁰Y-based radiopharmaceuticals

Méthode: Optimization of the electrochemical separation and purification of ⁸⁶Y from the target material was initially done by modeling the production cycle using ⁹⁰Y. In the first step, two Pt plate anodes and a Pt Winkler cathode were used. Electrodeposition yield was determined for constant current between 30-3000 mA. Influence of the pH and temperature on recovery of ⁸⁶Y was also investigated. The second electrolysis was performed at 200-400 mA by using the Winkler electrode and a Pt wire, respectively as anode and cathode.

Résultats: After bombardment of enriched ⁸⁶SrCO₃, the target material was dissolved in HNO₃ and conditioned with NH₄OH. Subsequently, ⁸⁶Y was isolated by means of two electrolytic steps performed according to the optimized conditions previously identified using ⁹⁰Y. Thus, the first electrolysis was realized under 2000 mA for 30 min, while the second electrolytic step was done at 400 mA for 15 min. Deposit of ⁸⁶Y on the Pt wire was then collected with 200 ul of CH₃COONa buffer (pH 4.6), providing a solution which is directly applicable for labeling of biomolecules. Recovery of ⁸⁶Y from the target material resulted in an overall yield of 93.6% normalized to EOB. Specific activity of ⁸⁶Y was also determined (0.2 Ci/umol), and was comparable with highly pure commercially available ⁹⁰Y.

Conclusion: Our process is faster and simpler than the previous reported electrochemical methods. Our method is also non pH-dependant and more convenient for automation of the routine production of ⁸⁶Y.

P43**ACCURACY OF EEG SOURCE IMAGING OF EPILEPTIC SPIKES IN PATIENTS WITH LARGE BRAIN LESIONS***Verena Brodbeck¹, Agustina M. Lascano¹, Laurent Spinell², Margitta Seeck², Christoph M. Michel¹*¹Functional Brain Mapping Laboratory, University Hospital Geneva²Presurgical Evaluation Unit, Neurology Clinic, University Hospital Geneva

Introduction: To test the accuracy of EEG source imaging in epilepsy patients with large cerebral lesions. It is hypothesized that lesions are most likely to change conductivity properties and to significantly impair the accuracy of electromagnetic source imaging (ESI) based on the EEG. This has, however, not been tested in patients' EEG.

Méthode: Fourteen patients with focal epilepsy and large cerebral lesions underwent high-resolution (128–256 channels) interictal EEG recordings. Thirteen patients were operated, leading to seizure freedom in 12. The spike sources were localized with a distributed linear inverse solution (LAURA) and compared to the post-operative MRI or the results of other invasive or non-invasive exams.

Résultats: In 12 patients ESI indicated the maximum source of the epileptic activity to be located within the epileptogenic zone (85%). One of the remaining cases was not seizure free after surgery. According to the ESI result, however, the focus was incompletely removed.

Conclusion: High resolution ESI constrained to the individual anatomy identifies the epileptogenic focus in patients with volume relevant brain lesions with excellent accuracy, comparable to that of other non-invasive methods.

P44**CAN THE GASTROCOLIC TRUNK OF HENLE SERVE AS AN ANATOMICAL LANDMARK IN LAPAROSCOPIC RIGHT COLECTOMY? A POSTMORTEM ANATOMICAL STUDY**

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Introduction: The use of the gastrocolic trunk of Henle (GTH) as a landmark has been advocated in laparoscopic right colectomy. Aim - to evaluate the GTH as a possible landmark in laparoscopic right colectomy, in the context of the adjacent arteries.

Méthode: Material and methods - corrosion casting (30 specimens) and anatomical dissection on formol-fixed cadavers (12 specimens).

Résultats: The GTH was found in 34 specimens (81.0%). Among its close-related neighboring arterial vessels, the right colic artery was the most frequent one (19 cases, 55.9%). It passed by the GTH at a distance of 3.6 mm (mean). The course of the arteries in relation to the GTH was caudal and parallel in the majority of cases – 29 (85.3%), but there was also a significant portion of crossing schemes (11.7%).

Conclusion: Although the GTH is a constant and conspicuous anatomical entity, it is not easily accessible due to its tight relations to the right colon arteries. Instead, we advocate the use the superior right colic vein as an anatomical landmark leading to the GTH, during laparoscopic right colectomy.

P45**EFFET DES DIFFERENTES DISCIPLINES SPORTIVES SUR LES VARIATIONS JOURNALIERES DU SYSTEME NERVEUX AUTONOME***Juan Sztajzel¹, Michel Jung¹, Katia Sievert¹, Antonio Bayes de Luna²*¹Service de Cardiologie et SMIG, Hôpitaux Universitaires de Genève²Institut Catalan des Sciences Cardiovasculaires, Hôpital San Pau, Barcelone, Espagne

Introduction: L'exercice physique et le sport ont un effet bénéfique sur le système nerveux autonome ainsi que sur ses répercussions cardiaques. Cependant, l'impact précis des différentes disciplines sur l'activité cardiaque autonome reste actuellement mal connu.

Méthode: Nous avons étudié les variations de l'activité cardiaque autonome journalière en utilisant une méthode électrocardiographique non invasive, la variabilité de la fréquence cardiaque (VFC), analysée à partir d'enregistrements Holter de 24 heures chez 12 athlètes (29±5 ans) pratiquant des disciplines sportives d'endurance (cyclisme, marathon), chez 14 (26±3 ans) pratiquant un sport d'équipe (hockey) et chez 14 volontaires (29±3 ans) sans entraînement physique particulier (groupe contrôle). Une VFC diminuée représente un risque augmenté d'événements cardiaques majeurs.

Résultats: Toutes les valeurs de la fréquence cardiaque sur 24 heures étaient plus basses et tous les indices de la VFC reflétant la composante parasympathique étaient plus élevés chez tous les sportifs comparés au groupe contrôle. Toutefois, le paramètre de la VFC déterminant l'équilibre sympatho-vagal global était meilleur seulement chez les sportifs d'endurance.

Conclusion: L'activité physique induit une augmentation du tonus parasympathique aussi bien chez les sportifs d'endurance que ceux d'un sport d'équipe. Cependant, seuls les sportifs pratiquant une discipline d'endurance présentent un profil cardiaque autonome global meilleur, dénotant par là que ce type d'activité physique peut jouer un rôle cardio-protecteur plus important.

P46 – non affiché

NEW INSIGHTS INTO RHINOVIRUS AND ENTEROVIRUS DIVERSITY

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Introduction: Human rhinoviruses (HRV) are divided into 3 species, HRV-A, B and C and are closely related to human enteroviruses (HEV). Despite common genomic features, these viruses present different phenotypic characteristics; rhinoviruses are restricted to the respiratory tract, whereas enteroviruses infect the gastrointestinal tract and can spread to other sites such as the central nervous system. Both viruses are characterized by an important genetic variability. Our goals were 1) to identify genomic features supporting the different phenotypes between HRV and HEV and 2) to study the molecular epidemiology of circulating strains.

Méthode: We achieved the complete genome sequence of HRV reference serotypes, enabling a phylogenetic comparison of HRV and HEV at the polyprotein level. We then screened a large number of persons with acute respiratory diseases by using assays designed to overcome the diversity of rhinoviruses and enteroviruses circulating in humans. Whenever possible, we systematically sequenced 5' untranslated region, capsid protein VP1, and protease precursor regions of strains.

Résultats et conclusions: The phylogenetic comparison of HRV and HEV revealed that HRV-A are closer to HEV than to HRV-B except for the capsid proteins. This analysis also led to the characterization of new cis-acting replication elements. Second, the screening and sequencing of circulating strains (1) revealed that the number of HRV genotypes circulating in a given population is very large, (2) led to the identification of a new enterovirus genotype with a respiratory tropism and (3) allowed to demonstrate that in its natural host, rhinoviruses can also evolve by recombination.

P47**LOW INCIDENCE OF HEMATOGENOUS SEEDING TO TOTAL HIP AND KNEE PROSTHESES IN PATIENTS WITH REMOTE INFECTIONS***Ilker Uçkay, Anne Lübbeke, Stéphane Emonet, Luisa Tovmirzaeva, Richard Stern, Tristan Ferry, Mathieu Assal, Daniel Lew, Pierre Hoffmeyer*

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Introduction: The exposure of joint prostheses to remote infections is unknown. We wanted to estimate a) the exposure of arthroplasty patients to severe remote infections, and b) the incidence of secondary arthroplasty infections.

Méthode: Prospective cohort study of all elective hip and knee arthroplasties performed March 1996 - September 2008. Retrospective documentation of remote infections in hospitalized patients.

Résultats: A total of 6,101 elective total joint arthroplasties, 4,002 hip replacements (66%) and 2,099 knee replacements (34%), were included. The mean follow-up was 70 months. During the study period, the cohort patients experienced 553 remote infections after a median delay of 33 months post-arthroplasty. Furthermore, 71 prosthetic infections were detected, of those 7 (total incidence 7/6101, 0.1%) were secondary to a remote infection. The ratio of secondary infection to potential exposure was 1:79. Among hip arthroplasty patients the incidence rate was 1.4 secondary infections per 10,000 patient-years of follow up. Secondary infections occur red later than surgical site infections, (46 months vs. 19 months post-surgery, respectively; mean difference 27 months, 95%CI 8-45 months).

Conclusions: Secondary arthroplasty infections were rare compared to surgical site infections. Secondary infections and potential exposure occurred most often 24 months post-arthroplasty.

P47a**INFECTIOUS OLECRANON AND PATELLAR BURSITIS: EPIDEMIOLOGY AND RISK FACTORS FOR RECURRENCE IN ADULT HOSPITALIZED PATIENTS**

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Introduction: To characterize the epidemiology and risk factors for recurrence of septic olecranon and patellar bursitis in hospitalized patients.

Méthode: Case-control study at Geneva University Hospitals.

Résultats: We identified 343 episodes of infectious bursitis (237 olecranon, 106 patellar). *Staphylococcus aureus* predominated among the 256 cases with an identifiable pathogen (85%). 312 cases (91%) were treated surgically, 142 (46%) with bursectomy and closure in one-stage, 146 in two-stage. All received antibiotics for a median duration of 13 days with a median intravenous component of 3 days. Patients with one-stage bursectomy received a shorter antibiotic therapy than patients with multi-stage bursectomy (11 vs. 15 days) and were hospitalized shorter (6 vs. 10 days, Wilcoxon ranksum tests, $p < 0.001$). Cure was achieved in 293 (85%) episodes. Recurrences occurred often multiple times in the same individuals. In multivariate analysis, only immunosuppression was linked to recurrence (odds ratio 5.6, 95%CI 1.9-18.4), in contrast to age (OR 1.0, 1.0-1.1), Charlson Comorbidity Score (OR 1.5, 1.0 -2.1), one-stage bursectomy (OR 3.5, 0.6-21.0), or interval between bursectomy and closure (OR 1.0, 0.9-1.1). Total duration of antibiotic treatment (OR 0.9, 0.8-1.1) showed no association. Compared to ≤ 7 days, 8 to 14 days (OR 0.6, 0.1-2.9) or > 14 days of treatment (OR 0.9, 0.1-10.7) were equivalent as was the intravenous component (OR 1.1, 1.0-1.3). In a subgroup analysis of only immunocompromised patients, no surgical and medical parameter influenced cure.

Conclusions: In severe infectious bursitis requiring hospitalization, bursectomy and closure can be performed in one intervention. Adjuvant antibiotic therapy might be orally and be limited to seven days; saving antibiotics and hospitalization time. Immunosuppression is a risk for recurrence and difficult to compensate by surgical and medical parameters. The accumulation of recurrence in few patients suggests unknown endogenous risk factors.

P47b**SURGERY AND SIX WEEKS' ANTIBIOTIC TREATMENT ARE SUFFICIENT FOR PROSTHETIC INFECTIONS OF THE HIP AND KNEE**

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Introduction: The benefit of a prolonged antibiotic treatment of prosthetic joint infections (PJI) beyond 6 weeks after surgery is uncertain. We compare the incidence of cure according to the duration of antibiotic therapy (6 vs. 12 weeks).

Méthode: Case-control study including patients with hip and knee PJI.

Résultats: A total of 144 PJI (75 episodes in women) were retrieved: 62 total hip, 62 total knee arthroplasties, and 20 hip medullary prostheses with a median follow-up of 36 months post-surgery. 84 episodes (58%) were due to Staphylococcus sp, of which 26 due to methicillin-resistant S. aureus (MRSA). Median number of surgical interventions for curative purposes was 1 including 60 debridements with implant retention, 10 one-stage exchanges, 57 two-stage exchanges, and 17 Girdlestone/arthrodesis procedures. 70 episodes (49%) were treated with 6 weeks, 74 with 12 weeks of antibiotics. Cure was achieved in 115 episodes (80%) independently of surgical procedures and antibiotic treatment. When adjusted in multivariate analysis, no single parameter was associated with cure: Retention with debridement (odds ratio 0.3, 95%CI 0.1-1.1); two-stage exchange (OR 1.1, 0.2-4.8); number of surgical debridements (OR 0.9, 0.4-1.9); six weeks' antibiotic treatment (OR 2.7, 0.96-7.8); duration of intravenous antibiotic course (OR 1.0, 1.0-1.0); presence of sinus tract (OR 0.6, 0.2-1.7); or MRSA infection (OR 0.5, 0.2-1.5). 18/20 episodes (90%) with implant retention and six weeks' antibiotic treatment were cured. Cure incidence in patients treated with parenteral antibiotics alone was similar to those treated by oral antibiotics alone (36/47 vs. 5/6, Fischer exact-test, p=1).

Conclusions: Provided that surgery has been performed, antibiotic treatment for PJI can be limited to 6 weeks postoperatively, with only few days of intravenous administration.

P47c**SHORT PARENTERAL ANTIBIOTIC TREATMENT FOR NATIVE SEPTIC ARTHRITIS AFTER SUCCESSFUL DRAINAGE-DEBRIDEMENT**

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Introduction: The ideal duration of antibiotic treatment in the therapy of septic native joint arthritis is unknown. We assess the epidemiology of septic arthritis at Geneva University Hospitals, with emphasis on surgical and medical treatment parameters.

Méthode: Case-control study

Résultats: A total of 169 episodes in 157 patients (median age 63 years, 65 females) were retrieved. The infected joints were: knee (n=51), hip (n=21), shoulder (n=32), ankle (n=9), sterno-clavicular (n=2), elbow (n=2), sacroiliac (n=1), and interdigital (n=43). In 21 episodes (21/169, 12%), arthritis recurred after the end of antibiotic treatment. In multivariate analysis, lack of surgical intervention (odds ratio 11.3, 95% confidence interval 2.7-46.2), Gram-negative infection (OR 5.9, 1.4-25.3), and immunosuppression (OR 5.3, 1.3-22) were significantly associated with recurrence, while open arthrotomy vs. arthroscopic drainage (OR 0.5, 0.2-1.8), total duration of antibiotic therapy (OR 1.0, 1.0-1.0), or duration of intravenous antibiotic therapy (OR 1.0, 1.0-1.0) were not. Seven days of intravenous therapy had the same effect than 8 to 15 days (OR 0.4, 0.1-1.7) or < 21 days of intravenous treatment (OR 1.1, 0.4-3.1). 2 weeks of total antibiotic treatment had the same outcome as a therapy of 2 to 4 weeks (OR 0.4, 0.1-2.3) or > 4 weeks (OR 0.4, 0.1-1.6).

Conclusions: Among modifiable parameters, at least one surgical intervention is of utmost importance in the treatment of septic native joint arthritis. The modalities of concomitant antibiotic therapy are secondary. Selected antibiotics might be administered orally after few days of parenteral regimen for a total duration of two weeks.

P47d**MINIMAL INFECTION RISK OF ELECTIVE TOTAL JOINT ARTHROPLASTY INFECTIONS DUE TO METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS INFECTIONS DESPITE HIGH ENDEMICITY**

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Division of Orthopaedics, Service of Infectious Diseases, HUG Service of Infectious Diseases

Introduction: To investigate the incidence of arthroplasties infections due to MRSA in Geneva University Hospitals (MRSA endemicity of 30%) and its association with patients' MRSA carriage.

Méthode: We performed a prospective cohort study of elective knee and hip joint total arthroplasties performed March 1996-September 2008. Retrospective MRSA data from the Laboratory of Bacteriology.

Résultats: We performed a prospective cohort study of elective knee and hip joint total arthroplasties performed March 1996-September 2008. Retrospective MRSA data from the Laboratory of Bacteriology.

Conclusions: A high MRSA endemicity and the proportion of MRSA-colonized patients do not influence MRSA infection risk of elective total hip and knee arthroplasty. Provided that surgery is correctly performed, and hand hygiene and other prevention issues are respected, the total incidence of MRSA infections may remain very low.

P47e**OUTCOME OF ORTHOPAEDIC IMPLANT INFECTIONS DUE TO DIFFERENT STAPHYLOCOCCI**

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Introduction: Reports of the clinical impact of different staphylococci in orthopaedic implant infections are rare. We want to assess the features of all orthopaedic implant infections due to methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA) and coagulase-negative staphylococci (CoNS).

Méthode: Retrospective study at the Geneva University Hospitals.

Résultats: There were 44 infections due to MRSA, 58 due to MSSA, and 61 due to CoNS. Cure was achieved in 57% (25/44), 72% (42/58), and 82% (50/61) of all infections, respectively. In the subgroup of arthroplasty infections, cure was achieved in 39% (7/18), 60% (15/25), and 77% (30/39), respectively. In multivariate logistic regression analysis, arthroplasty (odds ratio (OR) 0.2, 95%CI 0.1-0.6) and MRSA infections (OR 0.3, 0.1-0.9) were inversely associated with cure, whereas CoNS infection (OR 3.0, 1.2-8.0) and the insertion of a new implant (OR 4.5, 1.6-13.1) enhanced cure. Methicillin-resistance, immunosuppression, sex, age, duration of antibiotic therapy, implant removal, the proportion of one-stage revisions, rifampin use, and the number of surgical interventions did not influence cure. Two patients died secondary to *S. aureus* bloodstream infection. MR! SA-infected patients had significantly more post-infection sequelae than patients with MSSA or CoNS (χ^2 -test 13/44 vs. 93/ 119, odds ratio 3.4, 95% confidence interval 1.3-8.9, $p=0.004$).

Conclusions: In orthopaedic implant infections, *S. aureus* is more virulent than CoNS. MRSA has the worst outcome and CoNS the best.

P47f**ACTIVITY AND IMPACT ON ANTIBIOTIC USE AND COSTS OF A DEDICATED INFECTIOUS DISEASES CONSULTANT ON A SEPTIC ORTHOPAEDIC UNIT**

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Introduction: The Orthopaedic Service of the Geneva University Hospitals engages dedicated infectious disease (ID) specialists to assist in the treatment of infected patients. We investigated the daily clinical activity and the impact on antibiotic costs in the Septic Unit since 2000

Méthode: Retrospective analysis of various databases. Prospective survey of clinical activity from January 2008 to March 2008.

Résultats: According to the survey, the ID specialist performed 265 first-time and 1420 follow-up consultations (average of 11.4 consultations per working day). In 88% of cases the antibiotic regimen initiated by the surgeons was approved. When the ID specialist had to change antibiotic treatment, it was for de-escalation in 43.7%, discontinuance in 32.4%, and initiation in 24.4% of cases. From April 2007 to March 2008, the ID specialist decreased total antibiotic use by 43 DDD/100 patients-days ($p < 0.0006$) in the Septic Unit. Direct antibiotic costs decreased by US\$64,380 over the same period, equal to the annual salary of the ID specialist. There was no change in the number of recurrent infections

Conclusions: A dedicated Infectious Disease specialist may substantially reduce antibiotic use and related costs in a Septic Orthopaedic Unit

P48**THE IMPORTANCE OF AN INTERNATIONAL HYPOTHERMIA REGISTRY FOR IMPROVING THE OUTCOME OF ACCIDENTAL HYPOTHERMIA VICTIMS**

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Introduction: Transient mild hypothermia is common and usually without consequences for the brain or other organs. However, prolonged deep hypothermia due to accidents is relatively rare and usually associated with premature death due, in part, to the lack of evidence-based guidelines.

Méthode: We created an internet-based International Hypothermia Registry to collect and analyse relevant information about accidental hypothermia in the hope of establishing guidelines for prevention, treatment and outcome of such victims. In a pilot phase, we analysed 6 cases treated in our centre in 2008. The predominant cause was suicide attempts followed by cold exposure.

Résultats: Three victims survived with minor damage, three died shortly after rewarming. The three surviving victims had witnessed cardio-respiratory arrest and core temperatures below 26°C. All victims arrived with CPR, were rewarmed with CPB, and could be discharged without sequelae. The three non-surviving victims were young, without vital signs at rescue (2/3 with questionable asphyxia) with core temperatures between 28° and 29°C and normal potassium levels. However, all were pronounced dead in the operating room, after successful rewarming and weaning from CPB, due to fulminant haemorrhagic pulmonary oedema.

Conclusions: Our limited experience from 2008 shows once again the importance of witnessed cardiac arrest combined with deep hypothermia for a positive outcome. The three fatal cases were in cardiac arrest of unknown time and most likely not attributable to hypothermia. The entry of these pilot cases in our internet-based International Hypothermia Registry was helpful to standardise the data in order to elaborate better outcome predictors.

P49**A NATIONAL SCREENING PROGRAM FOR BILIARY ATRESIA: A PILOT PROJECT***Barbara E. Wildhaber, Dominique Belli*

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Introduction: Biliary Atresia (BA) is a rare, neonatal disease characterized by bile duct obstruction. Untreated BA progresses towards biliary cirrhosis, and leads to death within a few years. BA treatment is sequential: in the neonate a porto-enterostomie (PE) is performed to reconstitute bile flow; in case of progression towards cirrhosis, liver transplantation (LT) becomes inevitable. The earlier (at best <45 days of life) PE is performed, the better the child's chances to live with its own liver, hence pediatric LT is avoided. In Switzerland median age at PE is late 68 days.

Méthode: Feces of BA babies are of gray-whitish color. Thus, BA can easily be diagnosed by observing the baby's stool color. Thus a stool color card (SCC) was designed showing different - normal and abnormal - stool colors. Parents receive the SCC after birth. One month thereafter the pediatrician 1) communicates the stool color to the coordination centre, and 2) in case of abnormal stool color performs urgent investigations. The coordination centre will later contact the physician of babies having an abnormal stool color to know the final diagnosis. The SCC original – signed by the parents, who that way give their consent for data transfer - remains in the baby's medical file.

Résultats: Etude de faisabilité à long-terme, résultats attendue en 2012.

Conclusions: This simple screening using a SCC aims to reduce the age at diagnosis of BA, to reduce the age when PE is performed, and to reduce the need for pediatric LT. Thus, the expected benefit is for the patient, as well as for the community.

P50**GRID COMPUTING INSIDE HOSPITALS USING VIRTUALIZATION TECHNOLOGY: A SECURE SOLUTION FOR HEAVY COMPUTING TASKS***Xin Zhou, Adrien Depeursinge, Marko Niinimaki, Antoine Geissbuhler, and Henning Müller*Service d'Informatique Médicale, Hôpitaux Universitaires de Genève

Introduction: The ever-increasing production of medical images requires higher computing power for analysis. Like most hospitals, until now HUG do not have any central computing infrastructure for researchers to execute computationally intensive applications. Using external computing resources can cause legal problems due to the patient data transfer. On the other hand, over 6'000 desktop computers are available inside HUG. Even a partial re-use of these resources could help to fulfil researchers' computational needs. The whole infrastructure is built up based on the ARC (Advanced Resource Connector) middleware.

Méthode: 20 desktop PCs of HUG are used as a test-bed for our intra-hospital Grid. On each machine a virtual Linux operating system was installed. This virtual machine serves as a computing node separated from the user's system. All components can be installed fully automatically and remotely (standard solution of HUG based on Microsoft active directory). The infrastructure is evaluated based on the usability and the possible disturbance of HUG network (through data transfers or slowing the desktop system).

Résultats: The infrastructure shows to be robust, and allows faster computation time than an expensive server used for comparison. The data transfers do not disturb the network. On recent desktop computers with dual core processors and 2GB of RAM (80% of the computers at HUG by mid 2009) the delay is almost unrecognizable.

Conclusions: An internal computation Grid was created to support researchers. Tests are based on medical image retrieval applications. Further extension of the Grid system can be foreseen to make the infrastructure available to a larger community and new applications.

Thème

L'information écrite destinée aux participants d'un essai clinique.

Bernard Hirschel, Samia Hurst

Le processus par lequel une personne consent à sa participation à une recherche ne se limite pas à la signature d'un document écrit, mais comporte également l'information orale donnée par l'investigateur, les réponses aux questions des patients, le temps de réflexion et de discussion avec des proches. Les documents écrits constituent néanmoins une partie importante de ce processus et méritent qu'on y consacre réflexion et efforts.

1. Bases légales

Art. 54 de la loi fédérale sur les médicaments et les dispositifs médicaux :

- 1/ Pour que des essais cliniques puissent être effectués, il faut notamment:
 - a. que les sujets de recherche aient donné leur consentement libre, exprès et éclairé, par écrit (...), après avoir été informés notamment sur:
 1. la nature et le but de l'essai;
 2. l'ensemble des actes et des analyses impliqués;
 3. l'existence d'autres traitements que ceux prévus dans l'essai;
 4. les risques, les inconforts et les bénéfices prévisibles;
 5. leur droit à une compensation en cas de dommages imputables à l'essai;
 6. leur liberté de retirer leur consentement à tout moment sans préjudice pour leur prise en charge thérapeutique (...)

Art 6 de l'ordonnance sur les essais cliniques (OClin)

- 1/ Dans le cadre d'un essai clinique, la protection des sujets de recherche doit être garantie (...).
- 2/ Le consentement éclairé des sujets de recherche doit être recueilli avant chaque essai clinique. Les exigences figurant au ch. 4.8 des Directives ICH (art. 4) doivent être respectées.

Le chapitre 4.8. des Directives de la conférence internationale d'harmonisation ICH fait partie d'un document de 59 pages décrivant les exigences gouvernant les essais cliniques. Ce chapitre traite de l'information du patient et contient notamment une liste de 20 points qui doivent être mentionnés dans la formule d'information et de consentement.

3. Qu'est-ce qui est raisonnable ?

Revenons au chapitre 4.8. du document qui décrit les bonnes pratiques cliniques. Dans la longue liste des sujets à mentionner il y a le point g) : «Les risques et inconvénient raisonnablement prévisibles...". Mais que veut dire "raisonnablement prévisibles..."?

Prenons, comme exemple, cet extrait d'une formule d'information récemment soumise au comité d'éthique du Département de Médecine:

"Des réactions allergiques graves peuvent se manifester par un arrêt du cœur et de la respiration. Dans ce cas, vous serez couché par terre, ou sur une table, ou une planche sera placée sous votre dos. Un soignant ou une soignante se mettra en califourchon sur vous et pressera sur votre sternum de manière rythmique pour faire circuler votre sang. Parfois, cette procédure résulte en des fractures de côtes. Un choc électrique peut être nécessaire pour redémarrer votre cœur. Un tube sera placé dans votre trachée et votre respiration sera assistée à l'aide d'un ballon. Aucune garantie quant à l'efficacité de ces mesures ne peut être donnée" (et ainsi de suite).

Il s'agissait de la phase 2 d'un médicament que nous appellerons X. Un des sujets ayant reçu X pendant la phase 1 s'était plaint de démangeaisons et de vertiges ; sa tension était normale; les symptômes ont disparu après la prise d'un antihistaminique.

Sachant cela, est-il raisonnable d'évoquer de manière drastique la possibilité d'un choc anaphylactique ? En l'occurrence, le comité d'éthique a décidé que non, et a demandé aux promoteurs d'enlever ce paragraphe.

CRC INFO

Bulletin 3

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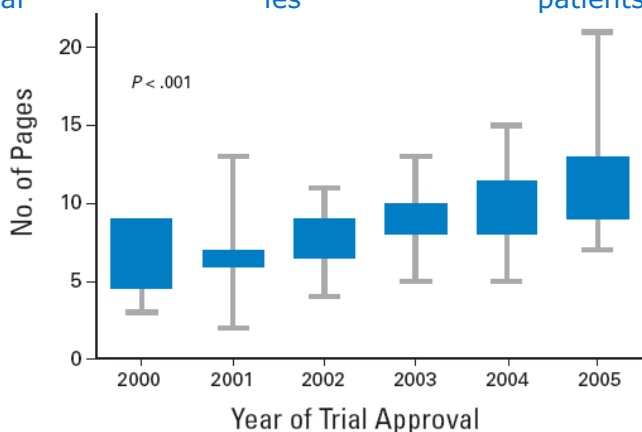
<http://crc.hug-ge.ch>

Un deuxième exemple: le raltegravir. Il s'agit d'un nouveau médicament anti-VIH auquel, jusqu'à présent, aucun effet secondaire ne peut être attribué. Ce médicament fut testé d'abord chez des patients très immunosupprimés, avec un virus résistant aux anciens anti-rétroviraux, en combinaison avec d'autres médicaments. Evidemment, de multiples événements adverses furent observés ; certains étaient dus à l'infection VIH sous-jacente, d'autres causés par les médicaments co-administrés.

Comment faut-il informer les patients ? Est-il raisonnable d'énumérer tous les malheurs qui sont arrivés à leurs prédécesseurs, même en absence de relation plausible avec le raltegravir ?

4. Longues...

A cette question, la plupart des formules d'information et de consentement proposé par des promoteurs industriels répondent résolument par "OUI". Elles ont donc tendance à s'allonger (voir graphique) et peuvent dépasser les 20 pages et 10'000 mots. A titre de comparaison, le New England Journal of Medicine limite la longueur de ces articles principaux à 2700 mots. Les formulaires trop longs ne sont ni lus ni compris par les patients.



5. ... et compliquées

"Dans un effort d'établir des corrélations étiopathogéniques, les investigateurs peuvent être amenés à pratiquer des ECG, portant une attention particulière à l'intervalle QTc, en accord avec les critères établis par les instances régulatrices tels que FDA, EMEA et Swissmedic, et tout en respectant les exigences de confidentialité et de protection des données selon les exigences légales".

Il s'agit, vous l'aurez compris, encore une fois d'une citation d'un protocole existant, passant largement en dessus de la tête des sujets de recherche (et de la plupart des médecins). L'exemple est malheureusement commun ; même si en théorie tout le monde exige simplicité et clarté, la pratique est à l'opposé. Les études et la pratique médicales peuvent induire une incapacité de s'exprimer simplement... C'est vrai aux Etats-Unis mais également en France, ou notre collègue Hummel a démontré comment les comités d'éthique ajoutaient des complications additionnelles à des formules déjà indigestes

6. Vers une solution

1. Longueur. Si le NEJM peut restreindre ses auteurs à 2700 mots, les comités d'éthiques peuvent faire pareil. Ainsi, le comité du Département de Médecine exige un résumé, chaque fois que la formule dépasse trois pages.
2. Formules toutes faites. La plupart des points mentionnés dans le chapitre 4.8. du document ICH-GCP concernent des informations standard – confidentialité, annonce qu'il s'agit de recherche, couverture en cas d'accident etc. Ces formules se répètent dans tous projets, et sont disponibles sur le site du CRC. Il ne sert à rien de réinventer la roue.
3. Pertinence. L'explication des risques (et des bénéfices) doit porter sur ceux qui sont *liés à la participation à l'étude*. C'est à dire ceux que les participants n'auraient eus s'ils avaient refusé leur consentement. Inclure tous les risques liés à la maladie sous-jacente, ou à des traitements qui auraient été administrés de toute manière, est un obstacle à la compréhension des enjeux de l'étude.
4. Mesurer la complexité de l'information et simplifier si nécessaire. L'ordinateur permet de mesurer la complexité de votre texte, par utilisation des échelles de Flesch et de Kincaid disponible sous Word ou d'un logiciel spécialisé français. En anglais, voici un guide pratique pour formuler de manière plus claire et plus simple. On peut compléter ces vérifications en demandant une relecture à une personne extérieure à la médecine...

version avec liens et annexes sur le site du CRC
http://crc.hug-ge.ch/bulletins_CRC.html

SOPAV1.4 : DOCUMENTS DESTINÉS AUX PERSONNES SE PRÊTANT À LA RECHERCHE

Rédaction : J. Chabert

Révision : I. König et J. Chabert 04/2009

Approuvé par : J. Desmeules

Signature



Version : GeV4

Date 04/05/2009

1. Introduction

Lors de l'élaboration de la lettre d'information et du formulaire de consentement informé, l'investigateur doit se plier aux exigences réglementaires et adhérer aux normes des bonnes pratiques cliniques qui découlent de la déclaration d'Helsinki dans sa dernière version.

2. But

Informier l'investigateur des éléments devant figurer dans les divers documents relatifs à l'information aux sujets de recherche, en conformité avec la réglementation internationale et nationale, et les exigences de la Commission Centrale d'Ethique de la Recherche sur l'être humain des HUG.

3. Responsabilités

La rédaction de l'information patient et du consentement éclairé peut-être le fruit d'une co-rédaction par le promoteur et l'investigateur. La responsabilité d'informer le sujet de recherche et de recueillir son consentement éclairé écrit incombe exclusivement à l'investigateur. Si le texte des documents destinés aux sujets de recherche doit être modifié au cours de l'étude, il doit être réexaminé par la commission d'éthique dans la cadre d'un amendement (ICH E6 4.8.2).

4. Lettre d'information

- elle doit être écrite de manière claire, intelligible, dans la langue des sujets de recherche. Les termes techniques sont à proscrire, ou à expliciter clairement (ICH E6 4.8.6).
- un temps de réflexion suffisant doit être accordée au sujet afin qu'il puisse décider en toute sérénité de sa participation et poser toutes les questions nécessaires (ICH E6 4.8.7)
- elle doit être rédigée sur papier avec en-tête des HUG et du service concerné sur chaque page
- le titre de l'étude, la date et la version du protocole doivent figurer
- les informations doivent être formulées et adressées sous forme d'une lettre : Madame, Monsieur...
- la lettre doit s'adresser au sujet de recherche s'il est capable de discernement, même s'il est mineur, et/ou aux représentants légaux pour approbation si le sujet de recherche est incapable de discernement; (l'obtention du consentement doit être réitérée auprès du sujet de recherche dès rétablissement de sa compétence), ou bien au représentant légal en cas de personne mineure jugée incapable de discernement concernant l'objet de l'étude en question.
- le document doit être aussi concis et informatif que possible. S'il excède 4 pages, il doit être accompagné d'un résumé d'une page, intégré à la pagination de la version longue ; les pages doivent être datées et numérotées et le nombre total de pages doit être indiqué.

- un texte explicatif compréhensible pour les lecteurs et incluant les éléments suivants :
 - nature et but de l'étude comprenant la raison de la sélection du sujet de recherche pour cette étude
 - en quoi consistent les charges subies par le sujet de recherche (ensemble des actes et des analyses impliquées, liste de tous les examens subis dans le cadre de l'étude)
 - notions de double aveugle, placebo, randomisation
 - modification ou non du traitement habituel pour le sujet de recherche
 - bénéfices escomptés pour le sujet de recherche lui-même ou pour d'autres patients futurs
 - risques éventuels, effets secondaires, la notion de risque encore inconnu
 - renseignements sur le produit d'étude, sa posologie, les instructions de conservation, de manipulation, de restitution le cas échéant
 - le nombre de sujets impliqués dans l'essai
 - la durée de la participation
 - le nombre de visites, leur déroulement
 - les responsabilités du sujet

- Doivent être stipulés les points suivants :
 - la participation est volontaire et le sujet peut se soustraire à l'étude à tout moment sans en donner de raison et sans que soit altérée sa prise en charge médicale et les soins prodigués
 - la possibilité pour l'investigateur d'exclure le sujet de recherche de l'étude en lui en précisant le motif (p. ex. s'il ne répond plus aux critères/exigences prévus par le protocole)
 - le sujet de recherche sera tenu au courant de toute nouvelle information importante, cela pouvant modifier son désir de continuer l'essai
 - les obligations du sujet de recherche : respect des instructions données par l'investigateur, obligation de communiquer les effets indésirables ou tout autre renseignement concernant d'autres traitements suivis par exemple
 - l'autorisation d'accéder au dossier médical du patient pour les divers intervenants de l'essai clinique, et les personnes représentant les autorités de santé réalisant des inspections
 - la confidentialité des données doit être assurée. Les résultats analysés peuvent faire l'objet de publications scientifiques et, pour de nouveaux médicaments, être soumis aux autorités sanitaires
 - le cas échéant, la conservation d'échantillons biologiques pour des tests ultérieurs, dont les résultats seront (ne seront pas) communiqués au sujet de recherche. Selon les directives de l'Académie Suisse des Sciences Médicales (ASSM), l'étendue de l'information doit être proportionnelle à l'utilisation des échantillons et des données. Les points suivants revêtent une importance particulière:
 1. le domaine d'utilisation des échantillons et des données
 2. le fait que le consentement doit être donné de plein gré et peut être révoqué;

3. les mesures en matière de protection de la personnalité et des données
4. la durée de conservation
5. le droit du donneur de consulter les données le concernant
6. les possibilités d'accès aux échantillons et données par des organes de contrôle et des autorités de surveillance, l'étendue de leur droit de consultation ainsi que, le cas échéant, l'obligation d'informer les assurances
7. le droit du donneur à être informé sur d'autres utilisations de ses échantillons et données;
8. l'éventuelle possibilité d'un transfert et d'une utilisation à des fins commerciales dans le domaine de la recherche médicale
9. l'information sur les résultats obtenus par la suite et qui pourraient être significatifs pour le donneur (droit de savoir) respectivement la possibilité de renoncer à ces informations (droit de ne pas savoir).

A noter qu'en ce qui concerne les banques de données génétiques, selon l'article 20 de la Loi Fédérale sur l'analyse génétique humaine (LAGH), « (1) Un échantillon ne peut être réutilisé qu'aux fins auxquelles la personne concernée a consenti, et (2) Une analyse génétique peut être effectuée à des fins de recherche sur du matériel biologique prélevé à d'autres fins lorsqu'il a été rendu anonyme et que la personne concernée ou, si elle est incapable de discernement, son représentant légal a été informée de ses droits et qu'elle ne s'y est pas expressément opposée. »

- la couverture financières des risques encourus par l'étude avec la formule suivante : "En cas de dommages subis dans le cadre de l'étude, vous bénéficierez d'une compensation pleine et entière; une assurance spéciale a été contractée pour couvrir cette responsabilité. Le cas échéant l'investigateur vous prêtera assistance pour entreprendre les démarches nécessaires". Le nom du promoteur de l'essai clinique doit être indiqué pour que le sujet de recherche sache qui en assume la responsabilité et a pris une assurance dans ce but.
- le protocole a été approuvé par le Chef de Service et le Comité d'Ethique de la recherche du département concerné
- la couverture des frais supplémentaires inhérents à l'étude (examens, durée de séjour,...) : pas de surcoût ni pour le sujet de recherche ni pour son assurance maladie
- en cas d'étude concernant des volontaires sains rémunérés, les modalités de paiement doivent être clairement détaillées
- la personne donnant son consentement peut s'adresser à tout moment au responsable de l'étude pour l'obtention d'information complémentaire : le nom de l'investigateur principal de l'étude et ses coordonnées doivent figurer, il doit être atteignable pour toute information complémentaire.

Le sujet de recherche doit donner son consentement libre, exprès et éclairé par écrit ou attesté par écrit, après avoir été informé sur les points cités ci-dessus.

5. Formulaire de consentement

Du point de vue de la traçabilité de l'information que le sujet de recherche a reçue, il est mieux d'intégrer le formulaire de consentement à la lettre d'information : cela permet de savoir directement à quelle information le sujet de recherche a consenti. Le formulaire de consentement doit être un document distinct mais intégré à la pagination de la lettre d'information (dernière page). Le sujet et l'investigateur gardent chacun un exemplaire de la totalité du document (information-consentement) (ICH E6 4.8.11).

Le formulaire de consentement doit être rédigé sur papier avec en-tête de l'institution et du service dans lequel se déroulera l'étude. Le nom de l'étude, la date et la version du protocole doivent figurer ainsi que les éléments d'acceptation de la part de la personne consentante :

- le médecin signataire m'a informé(e) oralement et par écrit des buts de l'étude portant sur ..., de son déroulement, des effets attendus, des avantages et inconvénients possibles ainsi que des risques éventuels.
- j'ai lu et compris le dossier d'information du patient du... pour l'étude susnommée. J'ai pu poser toutes les questions que je souhaitais et j'ai reçu des réponses satisfaisantes concernant ma participation à cette étude. Je peux garder le dossier d'information du patient et je reçois une copie de ma déclaration écrite de consentement.
- j'ai eu suffisamment de temps pour réfléchir avant de prendre ma décision
- je sais qu'une assurance couvre les dommages qui pourraient survenir dans le cadre de l'étude.
- j'accepte le fait que les spécialistes responsables travaillant pour le promoteur de l'étude, les représentants des autorités et des commissions d'éthique aient un droit de regard sur les données originales me concernant pour procéder à des vérifications, ces informations restant toutefois strictement confidentielles.
- je participe volontairement à cette étude. Je peux à tout moment retirer mon accord de participation à cette étude sans avoir à donner de raisons. Dans ce cas, je subirai un examen médical final pour ma propre sécurité. Aucun inconvénient pour mon suivi médical ultérieur ne doit découler de cette décision.
- je sais que les exigences et restrictions mentionnées dans le dossier d'information du patient doivent être respectées durant l'étude. Dans l'intérêt de ma santé, l'investigateur peut à tout moment décider de m'exclure de l'étude. C'est pourquoi j'informe l'investigateur d'un éventuel traitement simultané chez un autre médecin ainsi que de la prise de médicaments (prescrits par le médecin ou achetés de ma propre initiative.
- je consens à participer (si le patient lui-même consent) ou
- je consens à ce que mon proche...(en cas de représentant légal consentant) ou
- je consens à ce que mon enfant...(en cas de représentant légal)
- la date et signature des personnes donnant leur consentement
- dans le cas de consentement par un proche ou un représentant légal, mention du type de lien avec le patient
- la date et la signature de l'investigateur

Précisions sur les essais cliniques incluant des mineurs :

- c'est la signature du représentant légal de l'enfant qui doit être obtenue : les deux parents doivent signer sauf si l'autorité parentale est exercée par un seul des deux parents.
- selon ICH E11, il faut rechercher le consentement de l'enfant dès que possible. Cependant dans les textes aucune indication d'âge n'est donnée, et la capacité du mineur à exprimer sa volonté est laissée à la libre appréciation du médecin, tout comme c'est le cas en clinique : selon la Loi sur la Santé K 1 03 art 46 « Aucun soin ne peut être fourni sans le consentement libre et éclairé du sujet de recherche capable de discernement, qu'il soit majeur ou mineur ». Dès qu'un enfant est considéré capable de discernement, il doit donner son consentement. C'est pourquoi il convient de prévoir un espace pour la date et la signature de l'enfant (sous forme d'initiales par exemple). Il est également possible de faire une autre lettre d'information destinée aux jeunes, voire aux enfants, et rédigée de manière plus simple. Toutes ces versions doivent être jointes au dossier.
- dans tous les cas, les participants doivent être conscients de leur droit de se retirer de l'étude à n'importe quel moment, et ce droit doit être respecté. Il peut néanmoins exister des cas extrêmes d'études thérapeutiques portant sur des pathologies mortelles où, de l'opinion de l'investigateur et des représentants légaux, l'intérêt du mineur serait menacé si l'étude était interrompue. Dans ces situations le consentement maintenu du représentant légal suffit pour permettre la continuation de l'étude.
- les mineurs émancipés peuvent signer seuls le formulaire de consentement.

En ce qui concerne les biobanques (Directives de l'ASSM) :

Le consentement peut se référer généralement à l'utilisation ultérieure des échantillons et données pour des projets de recherche futurs (consentement général), mais il peut aussi être limité à un domaine de recherche spécifique. Le donneur doit toutefois consentir expressément à des projets de recherche dans le cas où le prélèvement de matériel biologique humain est réalisé à des fins de recherche uniquement, ou bien si la recherche est faite avec des échantillons non anonymisés, ou bien dans le cas de risques particuliers pour le donneur.

Références :

- *Déclaration d'Helsinki (octobre 2008)*
(<http://www.wma.net/f/policy/b3.htm>)
- *International Conference on Harmonisation (ICH E6)*
(<http://www.ich.org>) (suivre Publications, Guidelines, Efficacy Topics, E6)
- *Fil rouge pour la rédaction d'une déclaration de consentement éclairé et d'une feuille d'information à l'intention des sujets de recherche (Swissmedic)*
(http://www.swissmedic.ch/bewilligungen/00089/00282/index.html?lang=fr&download=NHZ_LpZeg7t,lnp6I0NTU042l2Z6ln1ae2lZn4Z2qZpnO2Yuq2Z6gpJCDdlB6gmym162epYbg2c_JjKbNoKSn6A--)

- *Suggestions méthodologiques (CER HUG)*
(http://ethiquerecherche.hug-ge.ch/library/information_consent_version6.doc)
- *Biobanques: Prélèvement, conservation et utilisation de matériel biologique humain pour la formation et la recherche (Académie Suisse des Sciences Médicales)*
(http://www.pharmacoclin.ch/library/pdf/f_RL_Biobanken.pdf)
- *Loi fédérale sur l'analyse génétique humaine (LAGH)*
(<http://www.admin.ch/ch/f/ff/2004/5145.pdf>)
- *ICH E11 (Clinical Investigation of Medicinal Products in The Pediatric Population)*
(http://www.ich.org/MediaServer.jserv?@_ID=487&@_MODE=GLB)
- *Guidance for Institutional Review Boards and Clinical Investigators (FDA)*
(<http://www.fda.gov/oc/ohrt/irbs/toc4.html>) (Recruiting Study Subjects)