SUPPLEMENT

Abstracts from Rambam Research Day, December 29, 2011

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FROM THE EDITOR-IN-CHIEF

Dear colleagues,

Maimonides, known as the *Rambam*, was one of the greatest Jewish arbiters; he was also a scientist, a researcher, and one of the greatest philosophers of the medieval ages. In fact, he was among the first to support evidence-based medicine.

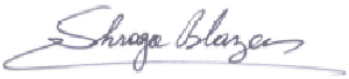
This Supplement of the Rambam Maimonides Medical Journal presents the abstracts from Rambam Research Day. These abstracts represent the newest basic and clinical research coming out of Rambam Health Care Campus—research that is the oxygen for education and development of today's generation of physicians. Hence, the research presented on Rambam Research Day is a foundation for future generations to understand patient needs and improve treatment modalities. Bringing research from the bench to the bedside and from the bedside to the community is at the heart of Maimonides' scholarly and ethical legacy .

We hope you will appreciate the potential represented in these abstracts, which touch on nearly every aspect of clinical practice .

I would also like to thank Ms. Deborah Hemstreet, for the invaluable and professional editorial work that went into making this special issue of RMMJ possible.

The Rambam Maimonides Medical Journal would be pleased to publish other original basic and clinical research articles, and related abstracts, which will subsequently be applied to patient care. In addition, we are open to publishing such abstracts from meetings, seminars, or conferences. For more information on seeing your event's abstracts published here, please contact our editorial board .

Sincerely Yours,



Shraga Blazer, M.D.
Editor-in-Chief
On behalf of the Editors

ABOUT RAMBAM RESEARCH DAY

We are proud to introduce you to the Fifth Rambam Research Day, now established as a key annual event at Rambam Health Care Campus (Rambam), which accompanies the yearly meeting of the International Scientific Advisory Board of the Clinical Research Institute at Rambam (CRIR).

First and foremost we would like to thank Nobel Laureate Professor Aaron Ciechanover for serving as Chair of the Scientific Advisory Board for its inaugural first term of five years. Professor Ciechanover's insights, contributions, and leadership have been a key ingredient in promoting the development of medical science and research at Rambam, with a particular emphasis on innovative programs for the clinician-scientist.

Over this period, Rambam launched two distinct competitive pathways for supporting clinician-scientists here: The "Ofakim" program provides start-up and bridge research funding for young staff physicians with strong research credentials and plans. The "Atidim" program is directed towards research training support for our residents, or as we call them in Israel "Mitmachim." The Atidim program has received wide recognition, and served as an especially important example of Rambam's dedication to medical trainees during the recent physician protest directed towards improving public health care in Israel's major teaching hospitals.

We would also like to acknowledge the excellent collaboration and the fruitful research ties between Rambam and the Technion-Israel Institute of Technology, in particular the Ruth and Bruce Rappaport Faculty of Medicine.

At the same time, we would like to welcome Professor Chaim (Howard) Cedar as the incoming new Chair of our Scientific Advisory Board; he is stepping into an important leadership role in this capacity. We wish him, and all involved, success in promoting medical research within the clinical environment of our hospital, in particular by laying a groundwork by which our young physician scientists may become world leaders in their field.

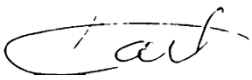
We also thank our international Scientific Advisory Board members, Professors Eugene Braunwald, Irun Cohen, Hedvig Hricak, Scott Freidman, and Jacob Sznajder.

We are particularly proud of the 110 abstracts that will be presented at the meeting, and which are published in this special issue of the Rambam Maimonides Medical Journal (RMMJ). The abstracts cover all areas of medicine. They reflect the rich spectrum of clinical applied and basic research endeavors that characterize our medical center's activities. Indeed, our primary mission of bringing health care to the community is achieved as we bring these research discoveries together with excellence in teaching. In reading through the abstracts, we were intrigued by the breadth and depth of the contributions, and by the commitment of Rambam's staff to this research endeavor.

We would also like to recognize the Office for Promotion of Research, which is charged with coordination and oversight of all research activities at Rambam, including clinical research, applied research, competitive grants management, patent protection, institutional review board ethical approvals, and bringing forward innovative ideas to clinical practice. We are in the process of creating the Rambam Innovation Fund, which will be another vehicle for supporting applied research and taking it from the bench to clinical practice. We value collaboration with industry, which serves as an integral part of health care progress; over the years, several Rambam-originated research projects have led to amazing success in Israel, with practical application to health care.

We are particularly pleased to see this first Supplement to RMMJ, following six quarterly issues of RMMJ appearing online as an institutional open access publication. The Rambam Maimonides Medical Journal, edited by Professor Shraga Blazer, has featured excellent articles from world leaders and Nobel Laureates in the sciences and medicine. We jointly congratulate Professor Blazer for this achievement. Supporting Rambam Research Day via RMMJ is another way we show commitment to our patients, via the furthering of health care facilitated by progress in science, innovation, and technology.

Rafi Beyar, M.D., D.Sc.
Director, Rambam Health Care Campus (RHCC)
and Associate Editor, RMMJ



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RHCC and Associate Editor, RMMJ

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PROGRAM FOR THE FIFTH RAMBAM RESEARCH DAY

Thursday, December 29, 2011
Rambam Health Care Campus, Haifa, Israel

07.30 **MEET & GREET**
VISIT POSTERS AREA

08.30 **OPENING SESSION: GREETINGS**
Professor Rafael Beyar
General Director, Rambam Health Care Campus (RHCC)

Professor Eliezer Shalev
Dean, The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology (IIT), Haifa, Israel

Professor Karl Skorecki
Director, Rappaport Research Institute, Technion-IIT, Director of Medical and Research Development RHCC

Professor Chaim Cedar
Department of Cellular Chemistry and Human Genetics, School of Medicine at the Hebrew University of Jerusalem, and Chairman, Scientific Advisory Committee of the Rambam Institute of Research, RHCC

Professor Michael Aviram
Director, The Clinical Research Institute at Rambam (CRIR), at RHCC

Professor Ehud Klein
Chairman, Research Division, RHCC

KEYNOTE LECTURE

09.00 **Professor Yadin Dudai**
Department of Neurobiology and Sara and Micahel Sela Chair in Neurobiology, Weizmann Institute of Science, Rehovot, Israel.
The Instability of Our Memories: Lessons from the Brain

RAMBAM RESEARCH AWARDS 2011

10.00 ***Ofakim* Program:** Basic & Clinical Research Awards to Young Staff Physicians
The Ofakim-Rambam Fund for Academic Excellence

***Atidim* Program:** Residents Basic & Clinical Research Awards
The Etai Sharon Rambam-Atidim Fund for Academic Excellence

The Meyer Children's Prize for research in Pediatrics

Awardees will be announced at the Session

PRESENTATION OF THE 2009 ATIDIM GRANTEES' RESEARCH WORK

10.20 **Dr. Danny Eytan**
Network Biology Research Laboratories, Lorry Lokey Interdisciplinary Center for Life Sciences and Engineering, Technion-IIT, Department of Pediatrics A, RHCC
Activity Fluctuations and Representation in Neuronal Networks

10.30 **Dr. Rabea Asleh**
Department of Anatomy and Cell Biology, The Ruth and Bruce Rappaport Faculty of Medicine, Technion-IIT, Department of Internal Medicine A, RHCC
Haptoglobin Genotype is a Key Regulator of Iron-mediated Lysosomal Destabilization in Diabetes Mellitus

10.45 **POSTER PRESENTATIONS WITH AUTHORS**

PLENARY LECTURES

11.30 **Professor Benjamin Brenner**
Director, Department of Hematology and Bone Marrow Transplantation, RHCC and The Ruth and Bruce Rappaport Faculty of Medicine, Technion-IIT
Cancer and Thrombosis: Mechanisms and Implications

12.00 **Dr. Ahmed Assalia**
Deputy Director, Division of General Surgery, RHCC and The Ruth and Bruce Rappaport Faculty of Medicine, Technion-IIT
Surgical Treatment of Morbid Obesity

Oral Presentations by Rambam Research Day Awardees

13.15 **Dr. Ilan Gruenwald**
Neurourology Unit, RHCC and The Ruth and Bruce Rappaport Faculty of Medicine, Technion-IIT
Low-intensity Extracorporeal Shock Wave Therapy for Erectile Dysfunction in Phosphodiesterase-5 Inhibitor Responders: A Randomized, Double-blind, Placebo-controlled Study

13.30 **Dr. Liran Shani**
Department of Cardiac Surgery, RHCC and The Ruth and Bruce Rappaport Faculty of Medicine, Technion-IIT
A Novel Amiodarone-eluting Biological Glue for the Prevention of Postoperative Atrial Fibrillation: First Animal Trial

13.45 **Dr. Anat Aharon**
Thrombosis and Hemostasis Unit, Department of Hematology and Bone Marrow Transplantation, RHCC and The Ruth and Bruce Rappaport Faculty of Medicine, Technion-IIT
Microparticles Effects on Apoptosis, Angiogenesis and Migration in Healthy and Pathological Pregnancies

14.00 **Dr. Odile Robicsek**
Laboratory of Psychobiology, Department of Psychiatry, RHCC, The Ruth and Bruce Rappaport Faculty of Medicine, and INSERTECH, INSERM-Associated Laboratory Technion-IIT
Human Hair Follicle Derived Induced Pluripotent Stem Cells (iPSC) and Their Differentiation into Dopaminergic Neurons as a Model to Study Neurodevelopmental Abnormalities in Schizophrenia

14.15 **Closing Session**

Concluding Remarks
Awards for Rambam Research Day Oral Presentations
Awards for Rambam Research Day Poster Presentations

PRESENTATION OF THE 2009 ATIDIM GRANTEES' RESEARCH WORK

Activity Fluctuations and Representation in Neuronal Networks (ATIDIM)

Danny Eytan[1,2], Asaf Gal[1], Avner Wallach[1], Einat Kermany[1], Netta Haroush[1], and Shimon Marom[1]

[1]Network Biology Research Laboratories, Lorry Lokey Interdisciplinary Center for Life Sciences and Engineering, Technion-Israel Institute of Technology; Haifa, Israel, and [2]Department of Pediatrics A, Rambam Health Care Campus, Haifa, Israel

Introduction: At the cornerstone of neuroscience lies the attempt to correlate behavior and thought to brain states and activity patterns and transitions between such states. The underlying assumption to the studies we will present is that the most relevant level of description allowing such correlations is that of neuronal populations and interactions between such populations. The function of the nervous system, at the population or neuronal network level, can be studied in terms of three axes: Representation, Development, and Learning.

Materials and Methods: The experimental system consists of large, random, cortical networks developing *ex vivo* coupled to multi-electrode-arrays. The networks are relatively free of predefined constraints and intervening variables, yet the electrophysiological, biochemical, and pharmacological properties of their neurons are mostly identical to neurons *in vivo*. The *ex vivo* developing model system enables extensive, multi-site sampling and manipulating of the relevant variables: electrical activity and the chemical milieu. The results presented here were collected by long-term recordings from these networks both at the level of the single, synaptically isolated neuron and at the level of the intact network under various environmental conditions and stimulation environments.

Results: Basic biophysical aspects of response dynamics and their long-term fluctuations will be presented, at two different levels of organization: the single, isolated neuron and the intact assembly. We show that individual neurons and networks display a very complex, history dependent response patterns that pose constraints on possible representation schemes. Moreover, we will show the feasibility of such representation schemes and implications of their usage. Representation schemes at the network level can be viewed as different "codes," with a gross division between rate and time-based codes. Finally, we will show some preliminary results regarding such fluctuations in the response dynamics at the level of intact organisms.

Conclusions: The neuronal system, at any given level of organization is not only very "noisy" in its response dynamics but moreover—it is inherently non-stationary. This non-stationarity reflects internal processes, some of which are activity dependent. Our results describe the dynamics of the fluctuations in the responses to stimulation; at the network level, we show how these dynamics affect possible representation schemes with interplay between rate-based and time-based schemes. We show the advantages to either scheme depending on the stimulus properties.

Citation: RMMJ 2012;3 Suppl:6.

Haptoglobin Genotype is a Key Regulator of Iron-mediated Lysosomal Destabilization in Diabetes Mellitus

Rabea Asleh[1,2], Nina S. Levy[2], Rachel Miller-Lotan[2], and Andrew P. Levy[2]

[1]Department of Internal Medicine A, Rambam Health Care Campus, Haifa, Israel; and [2]Department of Anatomy and Cell Biology, The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Introduction: Iron plays a major role in oxidative stress generation and its accumulation in lysosomes seems critical in lysosomal destabilization and cell injury. A major source of intralysosomal iron is the degradation of hemoglobin (Hb) uptaken by cells as a complex with haptoglobin (Hp) following intravascular hemolysis. We have demonstrated in several prospective studies that diabetic individuals with the Hp 2-2 genotype are at a 3-5 fold relative risk of cardiovascular disease (CVD) as compared to diabetic individuals with Hp 1-1 genotype. Moreover, we found that Hp 2-2 is an inferior antioxidant as compared to Hp 1-1 in blocking

hemoglobin and iron-mediated oxidation. We hypothesized that lysosomal loss of integrity is an Hp-genotype dependent, specifically in the setting of diabetes, and that vitamin E supplementation may reduce intracellular oxidation and lysosomal injury.

Methods: To test our hypothesis we used both tissue culture cells, including CHO cells constantly transfected with the Hp-Hb scavenger receptor CD163 and macrophages expressing endogenous CD163, and an Hp-transgenic mouse model with and without diabetes. Lysosomal destabilization was assessed after lysosomal purification using a fluorimetric substrate for the lysosomal marker enzymes N-acetyl-β-glucosaminidase and in live cells using lysosensor yellow/blue DND-160 staining and confocal microscopy. Lysosomal oxidation was assessed by measuring the amount of lipid peroxides and redox active iron in purified lysosomes. Hb-mediated oxidation of purified low-density lipoprotein (LDL) and the effect of pH on LDL oxidation was assessed using TBARS assay.

Results: We found a dramatic increase in lysosomal fragility in cells incubated with Hp 2-2-Hb complex and in lysosomes purified from Hp 2-2 diabetic mouse kidneys. Moreover, the amount of lipid peroxides and redox active iron associated with lysosomes purified from kidneys of Hp 2-2 diabetic mice, were significantly increased as compared to lysosomes purified from kidneys of Hp 1-1 diabetic mice. Vitamin E supplementation to Hp 2-2 diabetic mice resulted in a significant reduction in lysosomal fragility, lipid peroxidation, and redox active iron concentration. Iron-mediated oxidation proved to be more effective at acidic pH. We measured Hb-mediated oxidation of LDL at pH 4.5 (pH of lysosomes) and found that Hp 2-2 protein paradoxically increased oxidation of LDL while Hp 1-1 protein still conferred an antioxidant activity against glycated Hb.

Conclusions: Hp 2-2 type is associated with a markedly increased iron-mediated lysosomal oxidation and destabilization. Vitamin E may block lysosomal injury thus explaining its beneficial effect on the development of diabetic vascular disease, selectively in the Hp 2-2 diabetic population.

Citation: RMMJ 2012;3 Suppl:6–7.

PLENARY LECTURES

Cancer and Thrombosis: Mechanisms and Implications

Benjamin Brenner

Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus and The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Cancer and thrombosis are the two major disease states in the developed world. While the association of venous thromboembolism (VTE) with tumors was described over 150 years ago, clinical and basic research over the past 30 years have broadened our understanding of this association. The interactions of thrombosis and cancer are complex and involve issues related to pathogenic mechanisms, clinical presentation, prognosis, and treatment.

Pulmonary embolism is a major cause of death in cancer patients and cancer patients with VTE have an inferior survival compared to those without thrombosis. Recent epidemiological studies have reported on the prevalence of cancer-related VTE in solid tumors and hematological malignancies. Data obtained from VTE registries in North America and Europe have fostered our knowledge about the risk of developing deep vein thrombosis and pulmonary embolism in cancer patients with various tumor types in specific medical and surgical settings. Moreover, the information provided by registries such as RIETE, has enabled evaluation of the hemorrhagic risk in cancer patients with VTE, especially during anticoagulant therapy. Recent studies point towards a potential benefit that can be gained by applying risk stratification strategies, and may help in the management of cancer patients with VTE.

Procoagulant mechanisms on tumor cells primarily involve expression of hemostatic proteins on tumor cells, production of inflammatory cytokines, and adhesion of tumor cells to endothelium. Tissue factor (TF) plays a major role in tumor progression, metastasis, and angiogen-

esis through signaling via its intracellular domain. Recent data suggest that TF bearing microparticles (MPs) may play an essential role in these settings. The origin of these MPs varies and may include tumor cells, monocytes, platelets, and endothelial cells. Finally, cross-talk between TF and heparanase, which is known to increase angiogenesis and metastasis, has recently been reported. Exploring these mechanisms will potentially pave the way for novel therapeutic interventions in cancer patients as well as in those with thrombosis.

Cancer patients may present with systemic coagulation activation manifested as disseminated intravascular coagulation, which is frequently subacute or chronic in nature and may manifest with thrombosis. Thrombotic microangiopathy following chemotherapy or stem cell transplantation is a complex clinical presentation requiring elaborate laboratory evaluation, currently without satisfactory therapy and often associated with a dismal prognosis. Veno-occlusive disease of the liver is another example of a complex clinical manifestation following stem cell transplantation and chemotherapy.

The mechanisms of thrombohemorrhagic complications in acute promyelocytic leukemia can be partially ameliorated by vigorous platelet and blood products transfusion and early administration of all-trans-retinoic acid. The risk for thrombosis in childhood acute lymphoblastic leukemia is increased in patients harboring thrombophilia and during L-asparaginase therapy. Risk stratification and anticoagulant prophylaxis can reduce the thrombotic burden in these children.

A growing number of angiogenesis inhibitors have recently been approved for the treatment of a variety of solid and hematological tumors. Arterial and venous thrombosis is a major complication of many of these agents and ways for its prevention are currently under intense investigation. While potential contributors to thrombosis are related to the drug's mechanism of action, the epidemiological data on the rate of thrombohemorrhagic complications are not yet affirmed for many of these agents. Current antithrombotic pharmacological interventions in cancer patients include prevention of VTE in various clinical settings and anatomical sites. The type of antithrombotic agent and duration of VTE treatment in cancer patients have been partially explored, using currently available antithrombotic agents, and advantage in secondary prevention of VTE has been demonstrated. Whether novel anticoagulants will have similar activity in cancer patients remains to be established.

Thus, thrombosis and cancer are two major pathologies that are intricately associated. Studies on the basic mechanisms of these interactions may lead to substantial clinical implications and improved patient care.

Citation: RMMJ 2012;3 Suppl:7–8.

Surgical Treatment of Morbid Obesity

Ahmed Assalia

Department of General Surgery, Rambam, Health Care Campus, Haifa, Israel, and The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Morbid obesity (MO) is considered the epidemic of the 21st century. It is defined as body mass index (BMI) above 40 kg/m2, or a BMI > 35 with associated diseases. According to the National Institute of Health (NIH) consensus statement from 1992, conservative measures (diet and pharmacotherapy) for the treatment of MO will fail in the long term for more than 95% of cases. Currently, surgical management is the only effective proven modality in the treatment of MO.

Over the last decade, along with the introduction of minimally invasive techniques and new surgical procedures, we were able to improve surgical results, in terms of morbidity, mortality, and metabolic results. A great deal of data is available showing the favorable results of surgery for MO and type 2 diabetes mellitus (T2DM) associated with obesity (Diabesity). Mean weight loss after surgery is expected to reach a mean of 60-70% of the excess weight. Furthermore, following surgery, about 80-90% of patients with T2DM, more than 95% with obstructive sleep apnea and 70% with hypertension and hyperlipidemia, will recover from their disease. Significant improvement will be achieved in the rest. The durability of results is demonstrated in most of these patients for the mid- and long-term. The most common procedures include laparoscopic sleeve gastrectomy (LSG), laparoscopic gastric bypass (LGB), laparoscopic biliopancreatic

diversion (BPD), and laparoscopic BPD with duodenal switch (BPD-DS). Several new surgical procedures are still under evaluation.

The results of bariatric surgery are being achieved by combining the restriction of intake, malabsorption, and hormonal changes.

Recently, intensive research is investigating the hormonal and metabolic consequences of surgery; bariatric surgery is now considered a well-established metabolic intervention. To ensure long-term success, a multi-disciplinary approach and close follow-up are pivotal.

Citation: RMMJ 2012;3 Suppl:8–9.

ORAL PRESENTATIONS

Low-Intensity Extracorporeal Shock Wave Therapy for Erectile Dysfunction in Phosphodiesterase-5 Inhibitor Responders: A Randomized, Double-Blind, Placebo-Controlled Study

Yoram Vardi, Boaz Appel, Omar Massarwi, Ezra Gerber, Elliot Sprecher, Amichai Kilchevsky, and Ilan Gruenwald

Neurourology Unit, Rambam Health Care Campus, Haifa, Israel

Introduction: Low-intensity extracorporeal shock-wave therapy (LI-ESWT) has been shown to promote neovascularization in various tissues throughout the human body.

Research Hypothesis: Use of LI-ESWT can promote neovascularization in the penis thereby improving erectile function in men with erectile dysfunction (ED) of vasculogenic etiology.

Materials and Methods: We enrolled 60 men with vasculogenic ED who had International Index of Erectile Function ED domain scores (IIEF-ED) without PDE5-I therapy between 1–19 (mean, 12.2). These men had previously responded to PDE5-Is (mean IIEF-ED domain: 22.7). The men were randomized to 12 sessions of LI-ESWT or sham treatment. LI-ESWT was applied to the penile shaft and crura at five different sites. Assessment of erectile function was performed prior to the first treatment and at 1 month after the final treatment session, using validated sexual function questionnaires and penile and systemic endothelial function testing. A change in the IIEF-ED Domain score of more than 5 points was used as the main outcome measure of treatment success.

Results: The LI-ESWT treated group (treatment) evidenced a greater increase in Total IIEF and IIEF-ED from V1 to FU1 versus the sham group. Total IIEF: 12.2 ± 2.0 (change score mean ± SEM) vs. 3.2 ± 3.1, $P = 0.0196$. IIEF-ED: 6.7 ± 0.9 vs. 3.0 ± 1.4, $P = 0.0322$. Similar improvements were observed in the penile endothelial function, expressed by FMD maximum (FMD). For the treated group, FMD improved by a median 8.2 ml/min per deciliter (-17.0 to 124.8) vs. -0.1 (range -9.2 to 18.5) for the sham-treated group, $P < 0.0001$. Combining the objective and subjective parameters for each individual, we found that 22 patients in the active group (56%) showed significant improvement in both IIEF and FMD whereas only 1 patient in the placebo group (5%) showed an improvement in both, $P < 0.0001$. Importantly, the LI-ESWT treated group experienced a significantly greater increase in the IIEF Total Satisfaction category from visit 1 to follow-up 1, 1.9 ± 0.5, vs. the sham-treated group, 0.1 ± 0.4, $P = 0.0054$. None of the patients experienced adverse effects from the treatment.

Conclusions: The new LI-ESWT treatment is effective, long lasting, and well tolerated by men with erectile dysfunction who had previously responded to pharmacotherapy.

Citation: RMMJ 2012;3 Suppl:9.

A Novel Amiodarone-Eluting Biological Glue for the Prevention of Postoperative Atrial Fibrillation: First Animal Trial

Ziv Beckerman, Adi Azran, Ohad Kimhi, Liran Shani, Roni-Reuven Nir, and Gil Bolotin

Department of Cardiac Surgery, Rambam Health Care Campus, Haifa, Israel

Background: Postoperative atrial fibrillation is the most common complication after cardiac surgery, leading to increased morbidity and mortality. Routine prophylactic use of amiodarone is not recommended due to associated systemic

adverse effects. The aim of this study was to evaluate the efficacy of a novel local drug delivery system for the prevention of postoperative atrial fibrillation, while avoiding systemic distribution.

Methods: Nine goats (five study goats, four controls) underwent left thoracotomy and right atrial epicardial electrodes attachment. An alginate based novel proprietary glue with amiodarone (1 mg/kg bw) was applied to the right atrial epicardium of the study group. In the control group, glue without amiodarone was applied. Atrial effective refractory period (AERP), and atrial response to burst pacing (rapid atrial response, RAR) were assessed at the following intervals: before and after application, and in the first, second, and third postoperative days (PODs). Myocardial, plasma, and extracardiac tissue amiodarone concentrations were analyzed by high-performance liquid chromatography (HPLC).

Results: Mean HPLC drug levels were found to be within the therapeutic window in the right atrium of all tested animals from the first postoperative day (23510.86 ± 5230.69 ng/g). Amiodarone concentrations in plasma, skeletal muscle, and thyroid gland were below detection level. AERP did not change in both groups during the study. Baseline RAR inducibility was comparable between both groups ($P = 0.27$). Within the study group, a significant reduction in RAR inducibility was observed on POD3 (65% vs. 27%; $P = 0.019$). No such differences were found among the control group (44% vs. 41%; $P = 0.86$).

Conclusions: The local delivery of amiodarone reduced atrial vulnerability to tachyarrhythmias, while extracardiac drug levels remained below detection. This novel technology should be further validated for the prevention of postoperative atrial fibrillation.

Citation: RMMJ 2012;3 Suppl: 9–10.

Microparticles Effects on Apoptosis, Angiogenesis and Migration in Healthy and Pathological Pregnancies

Einat Shomer[1,2], Sarah Katzenell[1,2], Yaniv Zipori[3], Rami N. Sammour[4], Benjamin Brenner[1,2], and Anat Aharon[1,2]

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Introduction: Microparticles (MPs) are shed from activated or apoptotic cells and contribute to hypercoagulability in normal pregnancy and gestational vascular complications (GVC). However, the effects of MPs on vascular cells in pregnancy remain unknown.

Study Aims: The objective of the study is to evaluate the impact of MPs on apoptosis, angiogenesis, and migration of human endothelial cells (EC), and placental human villous trophoblasts (HVT).

Material and Methods: Microparticles were obtained in four study groups: non-pregnant women (NP), healthy pregnant females (HP), pregnant women with GVC, and pregnant females treated with low molecular weight heparin (LMWH). Microparticle characteristics and effects on EC and HVT were evaluated by TUNEL, ELISA, migration and tube formation assays.

Results: Microparticles from the HP group caused apoptosis in HVT obtained from term placentas; MPs significantly increased in the GVC cohort ($P < 0.0001$). For the LMWH-treated group, MPs significantly reduced HVT apoptosis ($P = 0.007$) compared to MPs obtained in the GVC cohort. For all pregnancy groups, MPs improved viability of 24-week gestation HVT, while not affecting EC viability. HP-MPs significantly increased HVT migration ($P < 0.0001$) compared to untreated cells. Migration was reduced in cells exposed to GVC-MPs; this reduction was ameliorated by the MEK 1&2 inhibitor, suggesting involvement of the MAP kinase pathway. Migration of cells treated with MPs from the LMWH-treated group was similar to that observed in the HP -MP-treated cells. Levels of matrix metalloproteinase 9 (MMP-9) were significantly higher in the HP-MPs compared to the NP-MPs ($P = 0.0008$), but appeared to be lower in GVC-MPs compared to HP-MPs. The HP-MPs induced tube formation in EC in contrast to untreated cells. Remarkably, tube formation was abolished by MPs isolated from the GVC cohort, while MPs from the LMWH cohort improved tube formation.

Conclusions: Microparticles obtained from pregnant women were found to have different effects on endothelial and trophoblast cells. While GVC MPs appear to increase apoptosis, reduce migration, and impair angiogenesis, compared to healthy pregnancy, MPs isolated from women treated with LMWH improve cell survival and function. These effects of MPs can determine the vascular cell fate and may influence pregnancy outcome.

Citation: RMMJ 2012;3 Suppl:10–11.

Human Hair Follicle Derived Induced Pluripotent Stem Cells (iPSC) and Their Differentiation into Dopaminergic Neurons as a Model to Study Neurodevelopmental Abnormalities in Schizophrenia

Odile Robicsek[1], Rachel Karry[1], Isabelle Petit-Pedrol[2], Nava Salman-Tabcharani[2], Ehud Klein[1], Daniel Aberdam[2], and Dorit Ben-Shahar[1]

[1]Laboratory of Psychobiology, Department of Psychiatry, Rambam Medical Center, The Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel; and [2]INSERTECH: INSERM-associated laboratory, The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Introduction: Reprogramming of somatic cells into induced pluripotent stem cells (iPSC) and differentiating them into different neuronal lineages is a new tool to model neurodevelopmental disorders, including schizophrenia. We hypothesized that keratinocytes isolated from hair follicles of schizophrenia patients could be an ideal source of somatic cells for reprogramming, due to their accessibility and common neuroectodermal origin with neurons.

Methods: Four schizophrenia, and two healthy subjects, derived iPSC lines (Sch-iPSC and CTL-iPSC, respectively) were produced from hair follicle keratinocytes by infection with lentiviral particles expressing the polycistronic plasmid STEMCCA (Oct4, Sox2, Klf4, and c-myc). Characterized pluripotent iPSC were differentiated into $Pax6^+/Nestin^+$ neuronal precursors and then further differentiated into $\beta3\text{-tubulin}^+/TH^+$ dopaminergic cells and forebrain $\beta3\text{-tubulin}^+/TBR1^+$ glutamatergic cells using SMAD and TGFβ inhibition protocol or prolonged spontaneous EB differentiation, respectively.

Results: While CTL-iPSC displayed a neuronal morphology and formed network-like structures, Sch-iPSC cells were much bigger, did not present morphological features of neurons, and seemed less developed. IF revealed that a large proportion of differentiated CTL-iPSC were $\beta3\text{-tubulin}^+/TH^+$. FACS confirmed that 70% of differentiated CTL-iPSC, yet only 3.6% of Sch-iPSC were β3-tubulin-positive. Differentiated CTL-iPSC released dopamine and its metabolite HVA significantly more than Sch-iPSC by HPLC. Levels of serotonin and its metabolite (5HIAA) were similar in both groups. Both CTL-iPSC and Sch-iPSC similarly differentiate into forebrain beta3-tubulin+/TBR1+ neuron-like cells. However, Sch-iPSC-derived neurons did not expressed TBR1, a marker of final stage of differentiation of forebrain neurons. Mitochondrial function including respiration, membrane potential ($\Delta\psi m$), and mitochondrial network dynamics were abnormal at various developmental stages in schizophrenia derived cells, including keratinocytes, iPSC, neuronal precursors and differentiated neurons.

Conclusions: The results of this study show neurodevelopmental impairments implicated in schizophrenia in a novel *in vitro* cellular model. Thus, the non-invasive painless means of HF keratinocytes-derived iPSC may provide new insights into neuron development and may serve as a tool for the design of alternative therapeutics to optimize drug therapy for the benefit of the patients.

Citation: RMMJ 2012;3 Suppl:11.

POSTER PRESENTATIONS

CARDIOLOGY

Poster #03A

Relation between Changes in Red Cell Distribution Width and Clinical Outcomes in Acute Decompensated Heart Failure

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Background: Increased red blood cell distribution (RDW) has been associated with adverse outcomes in patients with heart failure. We studied the association between baseline RDW and changes in RDW during the course of hospitalization with clinical outcomes in patients with acute decompensated heart failure (ADHF).

Methods and Results: We prospectively studied 614 patients with ADHF. Baseline RDW and RDW change during hospitalization was determined in all patients. The relationship between RDW and clinical outcomes after hospital discharge were tested using Cox regression models, adjusting for clinical characteristics, echocardiographic findings, and brain natriuretic peptide levels. During the follow up period, 286 patients (46.6%) died and 84 were readmitted for ADHF (13.7%). Median RDW was significantly higher among patients who died as compared to patients who survived (15.6% interquartile range (14.5 to 17.1) vs. 14.9% mg/L interquartile range (14.1 to 16.1), $P < 0.0001$). Compared with patients in the first RDW quartile, the adjusted hazard ratio (HR) for death or rehospitalization was 1.9 (95% CI 1.3–2.6) in patients in the fourth RDW quartile. Changes in RDW during hospitalization were strongly associated with changes in mortality risk. Compared with patients with persistent normal RDW < 14.5%), the adjusted HR for mortality was 2.0 (95% CI 1.2-3.3) for patients in whom RDW increased above 14.5 during hospital course, similar to patients with persistent elevation of RDW (HR was 1.7, 95% CI 1.2-2.3).

Conclusion: We have shown in a population of hospitalized patients with ADHF that RDW is a strong independent predictor of greater morbidity and mortality. An increase in RDW during hospitalization also portends adverse clinical outcome.

Citation: RMMJ 2012;3 Suppl:12.

Poster #23A

ERK1/2 Regulate the Balance between Eccentric and Concentric Growth of the Heart

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Introduction: The myocardium undergoes cellular and ventricular chamber remodeling and hypertrophy as a means of maintaining cardiac output in response to increased workload. An increase in cardiac afterload typically produces concentric hypertrophy characterized by an increase in cardiomyocyte width, while volume overload results in eccentric growth, characterized by cellular elongation and addition of sarcomeres in series. Concentric and eccentric growth likely result from orchestrated activation of specific intracellular signaling pathways, although the identity and mechanisms whereby these signaling pathways differentially regulate myocyte growth are not currently known.

Material and Methods: To determine the role of extracellular signal-regulated kinases 1/2 (ERK1/2) in regulating the cardiac hypertrophic response we used mice lacking all ERK1/2 protein in the heart by crossing $Erk1^{-/-}$ mice with $Erk2^{fl/fl}$

targeted mice and a cardiac Cre-recombinase expressing line ($Erk1^{-/-}$;$Erk2^{fl/fl\text{-}Cre}$). We also studied mice expressing activated MEK1 in the heart to induce ERK1/2 signaling and used mechanistic experiments in cultured myocytes to assess cellular growth characteristics associated with this signaling pathway.

Results: While loss of all ERK1/2 from the heart did not block the cardiac hypertrophic response per se, it did dramatically alter how the heart grew. For example, adult myocytes from hearts of $Erk1^{-/-}$; $Erk2^{fl/fl\text{-}Cre}$ mice showed preferential eccentric growth (lengthening) while myocytes from MEK1 transgenic hearts showed concentric growth (width increase). Isolated adult myocytes acutely inhibited for ERK1/2 signaling by adenoviral gene transfer showed spontaneous lengthening while infection with an activated MEK1 adenovirus promoted constitutive ERK1/2 signaling and increased myocyte thickness.

Conclusions: Taken together, these data demonstrate that the ERK1/2 signaling pathway uniquely regulates the balance between eccentric and concentric growth of the heart. Thus, the MEK1-ERK1/2 pathway may be the first identified signaling pathway capable of specifically directing the mode of cardiomyocyte hypertrophy.

Citation: RMMJ 2012;3 Suppl:12–13.

Poster #42A

Does the Early Use of Sodium Bicarbonate Improve Results of Cardiopulmonary Resuscitation Following Out-of-Hospital Cardiac Arrest—A Prospective, Controlled Clinical Trial

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Introduction: Out-of-hospital cardiac arrests (OHCA) account for over 60% of deaths from coronary artery disease. Outcome of OHCA and cardiopulmonary resuscitation (CPR) is very poor: Less than one third of the victims regain spontaneous circulation (ROSC), 40-60% of those achieving ROSC suffer significant neurological disability, and only 1.7-6.4% are discharged from the hospital. To minimize hypoxia time, the primary goal of CPR is to achieve ROSC as fast as possible. Lactic acidosis develops rapidly during cardiac arrest (CA) and is considered detrimental to CPR outcome. Sodium bicarbonate (SB), the generic, commonly used acid buffer, was subjected only to a single, small, controlled trial that found a trend towards improved outcome in prolonged OHCA and CPR. Another study indicated that emergency medical systems (EMSs) that used SB early and often during CPR had significantly higher ROSC rates and better long-term outcome compared with EMS's that used SB more seldom and administered it late in the course of CPR. The objective of this trial is to determine whether early administration of SB during OHCA and CPR improves short-term CPR outcome.

Methods: The proposed study will be a nationwide, prospective, randomized, double blinded, placebo-controlled clinical trial. A waiver of informed consent was approved by the Helsinki Committee of the Rambam Medical Center and by the Superior Helsinki Committee, Ministry of Health. The study will include adult patients who suffer OHCA, are treated by Magen David Adom paramedics, do not respond to basic CPR and to early defibrillation, and in whom advanced CPR is initiated. The first dose (1 mEq/Kg) of SB/placebo will be administered immediately following the first IV epinephrine dose. The SB/placebo vials will be masked and coded. The study endpoints will be the rates of ROSC and of admission to the emergency room. The calculated sample size is 2,130 patients. Patient recruitment will start in October 2011. The trial is supported by a grant from the Chief Scientist, Ministry of Health.

Expected Results: Based on previous analysis, we expect a 20% improved short-term outcome in the SB treated group. Sample size was calculated accordingly.

Importance and Probable Implications: Around 2.2 million OHCA's are treated by EMS worldwide annually. Current ROSC rate is approximately 30%. A 20% better short-term outcome would result in over 130,000 additional patients

regaining spontaneous circulation annually. Results of this study may have a direct impact on the ACLS Guidelines and on the conduction of CPR worldwide.

Citation: RMMJ 2012;3 Suppl:13–14.

Poster #52A

Arterial Wall Secretion of C-Reactive Protein versus Systemic Secretion: Is It Relevant when Evaluating CRP as a Cardiovascular Biomarker?

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Introduction: Atherosclerosis is an inflammatory disease involving different cell types, including macrophages. At early stages of atherogenesis, blood monocytes derived macrophages play a major role in the inflammatory process of the atherosclerotic lesion. C-Reactive Protein (CRP) is a sensitive systemic marker of inflammation and was first identified as a biomarker of cardiovascular diseases. However, it is still unclear whether determining CRP is functional in predicting cardiovascular diseases, and if CRP is an active component of the inflammatory cascade or simply a marker of inflammation. Histological investigations indicate that CRP is present in human arterial intima of atherosclerotic lesions, and we have previously shown that macrophages express CRP mRNA.

Hypothesis: We hypothesized that CRP could be locally secreted in the atherosclerotic lesion by arterial macrophages, and local regulation of CRP could affect its pro-atherogenic effects. Moreover, blood derived macrophages expression of CRP could reflect arterial lesion secretion of CRP.

Patients and Methods: Ten diabetic and ten non-diabetic patients scheduled to undergo carotid endarterectomy were enrolled in this study (Helsinki approval #0247-09). Blood samples isolated from the patients were used for serum CRP and lipid determination and for preparing monocytes derived macrophages (HMDM) that were analyzed for their CRP mRNA expression and CRP content. Carotid lesions were analyzed for CRP content and macrophages localization by immunohistochemistry.

Results: Lesions from diabetic patients showed substantially higher CRP levels (62%, $P = 0.05$) than lesions from non-diabetic patients and CRP co-localized with arterial macrophages. Although there were no significant differences in HMDM CRP content between diabetic and non-diabetic patients, CRP carotid lesion levels were positively correlated with CRP mRNA expression and with CRP content in patient's HMDM.

Conclusions: Pro-inflammatory effects mediated by CRP in the arterial wall could be caused by locally secreted macrophage CRP, and measurements of CRP in blood-derived macrophages could reflect arterial macrophages secretion of CRP. Further studies are needed to investigate the correlation between levels of CRP produced by arterial macrophages, and prediction of coronary artery disease. Understanding the locally produced macrophage CRP in the arterial wall during atherogenesis could be of major importance in identifying the underlying mechanisms of the inflammatory response pathways during atherogenesis.

Citation: RMMJ 2012;3 Suppl:14.

Poster #56A

Macrophages Activation by Heparanase: A Possible Determinant in Plaque Vulnerability

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Introduction: Atherosclerosis is the major cause of death and disability in the adult population. Activated macrophages secrete inflammatory cytokines, chemokines, proteases, reactive oxygen, and nitrogen radicals. This leads to degradation of the extracellular matrix, weakening the atherosclerotic plaque, and making it rupture-prone. Factors and mechanism that activate macrophages in the plaque are incompletely understood. Here, we examined the capacity of heparanase to activate macrophages.

Methods: Highly purified heparanase was added to mouse peritoneal macrophages (MPM) and macrophage-like cell line, J774 and the level of TNFα, MMP-9, IL-1; MCP-1 was evaluated by ELISA, and gene expression was determined by RT-PCR. Cells collected from Toll like receptor (TLR)-2 and -4 knockout mice (KO) were evaluated similarly. Heparanase levels in the plasma of patients with vulnerable plaque (VP), stable angina (SA), and healthy subjects were determined by ELISA. Immunohistochemistry was applied to detect the expression of heparanase in control specimens and specimens of patients with SA or acute MI.

Results: Addition or over expression of heparanase variants resulted in marked increase in TNFα, MMP-9, IL-1, and MCP-1 levels. Cytokine secretion was attenuated by inhibitors of MAPK, PI 3-K, and NFκB. Neutralizing anti-TLR-2 antibody reduced cytokines induction by heparanase; Likewise, MPM harvested from TLR-2 knockout mice were not activated by heparanase. Plasma heparanase level was higher in patients with VP, compared to patients with SA and healthy subjects. Pathologic specimens obtained from VP showed increased heparanase staining compared to specimens of stable plaque and controls.

Conclusions: Heparanase activates macrophages, resulting in marked induction of cytokine expression. This suggests a novel therapeutic target for attenuating plaque progression and vulnerability.

Citation: RMMJ 2012;3 Suppl:14–15.

CARDIAC SURGERY

Poster #66Ao

A Novel Emboli Protection Cannula during Cardiac Surgery: First Animal Study

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Introduction: Stroke after open-heart surgery is a major cause for morbidity and mortality. Up to 60% of intraoperative cerebral events are caused by emboli generated by manipulations of the aorta during surgery. This is the first animal study aimed at evaluating the safety and efficacy of a novel aortic cannula designed to produce simultaneous forward flow and backward suction in order to extract solid and gaseous emboli from the distal aorta upon their release during cardiac surgery.

Material and Methods: The research group consisted of seven domestic pigs connected to cardiopulmonary bypass using a Cardiogard 24F aortic cannula. Three pigs cannulated with a standard, widely used aortic cannula were defined as the control group. Several main flow and suction regimens were carried out. To simulate emboli release, osseous particles of different sizes were injected into the proximal aorta. An external filter was located on the suction tube in order to evaluate the amount of solid emboli caught by the cannula. The flow inside the carotid artery, with and without backward suction, was documented by ultrasound during injection of the particles. Efficacy was evaluated in terms of emboli retrieval rates, while safety was assessed through hemodynamic parameters, namely blood pressure and saturation, and hemolysis state, reflected by free hemoglobin and hemoglobin.

Results: In terms of efficacy, the Cardiogard cannula demonstrated an overall emboli retrieval rate of 77%. A rate of 88.5% was demonstrated using a suction rate of 1.5 liter/min and net flow of 1 liter/min, simulating a low-flow regimen clinically used during aortic manipulation. Gaseous and solid emboli were removed by suction, as demonstrated by epi-carotid ultrasound. In regards to safety, the Cardiogard cannula was

demonstrated comparable to the control aortic cannula in terms of hemodynamics and hemolysis.

Conclusions: The high rate of emboli removal demonstrated by the research cannula may substantially decrease the harmful impact of cardiac postoperative strokes. Furthermore, the safety profile of the Cardiogard cannula was similar to the control aortic cannula. Notably, the Cardiogard cannula was as simple to use as the widely used control aortic cannula.

Citation: RMMJ 2012;3 Suppl:15–16.

Poster #67Ao

Coronary Artery Bypass Graft (CABG) Surgery in the Post-Aprotinin Era: Are We Doing Better?

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Introduction: Cardiac surgery patients are routinely treated with antifibrinolytic agents in order to reduce intra- and postoperative bleeding as well as infusions of blood products. Until 2007, widespread use of two classes of agents was recommended: lysine analogues (aminocaproic acid and tranexamic acid), and serine protease inhibitors (aprotinin). In 2008, the FDA prohibited use of aprotinin due to associated postoperative complications, including cerebrovascular accidents (CVAs), acute kidney injury (AKI), and reduced graft patency. The aim of this work was to re-evaluate the efficacy and safety of aprotinin vs. Tranexamic acid among elective CABG patients.

Materials and Methods: The routine use of prophylactic aprotinin ceased in our institute in January 2008. Accordingly, two groups were enrolled; Group A (n = 256), operated before 2008, was treated with the half-Hammersmith aprotinin regime, while Group B (n = 104), operated after 2008, was treated with the full-dose tranexamic acid regime. All patients were elective, of low-risk profile, and underwent an on-pump CABG. The main outcome measures were (1) safety, assessed in relation to thrombosis-related cardiac, cerebral, and renal events; and (2) efficacy, investigated in terms of postoperative bleeding and infusions of blood products. All outcome measures were assessed during the first three postoperative days.

Results: The groups were comparable demographically. Postoperatively, group B demonstrated (1) greater total bleeding ($P < 0.001$); (2) greater requirement of blood and/or blood products infusions ($P = 0.024$); (3) higher postoperative AKI rates ($P = 0.028$); (4) lower platelet count ($P = 0.002$); and (5) higher postoperative increase in troponin levels ($P < 0.0001$).

Conclusions: Among low-risk patients undergoing CABG, the half-Hammersmith aprotinin-based antifibrinolytic management proved to be more efficacious in terms of bleeding and consumption of blood products, with no associated increased rates of postoperative complications. Accordingly, the usage of aprotinin should be reconsidered for treatment among cohorts of low-risk cardiac patients.

Citation: RMMJ 2012;3 Suppl:16.

Poster #68Ao

Malnutrition in Cardiac Surgery: Food for Thought

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Introduction: Undernourished patients treated in general surgery, internal medicine, and intensive care departments suffer from prolonged and complicated hospitalizations as well as higher mortality rates compared to well-nourished patients. Pivotal information regarding patients' nutritional status and its effect on clinical outcomes is lacking for cardiac surgery patients. The aims of the current study were to determine the prevalence of malnutrition risk and its association with 30-day-hospital mortality and postoperative complications.

Materials and Methods: Four-hundred and three adult patients who underwent cardiac surgery during 2008, and who were screened by the Malnutrition Universal Screening Tool

(MUST) on admission were included in the study. All patients were characterized using the euroSCORE, which is a risk model for death after a heart operation. Univariate and multivariate logistic regression analyses compared the association of high- and low-risk for malnutrition with length of hospitalization (LOS), in-hospital and 30-day mortality, and postoperative complications.

Results: Almost 20% of the patients were found to be at high-risk for malnutrition. Univariate analyses revealed that compared to the low-risk MUST group, the high-risk group demonstrated significantly higher rates of in-hospital mortality ($P = 0.03$), LOS longer than 21 days ($P = 0.002$), antibiotic treatment longer than 21 days ($P = 0.04$), vasopressor treatment longer than 11 days ($P = 0.02$), and positive blood culture ($P = 0.02$). Incorporation of the MUST into a multivariate model with the euroSCORE significantly improved the prediction of postoperative complications, in-hospital mortality, and 30-day mortality compared to the EuroSCORE alone.

Conclusions: Malnutrition is prevalent in patients undergoing cardiac surgery, and is associated with higher postoperative mortality and morbidity. The preoperative MUST screening emerged as highly relevant for enabling early diagnosis of patients at malnutrition risk, predicting postoperative mortality and morbidity, and thus, promoting well-timed treatment. Prospective interventional studies are needed to explore whether intervention will decrease malnutrition risk.

Citation: RMMJ 2012;3 Suppl:16–17.

Poster #69Ao

Numerical Model of Aortic Cannula Hemodynamics for Evaluation of Risk for Atheroembolism

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Introduction: Atheroembolism from the ascending aorta is a major cause of noncardiac complications following cardiac surgery. The hemodynamics of the aortic cannula has been proven to play a significant role in atheromatous emboli generation. Design of the aortic cannula is a main determinant of the flow pattern and flow velocity within the patient's aorta. The current study presents a detailed 3D numerical simulation of the flow inside the clamped aorta during cardiopulmonary bypass (CPB) and compares the flow characteristics of several cannulae designs.

Materials and Methods: Numerical models of different cannulae designs placed in a clamped aorta were created. The models were subjected to physiological blood flow in several conditions during CBP and different cannulae orientations were examined. The numerical models were validated using *in vitro* measurements of pressure drop and velocity. Risk evaluation and hemodynamic parameters were compared, including emanating jet velocity, aortic wall reaction, emboli path lines, distribution between upper and lower vessels, risk for hemolysis, stagnation regions, and pressure drop.

Results: Cannulae with straight tips generate large reactions on the aortic wall and divert more emboli from the clamp region to the descending aorta. However, cannulae with sharp angled tips exhibit stronger emanating jet, higher shear stress in the cannulae, more stagnant flow near the clamp region, and highly disturbed flow. Cannulae with moderate angled tips demonstrate less of a reaction on the aortic wall, and divert more emboli from the clamp region to the upper vessels.

Conclusions: The simulation results prove the significant role of cannula design and orientation in atheromatous emboli generation. The tip angle and cannula orientation in the aorta are crucial parameters in all hemodynamic aspects.

Citation: RMMJ 2012;3 Suppl:17.

MICROBIOLOGY/INFECTIOUS DISEASES

Poster #01B

Epidemiology and Clinical Significance of Nontuberculous Mycobacteria Isolated from Pulmonary Specimens

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Background: The growing awareness and the development of new molecular tools for the diagnosis of nontuberculous mycobacteria (NTM) have led to an increased number of cases associated with these pathogens. This study was designed to evaluate the clinical significance of NTM isolated from pulmonary specimens referred to the laboratory of clinical microbiology of a large tertiary care medical center in Northern Israel.

Methods: Clinical specimens were collected from the in-hospital population. NTM isolated by standard microbiological cultures were further identified by restriction enzyme pattern analysis of a PCR-amplified 439-bp fragment of the hsp-65 gene using DNA extracted from bacterial colonies. Identification was confirmed by direct sequencing of a PCR amplicon encompassing a 5′ region of 16S rRNA gene flanked by conserved sequences. Following identification of NTM, patients were followed, or their records were reviewed. Cases were classified as significant, non-significant, and inconclusive, according to the 2007 ATS\IDSA Criteria for disease.

Results: Between January 2004 and December 2010, 215 cases of respiratory isolation for NTM were identified in our hospital. Age range was 11 to 98 years. *Mycobacterium xenopi* was the most common species (85 isolates, 39.5%) followed by *M. simiae* (52 isolates, 24.2%). *M. simiae* was the most common isolate from 2004–2006, while *M. xenopi* is the leading isolate since 2007. Of the 215 cases, 167 (77.7%) were classified as non-significant, and 27 (12.6%) cases were considered inconclusive. Only 21 (9.8%) cases were clinically significant, the majority being *M. Kansasii* (7 isolates, 33% of significant isolates) and *M. avium* complex (6, 28%). Only one case of *M. simiae* and two of *M. xenopi* were clinically relevant. Among patients with significant disease, six had no underlying conditions. The rest of the patients (pts) had chronic obstructive lung disease (3 pts), cardiac disease (6 pts), HIV (3 pts), malignancy (2 pts) and CF (1 pt).

Conclusions: *M. xenopi* and *M. simiae* are the most prevalent isolates of NTM from respiratory samples in Northern Israel. However, most of these isolates represent colonization. Of the relatively small number of clinically significant isolations, *M. kansasii* and *M. avium* complex are the most common.

Citation: RMMJ 2012;3 Suppl:17–18.

Poster #02B

Elevated Red Cell Distribution Width Predicts Poor Outcome in Young Patients with Community Acquired Pneumonia

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Introduction: Community acquired pneumonia (CAP) is a major cause of morbidity and mortality. While there is much data about risk factors for severe outcome in the general population, there is less focus on younger groups of patients. Therefore, we aimed to detect simple prognostic factors for severe morbidity and mortality in young patients with CAP.

Methods: Patients 60 years old or younger, and diagnosed with CAP (defined as pneumonia identified 48 hours or less from hospitalization) between March 1, 2005 and December 31, 2008 were retrospectively analyzed for risk factors for complicated hospitalization and 90-day mortality.

Results: The cohort included 637 patients. The 90-day mortality rate was 6.6% and the median length of stay was 5 days. In univariate analysis, male patients and those with co-morbid conditions tended to have complicated disease. In multivariate analysis, variables associated with complicated hospitalization included post chest radiation state, prior neurologic damage, blood urea nitrogen (BUN) > 10.7 mmol/L, and red cell distribution width (RDW) > 14.5%. Whereas, variables associated with an increased risk of 90-day mortality included age ≥ 51 years, prior neurologic damage, immunosuppression, and the combination of abnormal white blood cells (WBC) and elevated RDW. Complicated hospitalization and mortality rate were significantly higher among patients with increased RDW regardless of the white blood cell count. Elevated RDW was associated with a significant increase in complicated hospitalization and 90-day mortality rates irrespective of hemoglobin levels.

Conclusion: In young patients with CAP, elevated RDW levels are associated with significantly

higher rates of mortality and severe morbidity. Red cell distribution width as a prognostic marker was unrelated to hemoglobin levels.

Citation: RMMJ 2012;3 Suppl:18–19.

Poster #10B

Eradication of Carbapenem-Resistant Enterobacteriacea Colonization with Non-Absorbable Oral Antibiotic Treatment

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Background: Carbapenem-resistant enterobacteriacea (CRE) had recently emerged around the world. Beginning in 2006, almost all major hospitals in Israel observed a continuous increase in the number of clinical isolates of CRE and this occurrence has rapidly become a major ongoing national outbreak. Despite stringent adherence to the national practice guidelines, which include strict contact isolation and cohorting of identified carriers, we have not been able to control the outbreak.

Objectives: We conducted a randomized prospective trial aimed at eradicating gastrointestinal tract CRE colonization, using oral antibiotic administration of gentamicin (GM), collistin (COL), or both.

Methods: Consecutive hospitalized adult patients identified as CRE carriers by rectal surveillance cultures were included in the study. Rectal isolates were tested for GM and COL susceptibility using E test. Patients who did not consent, or whose isolates were resistant to both drugs, were followed with repeated rectal swabs to assess spontaneous eradication rate (control group). Patients with gentamicin sensitive (GM-S) collistin resistant (COL-R) rectal isolates were treated with oral gentamicin sulphate, 80 mg q.i.d. Patients with isolates that were COL-S but GM-R were treated with oral colistin sulphate, 100 mg q.i.d. Patients with isolates sensitive to both drugs were randomized to three groups of oral antibiotic treatment: GM, COL, or both. Oral treatment was given until eradication, or for a maximum of 60 days. Eradication was defined by the presence of three consecutive negative rectal swabs for CRE including PCR testing of the third specimen. Failure was defined when: 1) rectal swabs remained positive after 60 days of treatment or follow-up; 2) relapse occurred after apparent eradication; 3) rectal isolates turned resistant to the administered drug.

Results: There were 152 patients in the study; 102 were followed for spontaneous eradication (controls) for a median of 150 days (range: 20-720), and 50 patients received one of three drug regimens: 26-GM; 16-COL; 8 patients received both drugs. Eradication rates in the three groups were 42%, 50%, and 37.5%, respectively; each of these were significantly higher than the 7% spontaneous eradication rate in the control group ($P < 0.001$, < 0.001 and 0.02, respectively), with no difference between the regimens. The eradication rate among the 50 patients on any treatment (44%), was also significantly higher than the 7% spontaneous eradication rate ($P < 0.001$). No significant side effects were observed, for any of the treatment regimens.

Conclusions: Oral antibiotic treatment, with non-absorbable drugs to which CRE is susceptible, appears to be an effective and safe measure for eradication of CRE carrier state, and by that, may reduce patient-to-patient transmission and the incidence of clinical infection with this difficult to treat organism.

Citation: RMMJ 2012;3 Suppl:19.

Poster #20B

Rapid Detection of Carbapenem-Resistant *Acinetobacter Baumannii* in a Clinical Setting

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Background: *Acineotbacter baumannii* (*AB*) plays a significant role in the colonization and infection of hospitalized patients. Starting in

2009, the prevalence of carbapenem-resistant (CR) *AB* isolates increased significantly in our institution, up to 76% in the beginning of 2011. Outbreaks of OXA-type carbapenemase-producing *AB* strains have been reported worldwide and $bla_{\text{OXA-23}}$ was reported as the most abundant acquired OXA gene. The aim of the present study was to establish a rapid and reliable PCR-based diagnostic assay for detection of CR-*AB*.

Material and Methods: Seventy-four *AB* clinical isolates (mostly from lower respiratory tract samples) were tested using a PCR-based assay targeting the $bla_{\text{OXA-23}}$ gene followed by identification and antimicrobial susceptibility testing according to CLSI standards.

Results: Out of 74 AB isolates, 64 were identified as CR-*AB* (Imipenem MIC > 16 μg/ml) and 10 as carbapenem sensitive (CS). None of the CS-*AB* isolates were $bla_{\text{OXA-23}}$ positive, while 60/64 (94%) CR-*AB* isolates were $bla_{\text{OXA-23}}$ positive, thus indicating that $bla_{\text{OXA-23}}$ could serve as a target for a rapid PCR-based detection of CR-*AB*. The PCR-based assay was then evaluated in a prospective setting using 77 rectal swabs that were taken as part of another routine surveillance program. These results were as follows: 55/77 rectal swabs were $bla_{\text{OXA-23}}$ positive, later confirmed by culture; in 2/77 swabs, $bla_{\text{OXA-23}}$ was not detected by PCR but later identified in CR-AB isolated from culture (96% sensitivity); and 20/77 swabs were $bla_{\text{OXA-23}}$-PCR negative, later confirmed by culture. Interestingly, 17 $bla_{\text{OXA-23}}$ positive swabs were obtained from patients with a confirmed CR-*AB* infection, suggesting that rectal swabs may serve as a reliable sample for CR-*AB* screening program.

Conclusions: There were two main conclusions from this study:

1. In our institution, 94% of CR-*AB* isolates carry the $bla_{\text{OXA-23}}$ gene, indicating $bla_{\text{OXA-23}}$ gene as a suitable target for a PCR-based rapid assay for CR-*AB* detection.
2. An efficient screening program can be established based upon this rapid PCR-based assay performed directly on rectal swab samples, reducing turnaround time for CR detection to a minimum of only 4h.

Citation: RMMJ 2012;3 Suppl:19–20.

Poster #21B

The Effect of Disinfection Material Accessibility on Hand Hygiene Compliance

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Introduction: Health care associated infection (HCAI) is a worldwide epidemic. Cross infections result in high hospital morbidity and mortality. Hand hygiene compliance among health care personnel (HCP) is a key factor in combating HACI. The quality of interventional studies examining hand hygiene compliance is disappointing. The aim of this study was to examine the effect of personal feedback and alcohol dispenser accessibility on hand hygiene compliance.

Materials and Methods: To monitor the hygiene efforts of staff, transmitters were worn as "smart" bracelets on the wrists of surgical ward personnel; transmitters were also placed under the alcohol dispensers at the entrance of each room. The transmitters communicated with sensor modules installed in each room's ceiling. The system continuously monitored hand hygiene habits regarding pre-defined compliance and quality. At the second stage, dispensers were installed at the foot of each bed.

Results: More than 300,000 hand hygiene-requiring events were recorded. Upon implementation of the surveillance system, a steep rise in personnel compliance to 24% was recorded. This decreased to a worrisome stable compliance of only 7.5% after a few weeks. For each collective/personal feedback, the compliance increased significantly, but again decreased within a short period. On-going surveillance and feedback helped maintain compliance above the minimal level. Compliance improved dramatically, to 29%, as alcohol dispensers became more accessible ($P < 0.034$).

Conclusions: Continuous feedback and surveillance of personal compliance monitoring is an effective method of improving hand hygiene. Accessibility of alcohol dispensers significantly raises the compliance of hand hygiene among HCP. Therefore, such dispensers should be

implemented in all surgical wards, simply by placing an alcohol dispenser on each bed.

Citation: RMMJ 2012;3 Suppl:20–21.

Poster #22B

Candida Infection: Scanning Electron Microscope Observations in a Human Skin Model

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Introduction: *Candida albicans* is the principal fungal infectious agent in human infection. Superficial infections of skin and mucous membranes are the most common types of candidal infections of the skin. It has been well demonstrated that specific *Candida* species, notably *C.albicans*, selectively adhere to vaginal and buccal mucosal cells. This selective adherence is thought to contribute in part to predominance of *C.albicans* colonization and infection in human hosts.

Non-pathogenic species adhere poorly to corneocytes or mucosal cells and do not invade the stratum corneum in animal models. In the present study, we report observations on the way *Candida* infect the stratum corneum in a human skin model.

Aims: The aim of this study is to characterize and compare initial adherence of *C.albicans*, *C.tropicalis*, and *C.parapsilosis* to the skin surface.

Methods: Skin sections were inoculated with low and high concentrations of *C.albicans, C.tropicalis*, and *C.parapsilosis*, followed for one and five days, and then viewed by SEM**.**

Results: *Candida albicans*: *C.albicans* adhered to human epidermis in greater numbers than the other species at every time point studied (after 24 hours and after five days), and with both concentrations (10^4 ml^{-1} and 10^6 ml^{-1}) after one day, and to a greater extent after five days, most of the *C.albicans* blastoconidia were coated with amorphous material linking adjacent blastoconidia and blastoconidia with the corneocyte surface. After five days, huge amounts of blastoconidia were shown, covering almost the entire skin model, the blastoconidia were embedded in a layer resembling biofilm. *Candida tropicalis*: Low amounts of blastoconidia were observed with *C.tropicalis* in comparison to *C.albicans*. After five days at the higher concentrations, the blastoconidia were coated with the material linking adjacent blastoconidia and they were covered with a biofilm. *Candida parapsilosis:* After one day at low and high concentrations, only a few blastoconidia were observed. After five days of incubation, more blastoconidia adhered in both concentrations. *Control skin:* After one day and after five days we observed normal epidermis.

Conclusions: Electron microscopy observations revealed that all three yeasts tested adhered to the skin, but *C.albicans* covered the entire skin model to a higher extent than *C.tropicalis* or *C.parapsilosis*. Mucin-like material coated the blastoconidia mainly in *C.albicans*. All *Candida* species have shown characteristics resembling biofilm formation.

Citation: RMMJ 2012;3 Suppl:21.

Poster #27B

Blood Stream Infections in Severe Burns Patients-Early and Late Bacteremia: A Nine Year Study

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Introduction: Bacterial infection is a major problem in the management of burn victims today. It is now estimated that about 75% of the mortality following burn injuries is related to infections. Bloodstream infections (BSIs) and the development of sepsis are among the most common infection complications occurring in severe burn patients. Therefore, it is important to carry out periodic reviews of the epidemiology of BSIs in these patients.

Aims: This study was designed to evaluate the microbiological data of BSIs and antibiotic susceptibility over a period of almost a decade, and specifically the changes during the hospitalization period with the distribution of early versus late bacteremia, in severe burn patients at the Rambam Health Care Campus.

Methods: Retrospective computerized data was retrieved for all severe burn patients hospitalized in our institution from January 2001 to December 2009. We further divided that period into three-year sub-groups, and the hospitalization period into four week-long segments.

For the first week, BSI was defined as early sepsis; for the second week on, BSI was defined as late sepsis.

Results: Out of the 159 severe burns patients included in the study, at least 74 had one BSI episode. The main blood infectious pathogens identified, with equal distribution, were *S.aureus*, *Acinetobacter baumannii*, *Klebsiella pneumonia,* and *P.aeruginosa*. Of note, the first episodes of bacteremia were diagnosed most frequently during the first week of hospitalization. When we differentiated between early and late bacteremia, we found that in early bacteremia the presence of resistant bacteria and Candida was minor, with no MRSA and Imipenem-resistant *P.aeruginosa* (PSE-IMP). In late bacteremia, we noticed an increased prevalence of resistant bacteria (MRSA, CRKP, and PSE-IMP). In addition, the only bacterium that was observed to increase significantly during the nine-year period was *Carbapenem Resistant Klebsiella Pneumoniae (CRKP).*

Conclusions: In severe burn patients, most of the first BSI episodes appeared very early during hospitalization, even at the beginning of the first week.

The incidence and variety of resistant bacteria and fungal isolates increased in accordance with the length of hospitalization (early vs. late bacteremia).

The only bacterium that increased significantly during the nine-year study period was CRKP.

Citation: RMMJ 2012;3 Suppl:21–22.

Poster #59B

Hospital-Acquired *Klebsiella pneumonia* Bacteremia: Risk Factors for Carbapenem-Resistance and Predictors for Mortality

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Introduction: Carbapenem-resistant Enterobacteriaceae, especially *Klebsiella spp*., has recently become a major health problem worldwide. Since 2006, the incidence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections has increased dramatically in Israel. Bloodstream infections (BSIs) caused by these strains were associated with high rates of treatment failure and mortality.

Aims: The aim of this study was to identify risk factors for carbapenem-resistance and predictors of mortality among adult patients with hospital-acquired bacteremia due to Klebsiella pneumonia.

Methods: The study was performed by means of a retrospective cohort study.

Results: Between January 1, 2006 and December 31, 2008, there were 510 patients with K. pneumonia bacteremia in our hospital. Of these, 317 patients, including 103 patients with carbapenem-resistant K. pneumonia (CRKP), fulfilled our inclusion criteria and were evaluated. When 214 patients with carbapenem-susceptible K. pneumonia (CSKP), were compared with the CRKP patients, several characteristics were significantly more common among CRKP patients, including hematological malignancy, renal failure, chronic liver disease, previous bone marrow transplantation, mechanical ventilation, central vein catheterization, urinary catheterization, hemodialysis, stay in the ICU or in the hematology department, and prior antibiotic use. On multivariable analysis, prior use of macrolides (OR, 3.3;95% CI, 1.295-8.45; $P = 0.012$) and any antibiotic exposure for ≥ 14 days (OR, 17.3;95% CI, 4.568-65.5;$P < 0.001$) remained independent factors associated with CRKP. The mortality rate

among patients with CRKP was significantly higher than that of patients with CSKP (45 of 103 CRKP patients, 43.7% vs. 62 of 214 CSKP patients, 29% respectively, $P < 0.001$). On multivariable analyses, bed ridden status (OR 2; 95% CI, 1–3.8, $P = 0.044$), chronic liver disease (OR 4.8; 95% CI, 1.8–12.8; $P = 0.002$), Charlson Comorbidity Index > 5 (OR 6.7; 95% CI, 2.4-18.9; $P < 0.001$), mechanical ventilation (OR 4; 95% CI, 2.2–7.2; $P < 0.001$), and hemodialysis (OR, 2.7;95% CI, 1.2–6.2; $P = 0.019$) remained independently associated with mortality among patients with K. pneumonia bacteremia.

Conclusions: This study confirms that previous antibiotic exposure is a risk factor for severe infections due to CRKP. Mortality among patients with K. pneumonia bacteremia is associated with severity of illness and many other well-known serious co-morbidities, but not with carbapenem-resistance.

Citation: RMMJ 2012;3 Suppl:22–23.

Poster #60B

Campylobacter Bacteremia: A 10-Year Single-Center Experience

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Introduction: Campylobacter bacteremia (CB) is a rare disease, occurring mainly in patients with immune deficiency or other serious underlying conditions, including liver disease, hypogammaglobulinemia, HIV infection, as well as in extreme ages.

Aims: This study was designed to evaluate the clinical characteristics and risk factors for CB in a tertiary referral center, serving over a million citizens in northern Israel, with over 40,000 blood cultures taken annually.

Methods: The study utilized retrospective computerized data from January 2000 to October 2010.

Results: There were 36 patients with CB, including seven patients less than 18 years of age, three neonates, and seven patients over 65 (mean age 42 years, range 1 month–91 years). Common underlying conditions were hematological malignancy (16), solid tumor (2), organ transplantation (2), chronic liver disease (3), and diabetes mellitus (2). Three patients had underlying disease. Of note were 23 (64%) patients on immunosuppressive therapy at the time of bacteremia. The most common symptom among these patients was fever followed by abdominal pain, diarrhea and vomiting. Campylobacter bacteremia was asymptomatic in three cases. Three patients had a concomitant positive stool culture.

Campylobacter jejunii was the most common isolated species (15 isolates, 41.6%), followed by C.coli (4 isolates, 11%), and C. fetus (2 isolates, 5.5%). Species were not identified in 15 cases (41.6%). Most isolates were susceptible to macrolide drugs (29/31 tested, 94%), Aminoglycosides (23/24 tested, 96%), and clindamycin (18/20 tested, 90%). However, 14/30 tested (53%) were resistant t fluroquinolones. Antibiotic treatment was given to 31 patients but the treatment was adequate (according to *in vitro* susceptibility) in only 18 patients (58%). The different regimens included quinolones, macrolides, penicillins, aminoglycosides, and a combination of aminoglycosides and beta-lactam drugs. Relapse occurred in three patients. The thirty-day mortality rate was 8.3% (3 patients); in only one case was mortality due to CB.

Conclusions: In this study, most episodes of CB occurred among severely immunocompromised patients and were caused by *C. jejunii*. The mortality rate was low despite the discrepancy between antibiotic regimens and *in vitro* susceptibility results.

Citation: RMMJ 2012;3 Suppl:23.

Poster #94B

Incidence and Risk Factor for Endocarditis among Patients with Hospital-Acquired and Health Care-Associated Staphylococcus Aureus Bacteremia

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Introduction: *Staphylococcus aureus* (SA) is an increasing cause of bacteremia, both in the community and in the hospital setting. Cardiac valves are probably the most important site of metastatic infection. The reported incidence of infective endocarditis (IE) among patients with SA bacteremia (SAB) varied from 5% to 30%. *Staphylococcus aureus* infective endocarditis (SAIE) is a characteristic community-acquired infection; however, most cases today occur in a health care setting. The purpose of the present investigation was to determine the incidence and risk factors for development of IE in a large cohort of patients with health care-associated (HCA) and hospital-acquired (HA) SAB.

Methods: Consecutive patients with health care-associated and hospital-acquired SAB) were prospectively recruited over a 30-month period. Patients were followed up for at least 12 weeks after the initial positive blood culture result. The primary end point was diagnosis of IE.

Results: Infective endocarditis occurred in 11 (3.6%) of 303 patients. Patient characteristics at diagnosis and associated with IE included the number of positive blood cultures obtained during hospitalization ($P = 0.003$), the duration of bacteremia ($P < 0.001$), bacteremia persisting for > 3 days (odds ratio (OR), 14.5; 95% confidence interval (CI), 4.0-52.8; $P < 0.001$), performance of echocardiography (OR, 1.88; 95% CI, 1.69–2.1; $P = 0.001$), presence of a well-known predisposing risk for IE (OR, 57.2; 95% CI, 13.6–240.5; $P < 0.001$), a non-fatal McCabe scoring (OR, 2.10; 95% CI, 1.4–3.1; $P = 0.02$), and fever duration related to the infection ($P = 0.02$). On multivariable analysis, the presence of a predisposing risk for IE, persistent bacteremia, and non-fatal McCabe scoring remained significantly associated with IE.

Conclusions: The incidence of IE among patients with HCA and HA SAB is lower than that found in different settings. We identified three clinical characteristics as risk factors for IE among patients with SAB acquired in a health care setting. Although TEE remains the best way to confirm or to diagnose IE in all patients with SAB, this goal is not achievable for all, and its results are not always definitive. Therefore, the present investigation enhances the clinician's ability to identify which patients with healthcare-related and nosocomial SAB are more prone to develop IE.

Citation: RMMJ 2012;3 Suppl:23–24.

Poster #98B

Reducing Surgical Site Infection Rates in Orthopedic Implant Surgery: Results of a Six-Year Infection Control Program

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Background: This work reports the results of an infection control program for on surgical site infections (SSIs) complicating total hip and total knee replacement.

Methods: This prospective cohort study involved patients undergoing total hip and total knee replacement. Interventions included prospective surveillance, chlorhexidine 4% showers, depilation before surgery, administration of preoperative antibiotic prophylaxis in the operating room, and comprehensive postdischarge follow-up. Infections were evaluated using the Center for Disease Control and Prevention definitions. Logistic regression models were fitted to assess infection rates over time, adjusting for factors known to affect SSI rates (National Nosocomial Infections Surveillance System risk index category, type of operation, sex, age, emergency operation, administration of preoperative antibiotic prophylaxis, and length of stay in hospital before surgery).

Results: From April 1, 2002 to May 31, 2008, 1720 consecutive procedures were evaluated. Rates of organ/space infections remained low, but unchanged over the study period (mean 1.09%). The overall infection rate, the rates of superficial (SUP) SSIs, and deep incisional SSIs during the first two years were 7.90%, 5.78%, and 0.96%,

respectively. By the end of the study, these rates decreased to 1.96%, 1.06%, and 0.0, respectively ($P < 0.001$, < 0.001, and 0.03, respectively). The rate of SSIs due to *S. aureus* decreased from 1.54% to 0.30% ($P = 0.02$). The adjusted odds ratios for these infections at the end of the study, as compared to March 31, 2004, were as follows: total number of infections, 0.23 (95% confidence interval (CI-95), 012-0.44), SUP 0.17 (CI-95, 0.07-0.39), and all SSIs due to *S. aureus* 0.14 (CI-95, 0.03-0.64).

Conclusions: We observed significant reductions in infection rates in most types of infections, particularly in the overall rate of SSIs and infections due to *S. aureus*. These differences remained significant when adjusted for potential confounding variables.

Citation: RMMJ 2012;3 Suppl:24–25.

Poster #99B

Compliance with Antibiotic Prophylaxis and Outcomes during a 10-Year Infection Control Program in Cardiac Surgery

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This study aimed at evaluating the correlation between compliance with appropriate antibiotic prophylaxis (AP) and the risk of surgical site infection (SSI) in cardiac surgery (CS).

Methods: Prospective cohort study. The use of a recommended preoperative AP regimen (cefazolin or vancomycin administered within 2h prior to the first incision) was accessed and SSIs were evaluated by a comprehensive post-discharge follow-up program. Definitions from the Center for Disease Control and Prevention were used. Logistic regression models were fitted to assess infection rates over time, adjusting for factors known to affect SSI rates (National Nosocomial Infections Surveillance System risk index category, type of operation, sex, age, emergency operation, administration of preoperative AP, and length of stay in hospital before surgery).

Results: From January 1, 1997 through December 31, 2006, 3,220 consecutive procedures were evaluated. As compared with a baseline period (first two years), by the end of the program there were significant reductions in rates of superficial (SUP) SSIs (4.7% vs. 2.6%, $P < 0.001$), mediastinitis (MED) (2.2% vs. 0.2, $P < 0.001$), and of all SSIs together (10.3% vs. 5.4%, $P < 0.001$). The adjusted odds ratios for these infections at the end of 2006, compared with December 31, 1998, were as follows: SUP 0.5 (95% confidence interval (CI-95), 0.26-0.96, MED 0.09 (CI-95, 0.01-0.72), and all SSIs 0.47 (CI-95, 0.3-0.75), respectively. Compliance with the recommended AP increased from 92.1% to 99.8% by the end of the program ($P < 0.001$). Of the 2,610 patients who received the recommended AP, 127 (4.9%) subsequently had SUP SSI. Of the 105 patients who received AP in a period of time different of that recommended, 14 (13.3%) had such infections ($P = 0.001$, RR 0.36 (CI-95 0.21-0.61)

Conclusions: Maximizing appropriate AP reduces SSI rates in cardiac surgery.

Citation: RMMJ 2012;3 Suppl:25.

ENDOCRINOLOGY/METABOLISM

Poster #04C

Influence of Vitamin D Status on Bone Density in Young HIV Infected Israeli Women

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Background: Decreased bone mineral density (BMD) was reported in HIV infected patients. Mechanisms leading to this decrease are poorly understood.

Aim: To assess degree of sun exposure, clothing habits, vitamin D status, and BMD in young HIV infected Israeli women of Ethiopian (ET) and Caucasian (CA) origin.

Patients and Methods: Seventy-five HIV infected women aged 34.5 ± 8.5 years with regular menses that were followed up at the Institute of Allergy, Clinical Immunology & AIDS were studied. HIV status and treatment regimen were collected from patients' charts. Patients filled a questionnaire about sun exposure, daily calcium intake and dress habits. Laboratory evaluation included routine biochemistry, hydroxyvitamin D (25(OH)D) by ^{125}I- radioimmunoassay, Intact parathyroid hormone (PTH) by STAT. Bone turnover was assessed by plasma total procollagen type1 amino-terminal peptide (P1NP) and collagen beta cross-laps (CTX). BMD measurements of lumbar spine (LS), femoral neck (FN) and total hip (TH) were performed using dual energy X-ray absorptiometry (Lunar DPX scanner). BMD results were expressed in comparison to aged matched controls (Z-scores).

Results: There were 43 Ethiopian patients (pts) (57.3%) and 32 (42.6%) Caucasian (CA) pts. Otherwise, there were no significant differences in demographics, actual and past HIV status, anti-retroviral treatment, and bone turnover markers between the groups.

The 25(OH)D serum levels < 10 ng/ml (severe vitamin D deficiency) were observed in 28 (65%) of ET vs. 2 (6.25%) of CA(p = 0.001). Plasma PTH was 72.14 ± 57.37 ng/l (normal 12-65), in ET vs. 31.23 ± 14.21 in CA ($P < 0.001$). Seventeen (40.4%) of the ET had sun exposure < 1 hour/day, vs. 6 (19.4%) of CA patients ($P = 0.07$); daily calcium intake was 514 mg (ET) vs. 164 mg (CA), $P = 0.001$. Avoidance of sun exposure was observed in 21 (67.7%) ET, vs. 16 (39%) CA, $P = 0.019$.

Z-scores in ET and CA were: at LS -1.8 ± 1.1 vs. -0.79 ± 0.88, respectively, $P = 0.001$; at FN -1.12 ± 1.1 vs. -0.59 ± 0.87, p 0.02, at TH -0.94 ± 1.1 vs. -0.25 ± .1.1, $P = 0.007$. BMD Z scores < -1 at LS were observed in 26 (89.7%) vs. 20 (48.8%), $P < 0.01$, at FN -20(69%) vs. 17 (41.5%), $P < 0.03$, at TH 17 (58.6%) vs. 9 (22%), $P < 0.001$ of severely vitamin D deficient pts vs. pts with 25(OH)D > 10 ng/ml, respectively.

Conclusions: Osteopenia was found to be frequent in young ET and CA HIV infected women. Vitamin D deficiency, low calcium intake, limited sun exposure, and clothing habits might affect BMD in this group of patients. A significantly lower BMD in dark skinned patients (ET) might be at least partially explained by their poorer vitamin D status.

Citation: RMMJ 2012;3 Suppl:25–26.

Poster #05C

Post Fracture Osteoporosis Treatment Program: Is it Efficient?

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Introduction: Low trauma events are common in the elderly. Patients with fragility fractures have a fivefold risk for further osteoporotic fractures. Orthopedic care usually does not include initiation of fracture prevention treatment.

Patients/Methods: A Fractures Prevention Program (FPP) was initiated at Rambam Health Care Campus in March 2009. All patients (pts) with fragility fractures were referred from the Department of Orthopedic Surgery to the Bone and Mineral Metabolism Unit for fracture prevention treatment (consult during hospitalization and outpatient clinic after discharge).

Results: A total of 900 pts were followed, ages 50-107 (75.18 ± 11.7), 247 (27.4%) men, and 653 (72.6%) women. There were 593 (66%) hip fractures, 60 (7%) vertebral fractures, 247 (27%) other fractures (humerus, wrist, tibia, and fibula); 155 (17%) pts had previous fragility fractures. All hip radiographs were retrospectively assessed by a bone radiologist; five pts (0.8%) met the atypical fractures criteria. These five were treated with alendronate for 2–9 years; none were diagnosed with an atypical fracture during hospitalization. Prior to hospitalization 156 pts (17.3%) received a fracture prevention treatment: 152 (23.2%) women (134 (88.2%) oral bisphosphonates; 10 (6.5%) raloxifen; 5 (3.3%) teriparatide); 4 (1.6%) men, alendronate. A 25OHD serum level prior to hospitalization was available for 239 (26.5%) pts. Mean 25OHD was 26.5 ± 14.7 (4-118) ng/ml; in 85 (35.6%) pts 25OHD ≤20 ng/ml, 25 (10.5%) 25OHD ≤10 ng/ml. 154 (17.1%) pts (23 (9.3%)

men, 131 (20.1%) women) adhered to the FPP. Femoral neck and midshaft fractures were found in 98 (63.6%) pts; other fractures were found in 56 (36.4%) pts.

There were 746 (82.9%) pts not included in the FPP. Of these, 693 refused to join, and 52 (10.6%) women and 1 (0.3%) man were treated in the community. Of the 693 pts that refused the FPP, 18 (2.4%) died. Of the patients being treated, 207 (23%) pts in FPP and 53 in the community, therapies were as follows: alendronate, 80 pts (38.6%); risedronate, 46 pts (22.2%); raloxifen, 5 pts (2.4%); zoledronate, 32 pts (15.4%); teriparatide, 28 pts (13.5%); and calcium and vitamin D prior to starting bisphosphonate, 16 pts (7.7%). Of the five patients with atypical fracture, four were switched to teriparatide, and one patient refused.

Conclusion: The majority of elderly patients remain untreated after fragility fractures. Hospital based FPP increased the rate of post fracture treatment by only 6%. Diagnosis of atypical fractures deserves special clinical and radiologic attention during hospitalization.

Citation: RMMJ 2012;3 Suppl:26-27.

Poster #06C

Assessment of PTH Response, Using New DIASORIN 1-84 PTH Third Generation Assay, to Oral 50000 Units Vitamin D3 Load

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Background: To date, measurement of intact 1-84 PTH serum levels in clinical research and practice was subject to assay-induced variability, due to use of antibodies that detect PTH fragments. The new DiaSorin 1-84 PTH, is a third generation assay that measures only 1-84 PTH and is hypothesized to provide better precision in the assessment of this hormone.

Methods: In order to test this hypothesis serum PTH was assessed in 57 healthy volunteers who were administered oral vitamin D3 load of 50,000 IU and in 31 pts who received placebo. Serum samples for 25OHD and PTH were collected before vitamin D administration and at day 1, 7, 14, and 28 thereafter. PTH was measured with Roche's second-generation assay and with new DiaSorin 1-84 PTH. Results were assessed using a two-way repeated measures multivariate model with Bonferroni correction.

Results: Serum 25OHD significantly increased in the vitamin D group from day 0 to 14 and 28. A weak significant negative correlation was demonstrated between 25OHD and PTH serum levels: r - 0.166 $P = 0.001$ for Roche and r - 0.267 $P = 0.0001$ for PTH DiaSorin that displayed a superior correlation to the increase in serum 25OHD, $P = 0.01$.

Conclusion: Correlation between Vitamin D and the DiaSorin new 1-84 PTH is better than the correlation with the intact PTH (Roche). This may indicate that measuring the 1-84 PTH could be of more accurate clinical value, might bring uniformity, and serve as a better tool for clinical and research evaluation.

Citation: RMMJ 2012;3 Suppl:27.

Poster #14C

AHNAK—A Novel Regulator of GLUT4: Role in Obesity and Insulin Resistance

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Introduction: High levels of free fatty acids play an important role in the pathogenesis of insulin resistance in obesity and Type 2 Diabetes. However, the mechanisms involved are yet unclear. Arachidonic acid (AA)—a well described

model for hyperlipidemia, repressed GLUT4 gene expression via a specific GLUT4 promoter region (-222/-197 bp), but the mediator remained elusive.

Methods: Using the GLUT4 promotor region as bait for mediators in AA-treated cardiomyocytes, followed by mass spectrometry analysis, we detected the AHNAK/desmoyokin giant protein in association with the GLUT4-promoter (GLUT4-P). This association was confirmed by ChIP assay.

Hypothesis: We examined the hypothesis that AHNAK—a novel giant protein—plays a major role in regulating glucose homeostasis *in vitro* and *in vivo* in human adipose cells. Unveiling this part of AHNAK function may serve as a potential molecular target for enhancing insulin sensitivity in obesity and diabetes.

Results: In subcutaneous adipose tissue obtained from obese patients undergoing bariatric surgery, AHNAK mRNA levels correlated with the degree of weight loss ($R^2 = 0.943$; $P = 0.005$). In human abdominal adipocytes, AHNAK and Glut4 protein levels were inversely correlated ($R = -0.810$, $P < 0.05$). Gene silencing of AHNAK by siRNA in primary rat adipocytes enhanced Glut4 protein levels by two-fold, and protected GLUT4 expression from AA-induced repression. The potential role of AHNAK on GLUT4 translocation was studied in muscle-derived L6 GLUT4myc cells. Compared to mock transfection, AHNAK silencing increased basal and insulin-stimulated cell surface levels of GLUT4 to ~150% and ~230%, respectively.

Conclusions: We have shown that AHNAK is a novel regulator of GLUT4, reduces its gene expression, and impairs its translocation machinery, thus contributing to the pathogenesis of insulin resistance. Hence, AHNAK may serve as a potential molecular therapeutic target in obesity and DM2.

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Poster #96C

Empirical Testing of the 'Infancy-Childhood Transition' Theory of Adaptive Life History

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Introduction: The infancy-childhood transition (ICT) theory claims an adaptive role for the age at ICT in maturation, body composition and growth, such that delayed ICT (DICT) results in short stature. To test this theory empirically, ICT was assumed to be controlled by weaning from lactation.

Material and Methods: First generation (F1) Sprague-Dawley pups, which usually wean on d21, were weaned by transfer to non-lactating foster-mothers on d16, d21, or d26. On d60, females and males were mated within the weaning groups and second-generation (F2) pups were followed for growth, maturation, puberty, and body composition by MRI.

Results: Early weaned pups (d16) reached d60 lengths of 41.9 ± 0.5 cm (F1) and 38.8 ± 1.6 cm (F2), vs. that of late weaned (d26) F1 and F2 pups with d60 lengths of 35.7 ± 1.5 ($P < 0.001$) and 35.4 ± 1.2 cm ($P < 0.001$), respectively. Likewise, the d16 F1 females grew faster ($P < 0.001$); however, early weaning led to reduced BMI. The d90 BMI was greater on d26 than d16 in males ($P < 0.05$) and females ($P < 0.001$); they showed glucose intolerance and insulin resistance, yet their body composition by NMR on d10 showed smaller body fat mass and greater lean body mass. Second generation pups shifted their infantile maturation: male pups of d16 parents had fur earlier at d8.7 ± 0.7 (d8.0 ± 0.5 in females) vs. d10.4 ± 1.6 in F2 d26 ($P < 0.05$), (10.7 ± 0.7 in females, $P < 0.05$). Pinnae detachment was also earlier on d10.7 ± 0.8 (10.6 ± 0.7 in F) in d16 F2 males as compared to 13.1 ± 0.6 in d26 F2 males ($P < 0.05$; $P < 0.05$ in females). Eye opening occurred on d15.7 ± 0.5 in d16 F2 males (15.5 ± 0.5 in females), as compared to 16.4 ± 0.5 ($P < 0.05$) in d26 F2 males (16.3 ± 0.5 in females, $P < 0.05$). Puberty also shifted: Vaginal opening and first estrous occurred in d16 F2 females on mean d35.0 and d40.1, respectively, as compared to d26 F2 on d36.9 ($P < 0.05$) and d42.4 ($P < 0.05$). Testicular growth of d16 F2 males started on d33, reaching a maximum volume of

4.1 ml on d58, as compared to d34 onset, maximum volume 3.3ml ($P < 0.001$) on d72 ($P < 0.001$) in d26 F2 males.

Conclusions: Long lactation and DICT in rats results in shorter bulkier animals with delayed development and puberty; these changes are transmitted to the next generations.

Citation: RMMJ 2012;3 Suppl:28–29.

Poster #108C

Trans-Generation Shift of Life History by Modulation of the Infancy Stage

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Introduction: The pre-adult life history of rats is divided into infancy, as defined by lactation, and juvenility to reach sexual maturity by age 45 days. In a previous study, we showed that late weaning results in short/obese/glucose intolerance phenotype.

Aims: Here we investigated the developmental and behavioral consequence of short vs. long infancy, as determined by weaning age.

Methods: Sprague-Dawley pups (generation F1), which are usually weaned at d21, were weaned by transfer to non-lactating foster-mothers at age d16, 21, or 26, and separated from the foster-mothers on d30. On d60, females and males were mated within the weaning groups and second-generation (F2) pups were followed for their developmental milestones and behaviors.

Results: Second generation pups shifted their infantile developmental milestones such that male pups of early weaning parents (d16) grew fur earlier (males, d8.7 ± 0.7; females, d8.0 ± 0.5), as compared to d10.4 ± 1.6 in pups of late weaning parents (d26) ($P < 0.05$), 10.7 ± 0.7 in females, $P < 0.05$. Pinnae detachment was also earlier in d16 F2 pups at d10.7 ± 0.8 (10.6 ± 0.7 in females) as compared to d13.1 ± 0.6 in d26 F2 ($P < 0.05$) pups, d13.4 ± 0.5 in females ($P < 0.05$). Eye opening occurred at d15.7 ± 0.5 in d16 F2 pups (15.5 ± 0.5 in females), as compared to 16.4 ± 0.5 ($P < 0.05$) in d26 F2 pups (females, 16.3 ± 0.5, $P < 0.05$). Vaginal opening of generation F2 pups also shifted, such that d16 F2 females opened at d35.0 ± 0.6, as compared to d26 for F2 pups, at d35.9 ± 0.7 ($P < 0.05$). Testicular volume of the d16 group was 1.0 ± 0.1 ml on d31, as compared to 0.8 ± 0.2 ml for d26 F2 pups ($P > 0.05$), and 2.8 ± 0.3 ml on d51 for the d16 F2 group, as compared to 2.3 ± 0.3 ml for d26 F2 pups ($P < 0.05$). The d26 offspring were less mobile, anxious before sexual maturation, and less novelty seeking.

Conclusions: The age at weaning determines the stages of growth, and this is transmitted over generations. Shorter infancy results in a trans-generational shift to earlier infantile and juvenile development, and hyperactive anxious behavior.

Citation: RMMJ 2012;3 Suppl:29.

HEMATOLOGY

Poster #25D

Contribution of Decreased Migration of Monocytes to Impaired Inflammation in Gaucher Disease

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Introduction: Gaucher disease (GD) is an autosomal recessively inherited lysosomal storage disorder caused by an inborn glucocerebrosidase (GBA) deficiency. This leads to accumulation of glycolipids in macrophages, resulting in organ damage. Recent studies suggest that clinical presentation of GD is primarily attributed to the impaired inflammatory process induced by "loaded macrophages," that could be explained by dysfunction of circulating monocytes.

Aim: The study investigated potential changes in migratory capacity of GD-derived monocytes (GD-Mo) that would contribute to the inflammatory response.

Material and Methods: Using immunomagnetic beads, $CD14^+$ monocytes were isolated from the blood of untreated GD patients and healthy volunteers (H-Mo). Monocyte migration capacity was assessed with Membrane Transwell inserts which contained either stromal cell-derived factor 1 (SDF1) or serum (0.25%) at the bottom chamber. Monocytes migrating from the upper chamber, over 4 hours were quantified by FACS. CXCR4 receptor blockage was examined using AMD3100. Serum SDF-1 levels were evaluated by ELISA.

Results: Upon exposure to SDF-1, migration capacity of GD-Mo ($n = 7$) was significantly lower than that observed in H-Mo ($n = 6$), (5.7% vs. 14%, $P = 0.02$, for 500 ng/ml SDF1 and 8.7% vs. 21.8%, $P = 0.013$, for 1000 ng/ml). Similar results were observed in the presence of autologous serum: migration capacity of 18.6% for GD-Mo ($n = 7$) vs. 45%, ($P = 0.05$) for H-Mo ($n = 5$). Notably, substitution of GD serum ($n = 7$) with healthy serum ($n = 7$) resulted in significant improvement in migration capacity of GD-Mo (18.6% vs. 33.6%, $P = 0.038$), while a reciprocal substitution of the serum caused a marked reduction in migration of H-Mo (34% instead of 45%). CXCR4 expression on GD-Mo was lower than that measured on H-Mo (64.5% ($n = 6$) vs. 83.6% ($n = 3$)). Blockage of the CXCR4 receptor led to a decreased migration capacity of H-Mo cultured in autologous serum (from 45.2% to 39.6%) ($n = 4$). This blockage had no impact on migration of both H-Mo and GD-Mo cultured with GD serum ($n = 6$). Of note, serum levels of SDF-1 were significantly increased in GD subjects compared to healthy ones (2603pg/ml vs. 2039 pg/ml; $P = 0.004$, $n = 10$).

Conclusions: Gaucher disease patients exhibit an impaired SDF1-dependent migration of monocytes, despite expressing an increased SDF-1 serum level that can be partly explained by low levels of CXCR4 on the monocyte surface. The reduced migration appears to be dependent on serum-derived factors, as demonstrated by the reversibility of this impairment with substitution of the GD serum for healthy serum. Reduction in migratory capacity may contribute to the abnormal inflammation accounting for GD-associated vascular and bone complications.

Citation: RMMJ 2012;3 Suppl:29–30.

HEMATO-ONCOLOGY

Poster #07

Reduced Specificity and Positive Predictive Value of Surveillance FDG-PET/CT for Diffuse Large Cell B Cell Lymphoma in the Rituximab Era

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***Introduction*:** The predictive value (PV) of surveillance PET in patients with diffuse large cell lymphoma (DLBCL), treated with rituximab (R) has not been explored. The current study compared the PV of surveillance PET in DLBCL patients receiving CHOP-R versus CHOP alone.

Methods: The institutional database was retrospectively searched for newly diagnosed adult patients with DLBCL, treated with CHOP or CHOP-R between 1995–2008, who achieved complete remission (CR), had surveillance PETs, and were followed until relapse/death or ≥ 12 months after the last scan. Clinical and imaging data at staging, follow-up (FU), and recurrence were analyzed for patients receiving CHOP alone (Group 1) vs. CHOP-R (Group 2). The ability of PET-FU to detect recurrence was assessed, in correlation with R administration. The PET-FU results were confirmed by biopsy, further imaging, and clinical FU.

Results: The study group consisted of 119 patients, 35 treated with CHOP and 84 with CHOP-R. There were no statistically significant differences in patient characteristics between the two groups. Within a median FU of 3.4 years, 31 patients relapsed (17 confirmed histologically), 14 in the CHOP-R group (15%) vs. 17 in the CHOP cohort (47%), ($P = 0.02$). Nine (29%) relapses were initially detected by PET-FU in asymptomatic patients. A total of 422 PET studies were performed; 113 in Group 1 and 309 in Group 2. Eighty-three studies were positive, 23 in Group 1,

and 60 in Group 2. However, in the CHOP-R group, only 23% (14/60) were truly positive compared to 74% (17/23) in the CHOP group (P = 0.001). The median time to false positive (FP) PET was significantly longer for patients receiving CHOP-R (1.3 vs. 0.6 years, P = 0.03). Specificity and positive PV (PPV) were significantly lower for patients receiving CHOP-R vs. CHOP only (84% vs. 95%, P = 0.023 and 23% vs. 77%, P = 0.0001). An FDG uptake involving head and neck lymph nodes was more likely to be FP, especially in Group 2 (88% vs. 4%, P = 0.0004).

Conclusions: Surveillance PET provides the first indication of relapse in 29% of patients with DLBCL. However, specificity and PPV of PET-FU is significantly lower in the R era. Interestingly, late FP PET, involving nodal sites, uniquely observed in patients receiving R, is assumed to reflect lymph node "recovery" following the R-induced B cell depletion.

Citation: RMMJ 2012;3 Suppl:30–31.

Poster #19Do

Early Interim PET/CT Can Guide Tailoring of Therapy in Hodgkin Lymphoma with No Impairment in Outcome

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Introduction: The current aim of Hodgkin lymphoma (HL) therapy is to maximize response and minimize long-term toxicity. Our multicenter study, initiated in 2006, prospectively evaluates outcome of HL patients (pts) whose therapy is chosen according to baseline prognostic factors and further tailored depending on PET/CT results after two cycles of chemotherapy.

Patients and Methods: Patients with classic HL aged 18-60 years, stages I-IV are eligible. Those with early HL are categorized according to German Hodgkin Study Group criteria. After two ABVD cycles pts with early favorable disease and negative PET/CT undergo involved nodal radiation therapy (INRT), and pts with early unfavorable disease receive two more ABVD cycles (total four cycles) plus INRT. Patients with positive interim PET/CT receive two additional cycles of ABVD (total four–six cycles) plus INRT. Patients with advanced disease (B symptoms or stages III-IV) are assigned to IPS-based treatment: standard-risk (SR) patients (IPS 0-2) initially receive two ABVD cycles, pts with IPS ≥ 3 get two cycles of escalated BEACOPP (EB). If interim PET/CT is negative or shows minimal residual uptake in ≤ 1 site, an additional four ABVD cycles are given. If interim PET/CT is positive with no evidence of disease progression, EB is continued for high-risk (HR) disease, is escalated to EB in SR, and INRT is given to bulky mediastinal masses.

Results: In this ongoing study, 210 pts have been enrolled. Sixteen (8%) progressed, of which six had primary refractory disease. Two pts died: one during autologous BMT for progressive disease and the other from acute MI, 2 years after therapy. Two of 16 relapsed pts had positive interim PET/CT, and 13 pts with early disease (12%) had therapy escalation following positive interim PET/CT, one of whom had disease progression both within and out of irradiation field 3 years after therapy. Negative interim PET/CT was found in 88% of pts with advanced disease (SR and HR). Therapy was reduced in 85% of advanced HR pts. After a median follow-up of 24 months (7-59), the current study demonstrates a progression-free survival of 88%: 96% for early and 80% for advanced disease. The negative predictive value for interim PET/CT was 92%.

Conclusions: Use of minimal chemotherapy and INRT in pts with negative interim PET/CT and therapy de-escalation for HR HL pts is feasible and safe. Cautious interpretation of this interim positive study should be made, due to the low positive predictive value of 9%.

Citation: RMMJ 2012;3 Suppl:31.

Poster #62Do

Early Identification of Induction Failure in Acute Myeloid Leukemia: A Novel Approach towards Personalizing Therapy and Implications for Future Therapy Modification

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Introduction: Induction of complete remission (CR) is fundamental for cure in acute myeloid leukemia (AML), and the prognosis for primary induction failure (PIF) is grave. Current practice is to predict impending PIF if blasts are present in non-hypoplastic bone marrow at the 14th day of induction. However, day-14 marrow cellularity is low, sensitivity for induction failure is limited, and most important, residual blasts are scant and cannot be characterized. Successful re-induction may prevent PIF when administrated as early as day-14, and re-induction preceding day 14 may further improve remission rates. On diagnosis, multiple different leukemic clones with a spectrum of chemotherapy sensitivity co-exist. Different leukemic associated immunopheno-types (LAIP) are apparent in most patients. Small resistant clones may be masked by highly proliferative, chemo-sensitive clones and dominant LAIP often shift from diagnosis to relapse. Therefore, we launched a novel protocol for early evaluation of bone marrow to better characterize resistant clones and predict PIF.

Material and Methods: A bone marrow aspirate on day-5 was performed to evaluate response to regular continuous seven days of induction chemotherapy. Aspirate is subject to morphology, immunophenotyping, and comprehensive genetic evaluation. Blasts are characterized by a Panel of 17 immunophenotyping markers and Annexin V+PI staining. Specific blasts populations of interest are identified and sorted for detailed evaluation.

Results: Among 15 recruited patients, eight pts entered CR, six pts experienced PIF, and one pt succumbed. Morphologically, day-5 bone marrow blasts counts were lower than 15% in all remitting patients and < 80% in non-remitting patients. The higher sensitivity of early bone marrow examination was demonstrated in two patients whose fifth day marrow blasts counts were as high as 85% and 92% while their day-14 marrows were hypocellular; these patients were eventually diagnosed with PIF. In six patients, phenotype shift from diagnosis was detected as early as the fifth day of therapy. Rate of blasts elimination was different among specific blasts sub-populations. In remitting patients, > 80% of blasts were apoptotic on anexin-V staining while in non-remitting patients non-apoptotic blasts were significant.

Conclusions: During AML induction therapy, real-time evaluation of response is feasible, sensitive for predicting PIF, and allows identification of low responding blasts subpopulations. These blasts are relatively chemo-resistant and are the seeds for impending relapse. A comprehensive genetic evaluation of these blasts will enhance our understanding of resistance mechanisms and improve patient care.

Citation: RMMJ 2012;3 Suppl:32.

Poster #63Do

Predictive Parameters for Infections during Azacitidine Therapy in High Risk Myelodysplastic Syndrome Patients

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Background: Neutropenic fever is a common life-threatening complication during azacitidine therapy; however, predicting it is challenging. To identify patients at considerable risk who may merit infection prophylaxis, we retrospectively surveyed 98 patients with myelodysplastic syndrome (MDS)/ or acute myeloid leukemia (AML), and treated with azacitidine.

Methods: Eighty-two high-risk MDS patients and 16 AML patients were treated with 456 azacitidine cycles between September 2008 and July 2011 at 11 institutions from Israel. Detailed laboratory information was documented prior to each cycle.

Results: The median age of patients was 71 (range 27-92); 57 (58%) were males. Poor cytogenetics was detected in 30.8% of the patients, with 65 (67%) transfusion-dependent patients. Doses and schedule of azacitidine data were available for 98% (446/456) of cycles. Seventy-eight infections episodes (16.9% of all cycles) were recorded. Nine parameters were included in final analysis: age, sex, cytogenetics, being transfusion dependent prior to first cycle, time from diagnosis to the first cycle, azacitidine dose, neutrophil, thrombocyte, and creatinine values prior to each cycle. We considered a full 7-day versus a 5-day schedule, neutrophils above or below 500 cells/µl, platelets above or below 20,000 cells/µl, and creatinine levels prior to the first day of the cycle. In univariate analysis, neutrophils below 500, platelets below 20,000, creatinine levels, azacitidine dose, and transfusion dependence were correlated with infection. In a multivariate analysis, transfusion dependency and platelets lower than 20,000 were the only significant parameters. Risk of infection was higher when a full 7-day cycle was administrated, but this was of no statistical significance (P = 0.07).

Conclusions: Transfusion dependency prior to the first cycle, and platelets lower than 20,000 prior to each cycle, are risk factors for infections during azacitidine therapy. We assume those are surrogate markers of the disease status, which makes the patient more prone to infections. Our findings should be confirmed in a larger sample set, but may pave the way for prospective studies of infection prophylaxis during azacitidine therapy.

Citation: RMMJ 2012;3 Suppl:32–33.

Poster #84Do

Glutathione S-Transferase P1 (*GSTP1* RS 1695) Gene Polymorphism Associated with Decreased Busulfan Clearance in Patients with Acute Myeloid Leukemia

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Introduction: High-dose busulfan (BU) has become a mainstay in preparative regimens for hematopoietic stem cell transplantation (HSCT), despite its highly unpredictable response, narrow therapeutic index, and severe toxicity. Considerable interest has focused on identifying ways to predict BU toxicity prior to treatment. Busulfan metabolism occurs mainly in the liver by members of the glutathione *S*-transferase (GST) family of phase II detoxification enzymes. Specific gene polymorphisms in GSTs have been associated with altered activity leading to treatment failure or toxicity. The aim of this study was to search for biomarkers predictive of poor BU metabolism, which may enable preemptive identification of patients at risk for BU toxicity.

Procedure: The study provides an integration of genetic and pharmacokinetic data of 63 adult patients with AML preconditioned for HSCT with high-dose oral BU.

Results: Busulfan plasma levels, expressed as the area under the concentration time curve (AUC/F), demonstrated that 76% of the patients achieved target AUC/F measured after the second dose; the remaining 24% required dose reduction. The main finding in the present study was the statistically significant association of *GSTP1* rs1695 variant allele with reduced BU clearance and increased AUC/F. Subdividing patients according to combined *GSTP1*, *GSTA1*, *GSTT1,* or *GSTM1* genotype showed that only the *GSTP1* genotype was associated with BU clearance or AUC/F. Contrary

to some studies, including our own on children with thalassemia, no significant association was found between *GSTA1* polymorphism rs3957356 and BU clearance or AUC/F. No correlation between *GSTM1*-null and BU pharmacokinetics was found.

Conclusions: The *GSTP1* rs1695 variant allele appears to be associated with increased risk of developing supra-therapeutic BU AUC due to lower BU clearance. Genotyping patients with AML before exposing them to high-dose BU may help in achieving target BU AUC with less trial-and-error, thereby reducing the risk of treatment related toxicity.

Citation: RMMJ 2012;3 Suppl:33–34.

HEPATOLOGY

Poster #08E

Low Incidence of Liver Damage in Non-Alcoholic High-Risk Patients with Psoriasis Exposed to High-Dose Methotrexate

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Background: Recommendations to follow with liver biopsy patients receiving methotrexate for psoriasis are based on the risk to develop liver damage as outlined by the American College of Rheumatology. Recent data suggest that methotrexate may be less hepatotoxic than previously assumed.

Methods: We have retrospectively collected data in patients with psoriasis who had liver biopsies performed between 1995 and 2010.

Results: Of 30 patients (mean age 51.80 ± 9.14), 25 were classified as high risk according to the American College of Rheumatology. High body mass index (mean 28.28 ± 2.15), and hyperlipidemia (44%) were amongst the most common co-morbidities, but exposure to medications with liver side effects was also very common (42%). No exposure to significant alcohol consumption was noted in this High body mass index group. The median cumulative methotrexate dose was 2,522 mg (range 1500-6000) over a median period of 44 months (range 15-96). Twenty-five liver biopsies were analyzed and 68% were classified as Roenigk Grade 1, 20% as Grade 2, and 12% as Grade 3a. Six patients had follow up biopsies after exposure to a very high cumulative dose of methotrexate, median 5040 mg (range 3010-8000) over a median period of 68 months (range 35-110). Of those, three showed no change, one revealed improvement, and the remaining two biopsies, that previously were classified Roenigk Grade 1, changed to Roenigk Grade 2.

Conclusions: Methotrexate related liver injury in high-risk psoriatic patients exposed to high cumulative doses of methotrexate is less frequent than previously thought. The recommendation for liver biopsy in this population needs revision, especially in patients who are not exposed to significant alcohol consumption.

Citation: RMMJ 2012;3 Suppl:34.

Poster #101E

Microcapsules Made of Hydrogel Polymer Cell Constructs for Intravascular Liver Tissue Engineering

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Introduction: The liver is the natural micro-environment for hepatocytes transplantation, but unfortunately, engraftment efficiency is low. New polymer technology allows making biosynthetic hydrogels constructs with fibrinogen, cross-linked with polyethylene glycol (PEG) and diacrylates side chains. The cell construct polymerized upon exposure to UV light. Pluronic® FF127 (Invitrogen, Ltd., Paisley, UK) synthetic copolymer, exhibits a similar reversible reaction when exposed to 37°C. The hydrogel micro scaffolds after intravascular injection may reduce shear stress and immediate immunological pressure, and thus may improve engraftment. We first tested the two types of scaffolds *in vitro*.

Aims: The aims of this study were to assess *in vitro* Huh7 viability and function after polymerization within PEGylated fibrinogen hydrogel constructs and Pluronic® F127. We also assessed intraportal transplantation efficiency of PEG-Fib microcapsules constructs with adult hepatocytes.

Methods: Methods used were as follows:

- Assessment of Huh7 cells viability by propidium iodide (PI)/fluorescein diacetate (FDA), and MTT assays.
- Evaluation of cell function using albumin concentration and CYP1A activity.
- Evaluation of microcapsules with HUH7 or adult hepatocytes engraftment efficiency in rats model *in vivo* using semiquantitative PCR (human 16q23.1) or real time qPCR (rat SRY gene) and histology compares to isolated cells.

Results: Compared to non-encapsulated cells, viability of the PEG-Fib encapsulated cells was comparable to non-encapsulated cells (95% ± 1.1% after three days). The viability of cells inside FF127 hydrogels was extremely low (5% ± 2%). Activity at day 3, of CYP1A in PEG-Fib scaffolds was comparable to that of non-encapsulated cells (4.33 ± 1 pM/μg DNA/4h vs. 5.13 ± 1 pM/μg DNA/4h, respectively). Albumin increased at d3, in encapsulated (Peg-Fib) cells, 12.8 mg/dl ($P < 0.05$). Urea also increased to 2.75 mg/dl ($P < 0.05$). Cell (HUH7)-polymer (Peg-Fib) constructs were transplanted to the liver, spleen, and subcutis allowing cells to proliferate for two weeks. Microcapsule cell constructs (Peg-Fib) at a size of 200-700 μm comprising HUH7 or adult hepatocytes have been successfully injected into the portal vein and transplanted cells were shown at 24h, 72h, and 168h after procedure by histology and PCR. When adult hepatocyte viability was compared with and without the polymer, we found early loss of cells but very good long-term survival.

Conclusions: The *in vitro* Huh7 viability and function after polymerization in PEGylated fibrinogen hydrogel construct was comparable to cells without the polymer. Intravascular viability of adult hepatocytes within the constructs was very good up to 168 hours, but overall efficiency of the procedure needs to be improved.

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OBSTETRICS/GYNECOLOGY

Poster #11F

Magnesium Sulphate (Mg) Prevents Maternal Inflammation Induced Offspring Cerebral Injury Evidenced by Magnetic Resonance Imaging (MRI)

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Introduction: Fetal and/or maternal infectious processes may be associated with newborn neurologic injury, and data suggest that Mg may protect the preterm fetus from cerebral palsy. As infection/inflammation may be etiologic in preterm labor, we sought to assess the inflammation-associated neuroprotective potential of Mg. We examined the effect of Mg on prevention of maternal lipopolysaccharide (LPS)-induced neonatal brain injury using MRI.

Material and Methods: Pregnant Sprague-Dawley rats at 18 days gestation received i.p. LPS (500 μg/kg) or saline at time 0. Dams were randomized to treatment with s.c. saline or Mg (270 mg/kg loading followed by 27 mg/kg q20 min) for two hours prior to and following the i.p. LPS or saline. Pups were delivered spontaneously (e21) and allowed to mature until postnatal day 25. Female offspring (4-8 per group) were examined under isoflurane anesthesia by MRI brain imaging and analyzed using voxel based analysis (VBA) after spatial normalization. The T2 relaxation time was used to assess for white matter injury and diffusion tensor imaging for Fractional Anisotropy (FA) comparison.

Results: Offspring of LPS-treated dams exhibited (1) significantly increased T2 levels, and (2) reduced FA levels in white and gray (e.g., corpus callosum, thalamus, and hippocampus) matter, consistent with diffuse cerebral injury. In contrast, offspring of Mg-treated LPS dams demonstrated

similar T2 and FA levels as control in both white and gray matter.

Conclusions: Treatment with Mg significantly reduced evidence of neonatal brain injury associated with maternal LPS. These studies suggest that maternal Mg therapy may be most effective in human preterm deliveries associated with maternal/fetal inflammation.

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GYNECO-ONCOLOGY

Poster #15Fo

Diagnostic Implications of p16 Expression in Serous Papillary Endometrial Cancer

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Objective: The purpose of this study was to examine whether the overexpression or under-expression of the p16 protein in serous papillary endometrial cancer (SPEC) bears a prognostic significance. The secondary objective was to establish the value of p16 immunohistochemical staining as an adjunct to diagnosis.

Study Design: Archived paraffin blocks holding specimens from the uteri of 31 serous papillary carcinoma patients, and 31 endometrioid endometrial carcinoma patients were re-cut and re-stained for p16. The former group was also stained for p53.

Results: Overexpression of p16 was found in 78% of the serous papillary patients versus 36% of the endometrioid patients. P16 was not found to be an independent prognostic factor in serous papillary endometrial carcinoma. The combined sensitivity of p16 and p53 for the detection of SPEC was found to be 83%.

Conclusion: While p16 was not found to have prognostic significance in serous papillary endometrial carcinoma, it may be valuable as a diagnostic adjunct in histologically ambiguous tumors.

Citation: RMMJ 2012;3 Suppl:37.

Poster #16Fo

Preventing Double Jeopardy: The Significance of Maximum Standardized Uptake Value in PET-FDG of Cervical Cancer Patients as a Decision-Aiding Tool for Surgical or Radiation Treatment

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Introduction: Cervical cancer is one of the leading causes of death among women with gynecologic malignancies. Early stages of the disease (IB-IIA) are normally treated surgically. However, some patients are referred for postoperative radiotherapy, leading to increased morbidity. Maximal Standardized Uptake Value (SUV_{max}) is a PET-CT derived semi-quantitative measurement of FDG uptake in a defined lesion, and may reflect tumor aggressiveness. The purpose of this study was to determine if preoperative high SUV_{max} values can be used for selection of initial therapy, thus reducing side effects resulting from bimodal treatment.

Methods: The PET-CT studies of 47 cervical cancer patients who underwent surgery were reviewed and SUV_{max} data were collected. Statistical analyses were performed to determine the relationships between SUV_{max} values and clinical parameters and outcomes.

Results: The SUV_{max} was found to correlate with tumor depth of invasion ($r = 0.46$, $P < 0.003$). A significant relationship was found between SUV_{max} and histological grade, with mean and variance of SUV_{max} significantly lower for grade 1 compared with grades 2 and 3 (mean 1.10, 11.06, and 8.88, and variance 3.57, 45.60, 29.79, respectively; $P < 0.0001$).

A possible SUV_{max} cutoff value was identified indicating possible increased risk of bimodal

treatment—SUV_{max} > 10.08 (sensitivity: 61.5%, specificity:75.8%).

Conclusion: The SUV_{max} may be used as a decision-aiding tool for the first line of therapy in early stage cervical cancer, thus preventing the increased morbidity of bimodal treatment.

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Poster #55Fo

Early Assessment for Suspected Recurrent Ovarian Cancer -Optimizing PET/CT Performance using a Tumor Marker Based Analysis

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Objectives: Serum CA125 level measurements are used in the assessment of patients with ovarian cancer, with 35 µg/mL representing the upper normal value. This study aimed at determining the optimal cut-off value of CA125 levels for best PET/CT performance in early evaluation of suspected recurrent ovarian cancer.

Methods: We retrospectively reviewed 113 PET/CT studies of 61 patients with ovarian cancer. Indications for PET/CT included suspicion for recurrence due to increasing CA125 levels (n = 54) or CT findings (n = 13), and monitoring response to treatment (n = 41) or follow up (n = 5). All available Serum CA125 measurements at the time of the PET/CT study were recorded. Various CA125 values < 35 µg/mL were correlated with PET/CT performance using ROC analysis and with clinical follow-up.

Results: We found CA125 levels ≥ 35 µg/mL in 63 studies (56%); recurrent cancer was diagnosed in 60 of them (95%). PET/CT had a sensitivity, specificity, positive and negative predictive value, and accuracy of 93%, 100%, 100%, 43%, and 94% respectively. The ROC analysis found the CA 125 lowest cut-off value of 23 µg/mL to correspond to a similar PET/ CT sensitivity, specificity, positive and negative predictive value and accuracy of 94%, 100%, 100%, 50%, and 95%, respectively.

Conclusions: Yielding the same performance indices for PET/CT positivity, a lower Ca125 threshold value of 23 µg/mL, rather than the standard limit of 35 µg/mL, should be used as a referral guide at the decision time-point aiming at early diagnosis of recurrent ovarian cancer.

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Poster #64Fo

Late Toxicity of Definitive Radiotherapy using High Dose Rate Brachytherapy for Cervical Cancer: Long-Term Follow-Up

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Introduction: Radiotherapy is an important treatment modality of cervical cancer and often includes concomitant chemo-radiotherapy (intra-cavitary high dose rate (HDR) brachytherapy and external pelvic irradiation (EBRT)). The rectum and bladder tolerate radiation significantly less than the proximal vagina, and are thus considered as limiting structures. However, the proximal vagina (vault) may develop necrosis due to high dose irradiation, and the exact vaginal tolerance to HDR has never been estimated. In 2004, Nevelsky et al. published a method to evaluate dosimetric aspects of HDR brachytherapy calculated on 245 treatments plans of 50 cervical cancer patients treated between 1998 and 2002. The aim of this study is to evaluate tolerance of the vaginal vault, late complications, and to validate the vaginal points for dose reporting as calculated in our previous study.

Methods: A retrospective review of all medical records of 50 patients included in our previous study was conducted for radiation-associated late sequelae of the proximal vagina, bladder, and rectum. Vaginal toxicity was graded according to the PV examination recorded in the medical files,

and staged by a gyneconcologist to fourlevels (I, no toxicity up to level IV, complete vaginal obliteration). Rectal and bladder toxicity were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Results: Fifty patients included in the study. There were no records of acute grade IV toxicity during treatment. Follow-up ranged from 1 to 10 years. Seven were lost to follow-up. Ten (23%) patients recurred. The total maximal surface dose to the vaginal vault was 15775 cGy. Data of late vaginal toxicity (≥ 6 months) was available for 25 patients: 7 (28%) patients had level I, 7 (28%) patients, level II, 7 (28%) patients, level III, and 4 (16%) patients suffered from level IV. There were no cases of vaginal necrosis or fistulas (recto-vaginal or cysto-vaginal) or grade IV late rectal or bladder toxicity. Data of intercourse was available for 12 patients: 4 indicated they were sexually active, 8 were not. Nine of 43 (20%) patients had a second primary malignancy (2 out of 9 in the irradiated field).

Conclusions: Concomitant chemo-radiotherapy including pelvic radiotherapy with weekly cisplatin and HDR brachytherapy is relatively safe. The calculation method for surface dose introduced in our previous study for HDR brachytherapy is a reliable method. It appears that the vaginal vault can tolerate doses exceeding those delivered to our patients.

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ONCOLOGY

Poster #13G

The Role of Breast Cancer Cell-Line Microparticles in Thrombogenicity and Angiogenesis following Chemotherapy

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Introduction: Microparticles (MP) bearing tissue factor (TF) is involved in cancer hyper-coagulability and cell exposure to chemotherapy results in MP secretion. Vascular endothelial growth factor receptor 1 (VEGF-R1) mediates autocrine effects enhancing breast cancer cell invasion. We therefore assumed that tumor MPs could be involved in breast cancer-related tthrombogenicity and angiogenesis.

Study aims: Characterization of MPs obtained from human breast cancer cell line (MDA231) and evaluation of their thrombogenic and angiogenic effects on endothelial cells (EC).

Material and Methods: MPs were isolated from MDA231 cells following exposure to starvation or chemotherapy agents (Doxorubicin, Paclitaxel). MPs were characterized and their effects on EC were assessed by FACS, FXa chromogenic assay, migration and tube formation assay.

Results: Stimulation of MDA231 resulted in increased cell apoptosis and release of MPs; MDA-MPs were found to express low levels of TF (10%) compared to their parent cells (80%, $P = 0.0003$). Conversely, the TFPI level expressed by MDA-MPs appeared to be high (35%) compared to their parent cells, and went down following high-dose chemotherapy (9%, $P = 0.02$). Furthermore, MDA-MPs assessed after high-dose chemo-therapy, showed a five- to eight-fold increase in procoagulant activity compared to MPs evaluated following low-dose chemotherapy ($P = 0.016$). Microparticles explored after low-dose chemo-therapy expressed lower levels of VEGF-R1 (23%) than those observed post high-dose chemotherapy (54%, $P = 0.03$). The MDA-MPs evaluated follow-ing starvation adhered to EC, penetrated into the cells and affected cell hemostatic balance and tube formation, while MPs assessed after low-dose chemotherapy inhibited tube formation.

Conclusions: Breast cancer MPs exposed to low-dose chemotherapy present low thrombogenicity, low level of VEGF-R1 and inhibit angiogenesis, while MPs exposed to high-dose chemotherapy show high thrombogenicity and high VEGF-R1 levels. These findings may clarify, in part, the role of tumor MPs in hypercoagulability and angiogenesis associated with chemotherapy in cancer.

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Poster #44G

Carboplatin Dosing in Non-Small Cell Lung Carcinoma Patients using Calvert Formula and Cockroft-Gault Equation for GFR Estimation: A Reliable Method?

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Introduction: Carboplatin dosing is based on renal function rather than on body surface area. The most commonly used method to calculate carboplatin dose is the Calvert formula. Estimated glomerular filtration rate (eGFR) is calculated according to the Cockroft-Gault (CG) equation, which relies on serum creatinine level (Scr), age, and weight. However, Scr can change due to numerous (cancer and non-cancer) causes, and does not necessarily reflect true GFR. Paradoxically, a decrease in Scr unrelated to a change in renal function will be translated to a higher carboplatin dose. This study was undertaken to evaluate retrospectively the reliability of using the CG for eGFR used for carboplatin dosing according to the Calvert formula.

Patients and Methods: The records of patients with advanced non-small-cell lung carcinoma (NSCLC) treated with first-line carboplatin-containing chemotherapy were retrospectively analyzed, excluding patients with renal insufficiency. The theoretical carboplatin doses derived from the Calvert formula, using the CG equation, were calculated for each chemotherapy cycle using the actual Scr. The fluctuations in the theoretical carboplatin doses were analyzed. The discrepancies between the actual carboplatin doses prescribed by the physician and the theoretical doses were also assessed.

Results: The study group included 117 patients; the median age was 62 years. Compared to the first-cycle dose, subsequent doses were higher by > 10% in 79/320 subsequent cycles (24.7%) and lower by > 10% in 53/320 cycles (16.6%) ($P = 0.015$). Body mass index ≥ 30 was found to be associated with a tendency to increase in eGFR during subsequent chemotherapy treatments cycles ($P = 0.009$).

A comparison between the actually prescribed carboplatin doses and the theoretical doses showed that physicians tended to lower the prescribed dose by using a higher Scr for dose calculation than that actually measured.

Conclusions: Calvert formula derived carboplatin dose widely fluctuate during repeated cycles if actual Scr is used for eGFR. Discrepancies of > 10% compared to the initial dose were noted in more than 40% of subsequent doses, and about one quarter of the theoretical subsequent doses were higher by more than 10% from the initial dose, due to decrease in Scr. Physicians tend to prescribe a lower dose than the theoretical dose derived from Calvert formula by using a Scr higher than the one actually measured. Thus, it is advised to reconsider measurement of 24h creatinine clearance in patients with observed serum creatinine reduction during therapy.

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Poster #45G

Niche Dependent Support of Heterogeneous Malignant Ovarian Ascites-Derived Cancer Cell Sub-Populations

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Introduction: Solid tumor complexity emanates from the requirement of a supportive microenvironment that provides a compatible network of interactions between the heterogeneous cancer cells and various tumor-supporting cells. We have established and validated a tumor microenvironment model based on the potential of human embryonic stem cells (hESC) to generate *in vivo* teratomas, comprised of a wide variety of differentiated tissues and structures, for studying human tumorigenesis. We extended this approach to examine the attributes of such a cellular microenvironment in supporting the growth of human cancer cells freshly harvested from

malignant ovarian ascites, and to determine whether there are differences among subsets of ascites-derived cancer cells in terms of tumorigenic capacity, self-renewal and tumorigenic differentiation capacities, in the conventional murine xenograft model and in the hESC-derived microenvironment.

Material and Methods: Human cancer cells were harvested from malignant ovarian ascites fluid collected from a 64-year-old patient diagnosed with stage IV clear cell carcinoma of the ovary. Separation processes enabled the identification and characterization of six different cancer cell subpopulations (CCSPs).

Results: Only four of the six CCSPs developed into tumors in a conventional xenograft model; all six of the CCSPs robustly generated tumors in the hESC-derived cellular microenvironment, demonstrating niche dependent tumorigenic capacity. Detailed analyses indicate that the CCSPs are six different 'cancer stem cell' (CSC) populations that exhibit the capacity for both self-renewal and tumorigenic differentiation in a niche-dependent manner, and are characterized by the expression of specific markers for CSC. Remarkably—in the embryonic stem cell based model—these ovarian cancer cell subpopulations from a single patient, recapitulated the broad repertoire of properties that can be seen in tumors observed across the entire spectrum of many different patients. Despite the diverse histological phenotypes and niche preferences, genomic analyses demonstrated a monoclonal tumor origin for the different subpopulations. Moreover, the hESC-based model, exposed subpopulations of ovarian cancer stem cells (CSC) —which are believed to serve as relevant targets for a sustained response with anti-cancer therapy. Accordingly, we have performed gene expression analyses using laser micro-dissected tissues from tumors generated in both *in vivo* models to examine the attributes of the hESC-based model in supporting the capacity of distinct CCSPs to generate tumors and the maintenance of CSC properties such as self-renewal and tumorigenic differentiation.

Conclusions: We suggest that the hESC-based model provides an integrated platform to scrutinize critically the 'cancer stem cell' paradigm and to develop and test multimodal anti-cancer therapies.

Citation: RMMJ 2012;3 Suppl:39–40.

Poster #47G

Pleural Effusion C-Reactive Protein Predicts Pleurodesis Success in Malignant Pleural Effusion Patients

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Introduction: Malignant pleural effusions (MPEs) often cause debilitating symptoms that result in impaired quality of life. Pleurodesis is commonly indicated for symptom relief in MPE patients. The relatively limited clinical success of pleurodesis procedures necessitates the advancement of MPE management. The aim of the current study was to determine the predictive accuracy of pleural fluid C-reactive protein (CRP) levels for identifying MPE patients among whom pleurodesis will be successful.

Materials and Methods: Sixty-three consecutive patients with symptomatic MPE were eligible to participate in this study. Four grams of talc mixed in 150 ml of normal saline were administered in 54 patients via tube thoracostomy after complete drainage of the pleural effusion. The CRP levels in the intrapleural fluid were assessed before the pleurodesis procedure, the success of which was evaluated one month post-treatment objectively by chest X-ray and subjectively via reports of respiratory symptoms.

Results: Successful pleurodesis was achieved in 19 of 35 eligible MPE patients (54.29%). ANOVA indicated a significant difference between the pre-treatment CRP levels in the groups which underwent successful vs. non-successful treatments (95% CI: 18.96-49.58, 8.05-19.11, respectively; $P = 0.046$). Except for two patients, the subjective and objective success criteria were correlated ($P < 0.001$).

Conclusions: Current findings suggest that pleural fluid CRP levels, which reflect the inflammatory state, may predict pleurodesis success and symptomatic failure among MPE patients. Accordingly, pleural fluid CRP levels should be used in selecting patients for pleurodesis.

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Poster #48G

Diagnostic Accuracy of Fine-Needle Aspiration Cytology in Parotid Tumors

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Introduction: Fine-needle aspiration cytology (FNAC) has gained widespread acceptance and popularity among head and neck surgeons in the assessment of neck masses. The use of FNAC in parotid gland masses is still controversial, regarding its sensitivity and specificity, which varies between 41–100% and 86–100%, respectively.

Research Hypothesis: To assess the sensitivity and specificity of FNAC in the diagnosis of parotid tumors compared with the final pathology, and tumor location on pre-operative computerized tomography.

Materials and Methods: Final pathology and CT data for FNAC were retrospectively reviewed and compared for all patients who underwent Parotidectomy between 2000 and 2010. Literature review was based on trials comparing FNAC with final histological evaluation of parotid tumors identified through an extensive Medline search of the English literature. Outcome measures analyzed included percentage of non-diagnostic samples, sensitivity, specificity, positive predictive value, negative predictive value, and the accuracy of FNAC.

Results: Sensitivity of FNAC in the present study (90%) was higher compared to previous series. Specificity of FNAC in the present study (98%) was equally high as that calculated. Diagnostic accuracy of FNAC was equally high (88%) in our study compared to previous series.

Conclusions: Fine-needle aspiration cytology should be interpreted as a complementary diagnostic tool and combined with clinical features, physical examination, and imaging to increases the diagnostic yield. Fine-needle aspiration cytology can contribute to the diagnosis of parotid gland malignancy and should be performed in all patients, especially those over 60. Ultrasound guidance is recommended in lesions smaller than 25 mm.

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Poster #49G

Maxillary Resection: A Retrospective Study

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Introduction: The term maxillectomy is used currently to describe a variety of surgical approaches performed to treat broad spectrum of diseases involving the maxillary bones, mainly neoplastic tumors. This work reports our experience in the variety of maxillary diseases such as odontogenic and non-odontogenic tumors, mucormycosis, and others as malignant tumors requiring surgical intervention, and analyses of our data with regards to neck dissection performed in malignant tumors, squamous cell carcinoma (SCC) of the maxilla.

Materials and Methods: A retrospective analysis of 66 maxillectomies were reviewed and recorded between the years 2000 and 2009. Each patient's data sheet was reviewed; epidemiology analysis was performed and recorded for age, gender, histopathological diagnosis, and size of tumor. For SCC, neck dissection, chemoradiotherapy and survival rate was also analyzed.

Results: The average age was 54 years (range 5-84 years). The majority of patients receiving maxillectomy suffered from malignant tumors (41, 59%) compared with non-malignant pathologies (25, 41%). Squamous cell carcinoma accounted for 40% of all cases. Male to female ratio was almost equal (1.6:1). However, when looking at oral maxillary SCC patients, the male group was dominant at 2:1. The overall mortality rate was 23%; however, two groups showed a higher mortality rate: the SCC group showed a 41% mortality rate, and a much higher mortality rate was found in the mucormycosis of the upper jaw group, which accounted for five deaths out of six patients with maxillary mucormycosis. Twenty-

five patients had SCC of the upper jaw and paranasal sinuses. Seventeen of them had neck dissections. Out of the SCC group, six patients (24%) were identified with loco-regional lymph node metastases.

Conclusions: In the present study, we presented our experience in maxillectomies regardless of the reason. Since the primary disease is not always due to oncological reasons, a global and accurate classification is needed to describe the surgical procedure that will be carried out. A high percentage of the SCC patients (24%) had cervical metastases. This strongly supports the need for routine elective neck dissection for treatment of maxillary SCC, even if clinical examination is negative.

Citation: RMMJ 2012;3 Suppl:41–42.

Poster #50G

Incidence of Oral Cancer Occult Metastasis and the Survival of T1-T2, N0 Oral Cancer Patients

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Introduction: In head and neck cancer, the most important prognostic factor is the presence or absence of neck metastasis. Although a debate is still present in the current literature regarding the "wait and see" policy in T1/T2 oral cancers, a large number of clinicians support the necessity of neck dissection especially in cases of oral tongue carcinoma due to poor prognosis and high risk of recurrence.

This present study summarizes and reports the incidence of occult metastasis in oral cancer treatment in the department of oral and maxillofacial surgery at the Rambam Medical Center in the last 10 years.

Materials and Methods: A total of 142 neck dissection performed in our department in the last 10 years (1998-2009), a series of 68 patients (44 males and 22 females) treated for T1,T2, N0 oral cancer were included in this retrospective study. All patients underwent surgical resection of the oral cancer and selective neck dissection of the ipsilateral side.

Results: Occult lymph node metastasis were detected in 11 patients (16% overall, 9 tongue, 1 buccal mucosa, 1 gingiva of mandible). Occult metastasis frequency from tongue carcinoma was 34% (9 of 26 cases). The 5-year-survival in the present study was 78.9%. In patients treated following the surgical management with either chemotherapy, radiotherapy or brachytherapy, or a combination of the three, the overall survival decreased significantly to 22.5% ($P = 0.006$, Log Rank).

Conclusions: The incidence of occult metastasis in oral cancer patients, in the present study, was 16% overall. In tongue carcinomas, a much higher incidence (34%) of occult metastasis was detected. Furthermore, the need for chemo-radio therapy following the initial surgical management, mainly due to occult metastasis, was found to be a significant negative predictor of patient's outcome. The results of the present study emphasize the need for prophylactic neck dissection in oral cancer patients diagnosed with T1, T2, N0 disease, especially when the primary lesion is localized in the tongue.

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Poster #51G

Mouse Model for the Study of Hepranase Role in Oral Cancer Formation

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Introduction: Numerous studies have shown that metastases formation depends on the ability of tumor cells to invade basement membranes and tissue barriers in a process involving enzymes capable of degrading extracellular matrix (ECM) components. One of these enzymes is heparanase, an endoglycosidase that degrades heparan sulfate.

Research Hypothesis: In a previous study, we have shown that the nuclear localization of

heparanase is found in all oral verrucous carcinomas, very well differentiated tumors that do not metastasize, as opposed to only 28% of nuclear localization detected in oral squamous cell carcinomas. Heparanase expression level also significantly correlated with the degree of tumor differentiation. Moreover, while cytoplasmic localization of heparanase was associated with high-grade carcinomas, nuclear localization of the enzyme was found primarily in low grade, well-differentiated tumors, the aim of the present study was to use an *in vivo* model to study heparanase role in cancer formation and progression.

Materials and Methods: 4NQO is a water-soluble carcinogen, which induces tumors predominantly in the oral cavity. It produces all the stages of oral carcinogenesis and evidences suggest that similar histological as well as molecular changes are observed. We used this carcinogen to establish a mouse model of oral tongue SCC. Heparanase expression and activity was evaluated using immunohistochemical analysis and real time, heparanase activity was studied on both cytosolic and nuclear fractions of total proteins that were analyzed using radiolabeled ECM and a scintillation counter.

Results: Heparanase was over expressed in tongue cancer from hyperkeratosis to invasive SCC stage, heparanase enzymatic activity was significantly higher in the nucleus in normal tissues as opposed to developing cancer, which exhibited a higher cytoplasmic activity of the enzyme.

Conclusions: Heparanase nuclear expression is correlated with normal tissue and is important since, when carcinogenesis is initiated, heparanase translocates to the cytoplasm as the cancer progresses, and heparanase overall expression is increased in cancer formation from pre-malignant to invasive SCC. Expression level and cellular localization of heparanase could serve as reliable predictive indicators of oral carcinoma development, metastatic potential, and patient prognosis.

Citation: RMMJ 2012;3 Suppl:42–43.

Poster #54G

TSEI-Associated Malignant Melanoma in Mycosis Fungoides

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Introduction: The incidence of MM in the Israeli population according to the Annual Report for 2007 of the Israeli National Cancer Registry is 13.54 per 100,000. The risk of second primary malignancy in cutaneous T-cell lymphoma (CTCL), including non-melanoma skin cancer, has been well documented. However, reports of malignant melanoma (MM) as second primary malignancy in CTCL are rare.

Patients and Methods: The National Cancer Registry and the Rambam Health Care Campus databases were queried to identify second primary malignant melanoma in CTCL patients. As a result, a database of 196 patients was developed, encompassing the period from 1950 until June 2010.

Results: Seven mycosis fungoides (MF) cases associated with MM were identified. Five had been treated with total skin electron irradiation (TSEI), one with involved field skin electron irradiation, and one had no irradiation treatment. Two patients were treated with PUVA or MN topically and one received total body irradiation. The patients had early stages (IA-IB) of MF.

Conclusions: In CTCL patients, we found the incidence to be 7 per 196. The mechanisms of the phenomenon may lay in CTCL pathogenesis and/or in the negative influence of electron beam treatment combined with the sun light exposure among patients with MF.

Citation: RMMJ 2012;3 Suppl:43.

Poster #57G

The Role of Apoptosis and Proliferation in Anorectal Melanoma: Analysis of 61 Cases

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Introduction: Melanoma of the anorectum is a rare yet lethal malignancy. It has worse prognosis compared to cutaneous melanoma, and to date, very little in known about the pathogenesis of ARMM. Additionally, there is a need to identify prognostic markers in ARMM. Dysregulation of apoptosis is a common finding in various malignancies; many times, it is associated with disease prognosis. The aim of this study was to determine whether the expression of apoptosis and proliferation markers are associated with prognosis in ARMM.

Material and Methods: We collected clinical and prognostic data from 61 cases of ARMM. Tissue samples from these patients' tumors were analyzed for apoptosis using TUNEL staining and immunohistochemistry for the apoptosis markers bcl-2 and p53. Additionally, the tumors' proliferation index was determined using a stain for Ki67. We then correlated between the immunohistochemical results and the patients' prognosis.

Results: The median survival in the group was 13 months. Of the 61 patients included in the study 43 (70%) underwent curative surgery. In the group that underwent curative surgery patients with less than 50% of cells positive for Ki67 survived a mean of 42.5 ± 8.7 months while those with more than 50% of cells positive for Ki67 survived a mean of 16.4 ± 3.9 months ($P = 0.03$). Bcl2, p53 and TUNEL staining did not show statistically significant associated with patients' prognosis.

Conclusions: Apoptosis as well as the levels of expression of the apoptotic markers bcl2 and p53 was not associated with patients' prognosis. Proliferation index was an independent prognostic factor for ARMM in cases that were treated with curative surgery.

Citation: RMMJ 2012;3 Suppl:43–44.

Poster #58G

Intra-Tumor KRAS Mutation Status Heterogeneity: A Molecular Morphometric Study

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Introduction: KRAS mutation status has a significant role determining anti-EGFR treatment response in colon carcinoma patients. Malignant transformation is a dynamic process and therefore, it is plausible that at a certain point the tumor cells mass will be heterogeneous for particular mutations. Therefore, the fraction of tumor cells carrying a particular mutation may be more relevant for treatment than the simple determination of presence or absence of mutation. The purpose of this study is to assess the degree of KRAS mutation status heterogeneity in colon carcinoma samples.

Material and Methods: DNA was extracted from formalin fixed paraffin embedded samples of colon carcinoma and scrutinized for the presence of KRAS mutation. The relative fraction of mutated versus wild-type KRAS was evaluated by real-time PCR. Additionally, the relative fraction of cancer cells was evaluated using computer assisted morphometric analysis. Using this data, we calculated the fraction of mutation-containing cells in the samples.

Results: One-hundred and sixty-nine cases of colon carcinoma were analyzed and KRAS mutation was found in 75 cases (44%), of which 42 were available for morphometric analysis. In 41 (97.6%) of these cases the fraction of mutation containing tumor cells was 50% or higher, indicating the absence of significant KRAS-mutation-status heterogeneity. There was a strong positive correlation ($R = 0.66$, $P < 0.0001$) between the fraction of mutated KRAS and the fraction of cancer cells in the samples.

Conclusions: The strong positive correlation between the fraction of mutated KRAS and the fraction of cancer cells in the samples indicate homogeneity of KRAS mutation status in colorectal carcinoma.

Citation: RMMJ 2012;3 Suppl:44–45.

Poster #73G

A Survey of Israeli Cancer Patients' Attitudes towards Spiritual Care

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Introduction: Spiritual care is "The practice of supporting individuals and families in crisis by helping to reveal, support, and strengthen their own senses of meaning and spirit." In the past six years, several Israeli hospitals have begun incorporating professional spiritual care into their standard patient services. Most of our patients are entirely unfamiliar with this service. The primary goal of this study is to understand patients' attitudes to meeting with the Spiritual Caregiver as part of the comprehensive care they receive.

Patients/Methods: Questionnaires were distributed to inpatient and outpatient cancer patients. The questionnaire was a composite of several tools used by previous studies, adjusted slightly for the Israeli context. We received 364 sufficiently complete surveys from respondents who were 55% female, 52% over age 60, and 79% Jewish.

Results: The study's key question was "How open do you think you would be to a visit from the spiritual caregiver?" There were 41.5% ($N = 151$) positively inclined patients; 33.0% ($N = 120$) were uninterested in receiving the service. Using univariate analysis, several factors were identified. Self-identifying as "very spiritual" (61%; $P < 0.001$) or "somewhat spiritual" (43%; $P < 0.001$) indicated a greater likelihood of wanting to receive spiritual care than self-describing as "not spiritual" (16%). Hospitalized patients who received visits from family and friends once a week or less were interested in spiritual care 73% of the time, versus 41% of those receiving daily visits ($P = 0.004$). Interestingly, people identifying "Helping others" as being important to them were more inclined to want to receive the spiritual caregiver's help (47% vs. 27%, $P = 0.007$). A previous encounter with the spiritual caregiver ($N = 43$) dramatically raised patients' interest to 69.8% ($P < 0.001$). In addition, 62% ($N = 225$) of respondents thought they understood the task of a spiritual caregiver; this correlated strongly with wanting to receive spiritual care ($P < 0.001$). Another set of questions focused on what specific support patients would want from the spiritual caregiver ("support for my family"; "ability to face things with calm and dignity"; etc.), and a Chaid classification analysis of the results identified subpopulations that are particularly interested or uninterested in these specific kinds of care.

Conclusions: Israeli hospitals are trying to introduce a new service for their patients—spiritual care. This study showed that a substantial percentage of patients are actively interested in receiving this service, and it starts to build a screening system to identify patients most likely to be good candidates for it.

Citation: RMMJ 2012;3 Suppl:45.

Poster #80G

Plasma Levels of Heparanase as Marker of Tumor Aggressiveness and Stage of Disease in Patients with Colorectal Cancer

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Introduction: Heparanase enzyme upregulation was documented in large number of tumors, including colorectal cancer, associating with increased tumor aggressiveness. This study evaluates the correlation between plasma heparanase levels and clinical and pathological parameters, such as tumor burden and response to antineoplastic treatments.

Materials and Methods: Plasma heparanase levels were assessed in 92 colorectal cancer patients, treated at the Division of Oncology,

RHCC. Patients were divided into three groups, according to their tumor burden. The first group comprised 47 patients with recurrent or metastatic disease. In this group, blood samples were collected at onset of treatment and at restaging. The second group included 27 patients without evidence of disease up to 6 months after surgery. The third group included 18 patients without evidence of disease at least two years after surgery. Plasma heparanase was measured by ELISA.

Results: Mean serum heparanase concentration in the first sample of the entire population was 179.6 ± 595.3 pg/ml. In the first, second, and third group of patients the mean plasma heparanase levels were 221.9 ± 703.8 pg/ml (n-47), 28.3 ± 102.6 pg/ml (n-27), and 295.8 ± 696.4 pg/ml (n-18), respectively. A trend for higher mean serum heparanase levels among the patients with active disease (first group) as compared to patients without evidence of disease (second and third groups), 221.9 ± 703.8 pg/ml and 135.3 ± 459.5 pg/ml, respectively, (P = 0.1). Smoking history (P = 0.004), lymph node sampling (P = 0.02), and oxaliplatin-based chemotherapy (P = 0.007) were independent predictors of plasma heparanase levels in univariate analysis. A trend for higher serum heparanase concentration among the patients with metastatic disease (P = 0.2), and high-grade tumors (P = 0.3) was observed, also the trend for lower plasma heparanase concentration in oligometastatic disease (P = 0.08) was seen. A non-significant correlation between response to oncological treatment and plasma heparanase alterations was observed (P = 0.18).

Conclusions: A positive, but non-significant correlation between plasma heparanase level and tumor aggressiveness and response to oncological treatment in patients with colorectal cancer was observed. Smoking history, lymph node sampling, and oxaliplatin-based chemotherapy were independent predictors of plasma heparanase level. Further studies are required to validate plasma heparanase as a marker of colorectal cancer aggressiveness.

Citation: RMMJ 2012;3 Suppl:45–46.

Poster #86G

May Personalized PET-CT-Based Clinical Staging of Non-Small Cell Lung Cancer (NSCLC) Reduce the Need of Invasive Procedures?

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Introduction: An accurate clinical staging of patients with a non-small cell lung cancer (NSCLC) is pivotal for deciding on the most efficacious treatment and prognosis. Compared to using the conventional NSCLC clinical staging alone, adding the PET-CT improves the staging accuracy and reduces the frequency of futile thoracotomies. However, the accuracy and futility rate of the clinical staging based on PET-CT alone remain equivocal. We prospectively addressed this topic in our Thoracic Surgery department, where clinical staging is routinely PET-CT based.

Materials and Methods: Sixty-six patients were consecutively recruited from November 2009 to November 2010. Inclusion criteria included (i) an abnormal lung finding on a CT scan diagnosed as, or highly suspected with NSCLC; (ii) suitability for anatomical resection; (iii) confirmed lack of distant metastases; and (iv) positive PET-CT imaging of the finding. Clinical staging was determined in weekly multidisciplinary meetings. Pathological staging was evaluated according to the final pathological report.

Results: PET-CT-based staging accuracy was 0.84 (4 PET-CT false positives; 6%). Ten patients had futile thoracotomy (15.15%) defined as stage IV (n = 1), stage IIIA with N2 involvement (n = 3), benign lung lesion (n = 4) or breast cancer (n = 2). No systemic upstaging or downstaging took place (P = 0.607).

Conclusions: This study suggests that PET-CT, together with multidisciplinary meetings, may serve as an accurate staging strategy in early stage lung cancer, and as an efficient determinant of NSCLC patients' operability. This strategy may (i)

obviate invasive staging procedures, (ii) maximize the clinical PET-CT staging accuracy, and (iii) minimized the frequency of NSCLC-related futile thoracotomies.

Citation: RMMJ 2012;3 Suppl:46–47.

Poster #95G

Quality of Oncology Care at the Hospital-Community Interface

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Introduction: Oncology patients receive care from various providers and experience frequent transitions between different care systems. Oncology patients face many challenges to navigating their care. Recent evidence shows that good linkages between oncologists and Primary Care Physicians (PCPs) can result in significant improved quality of care and even reduction in the length and number of hospitalizations. Yet, care transitions remain a weak-link in the cancer care trajectory and breakdowns in communication are common. This study aimed to examine the quality of care at the hospital-community interface and elicit the perspectives of patients and providers in order to better acknowledge the facilitators as well as barriers to seamless care.

Material and Methods: The study combined quantitative and qualitative methods. In-depth personal interviews and focus groups were conducted with patients and family members (25 patients total). Additionally, 33 providers were interviewed including doctors, nurses, social workers, and administrative managers, at hospital and community settings. The quantitative phase included a survey of 422 patients, using validated questionnaires assessing the quality of primary care and the transition from the hospital to community (Care Transition Measure (CTM)). Patients from the Rambam Oncology Center, aged 18 and over, who speak Hebrew, Arabic, or Russian were included. Data regarding utilization of healthcare services during the year after the hospitalization was collected (only for members of Clalit Health Services) from Clalit's databases.

Results: Qualitative analysis revealed two major challenges: ambivalence and confusion regarding the roles of healthcare providers and overcoming healthcare system barriers. Patients and family became their own case managers and used informal routes of communication. Nurse specialists played a significant role in managing care. Quality of primary care attributes that were ranked the lowest were those pertaining to organizational characteristics (e.g., coordination of care). Patients' ratings of their transitional care indicated moderate quality of the transition process (60-70 on a 0-100 point scale), with reports on insufficient understandings of their ongoing care plan and medication regime.

Conclusions: The high morbidity burden, high health care service utilization, and the difficulties embedded in navigating care between many providers and across settings necessitate the formulation of system-wide interventions for improving the quality of oncology care at the hospital-community interface.

Citation: RMMJ 2012;3 Suppl:47.

Poster #100G

Whole Brain Irradiation with Hippocampal-Sparing Technique: A Treatment Planning and Dosimetric Study

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Introduction: Whole brain radiation therapy (WBRT) is the most effective treatment for patients with multiple brain metastases. However, months to years following WBRT, patients can present with progressively severe deficits in learning functions, memory (short and long-

term), and spatial information processing due to the irradiation of the hippocampus. The hippocampus is located inside the medial temporal lobe, beneath the cortical surface, and belongs to the limbic system. It plays a role in the consolidation of information from short-term to long-term memory and spatial navigation. Avoidance of the hippocampus during WBRT may decrease and delay the onset of these complications. However, sparing during WBRT poses challenges with respect to contouring and treatment planning. We report our preliminary experience with WBRT using hippocampus-sparing in patients with brain metastases.

Methods: Patients treated with WBRT were re-planned using the original CT simulation scans and MR-CT fusion. The hippocampus was contoured, and hippocampal avoidance regions were created using a 5-mm volumetric expansion around the hippocampus. Linear accelerator-based intensity-modulated radiotherapy (IMRT) treatment plans using the Step and Shoot technique were generated for prescribing a dose of 30 Gy in 10 fractions to the whole brain while minimizing as much as possible the dose to the hippocampus.

Results: Ten patients (three males, seven females) at a mean age of 53 years treated with WBRT were re-planned, using the original CT simulation scans and MRI-CT fusion, and enrolled in this study. Primary diseases were breast cancer (five patients), lung cancer (three patients), endometrial carcinoma, and carcinoma of unknown origin (one patient each). The mean dose to the hippocampus using the Step and Shoot technique was 1133 cGy. The mean minimum absorbed dose (D100%) to the hippocampus was 857 cGy, and the mean maximum absorbed dose to the hippocampus was 1508 cGy. The mean dose to the whole brain was 3315 cGy, the mean near minimal absorbed dose (D98%) to the whole brain was 2570 cGy, and the mean near maximal absorbed dose (D2%) to the whole brain was 3733 cGy.

Conclusions: Modern IMRT techniques allow sparing of the hippocampus with acceptable target coverage and homogeneity. Long-term follow-up is needed to confirm the postulated neurocognitive benefit.

Citation: RMMJ 2012;3 Suppl:47–48.

NEUROSCIENCES

Poster #33H

Less-Efficient Conditioned Pain Modulation is Associated with Greater Pain Relief by Duloxetine among Neuropathic Pain Patients

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Introduction: This study aims at individualizing the selection of drugs for neuropathic pain by examining the potential coupling of a given drug's mechanism of action with the patient's pain modulation pattern. The latter is assessed by the conditioned pain modulation (CPM) and temporal summation (TS) protocols. We hypothesized that patients with a malfunctioning pain modulation pattern, such as less-efficient CPM, would benefit more from drugs augmenting descending inhibitory pain control than would patients with a normal modulation pattern of efficient CPM.

Methods: Thirty painful diabetic neuropathy patients received one week of placebo, one week of 30 mg/d doluxetine, and four weeks of 60 mg/d doluxetine. Pain modulation was assessed psychophysically, both before and at the end of treatment. Patient assessment of drug efficacy, assessed weekly, was the study's primary outcome.

Results: Baseline CPM was found to be correlated with duloxetine efficacy ($r = 0.628$, $P < 0.001$, efficient CPM is marked negative), such that less-efficient CPM predicted efficacious use of duloxetine. Regression analysis ($R^2 = 0.673$; $P = 0.012$) showed that drug efficacy was predicted only by CPM ($P = 0.001$) and not by pre-treatment pain levels, neuropathy severity, depression level, or patient assessment of improvement by placebo.

Furthermore, beyond its predictive value, the treatment-induced improvement in CPM was correlated with drug efficacy (r = -0.411, P = 0.033). However, this improvement occurred only in patients with less-efficient CPM (16.8 ± 16.0 to -1.1 ± 15.5, P < 0.050). No predictive role was found for TS.

Conclusions: The coupling of CPM and duloxetine efficacy highlights the importance of pain pathophysiology in the clinical decision-making process. This evaluative approach promotes personalized pain therapy.

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Poster #38Hp

Bedouin Wives on the Home Front: Living with Men Serving in the ISRAEL Defense Forces

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Introduction: With the ongoing military involvement in Iraq and Afghanistan and the high rate of mental health disorders among veterans returning from deployment, there has been growing interest in manifestations and costs of posttraumatic stress and awareness of its toll on veterans' families. Couples report impaired and more conflicted marital relationships, and partners experience elevated levels of psychiatric symptoms and somatic problems, low self-esteem, and feelings of loneliness. The term "secondary traumatization" describes the finding that family members residing with survivors of violent trauma can themselves become its indirect victims.

The applicability of findings from studies of Western veterans and their partners to members of non-Western ethnic minority communities is questionable. The current study was designed to examine the impact on Bedouin women of co-inhabiting with husbands exposed to military trauma and suffering from post-traumatic stress disorder (PTSD).

Methods: This community-based study, conducted in a Bedouin village in the Galilee, examined the emotional and somatic symptoms of 129 Bedouin women whose husbands serve in the Israel Defense Forces. Interviews conducted with the wives, in Arabic, included measures of adverse life events and trauma, PTSD, depression, and wives' assessment of husbands" aggression. Analyses included univariate analysis of variance (ANOVA) with Scheffe's post-hoc comparisons and χ^2 tests, Pearson product-moment correlations and hierarchical regression analyses with Sobel mediation tests.

Results: Wives of men diagnosed with PTSD reported more symptoms than wives of men diagnosed with other *DSM* disorders and wives of men with no diagnosis. Findings indicate that not only was PTSD in Bedouin servicemen positively and strongly associated with their wives' symptoms of posttraumatic stress and depression and somatic complaints, but that this relationship was fully mediated by husbands' aggression.

Conclusions: It is argued that the experience of Bedouin wives living with husbands who are suffering from PTSD is better described by the concept of *Burden of Care* than by the concept of *Secondary traumatization*, which assumes *stress contagion* through familiarity with the trauma experienced by the men. Unraveling the special circumstances of women from traditional backgrounds faced with the devastating effects of their husbands' combat-related posttraumatic pathology may inform an approach to the concept of vicarious trauma that is more specific to non-Western societies.

Citation: RMMJ 2012;3 Suppl:49.

Poster #70H

Can MR Spectroscopy Differentiate Patients with Amnestic Mild Cognitive Impairment from Alzheimer Disease and Healthy Individuals?

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Introduction: Amnestic mild cognitive impairment (aMCI) is a prodromal stage of Alzheimer disease (AD), characterized by memory decline yet unimpaired daily activities. Clinical deterioration from normal cognition to aMCI and to AD reflects a neurodegenerative process. Finding a biological marker that can follow this process is important for better staging of the disease spectrum and for clinical trials settings of potential disease modifying drugs. MR spectroscopy (MRS) enables *in vivo* quantification of certain metabolites found in the brain, such as N-Acetyl-Aspartate (NAA), Choline, and MyoInositol (mI) that can point at pathological conditions. We investigated the MRS profile in individuals with these different cognitive conditions in order to find out if they might serve as potential biological markers for monitoring the neurodegenerative process and differentiating between aMCI, AD and healthy individuals.

Materials and Methods: Thirty-two individuals aged 55-80, were included: 10 aMCI, 12 mild to moderate AD, diagnosed by the Neurocognitive Unit at Rambam and 10 healthy individuals. Memory tests of aMCI patients had scores lower than 1.5 standard deviations as compared to healthy individuals. The mean MMSE score was: for AD patients -19.5/30 ± 4.2 and for aMCI patients -26.5/30 ± 1.6 while for healthy individuals the MMSE score was above 28/30. MRI studies were performed with a 1.5T system (HDX 14, GE Milwaukee). The studies included basic sequences in different planes. Single voxel Proton MR Spectroscopy (1H MRS) was performed using point resolved spectroscopy (PRESS) technique. The voxel was located in the retrosplenial cortex known to be involved pathologically early in the course of AD. Metabolite ratio to Creatine and NAA ratio to mI were calculated using the vendor's software.

Results: Pairwise comparisons using the non-parametric Mann-Whitney-U test showed significant statistical decrease of NAA/Creatine ratio in the retrosplenial cortex in AD patients as compared to those with aMCI ($P < 0.019$,) and to healthy individuals ($P < 0.0001$). NAA/Creatine was significantly lower in the retrosplenial cortex in aMCI patients compared with normal controls ($P < 0.031$). NAA/ myoinositol ratio was significantly lower in the retrosplenial cortex in aMCI patients as compared to normal controls ($p = 0.013$).

Conclusions: Our study shows that NAA/Cr and NAA/mI ratios in the retrosplenial cortex have an important impact on the discrimination between aMCI and AD and might serve a possible biological marker that can differentiate them from one another and from individuals with a normal cognitive state.

Citation: RMMJ 2012;3 Suppl:49–50.

Poster #74H

Pre-Pubertal Interference with Sp1 Transcriptional Activity and Exposure to Chronic Mild Stress Later in Life as a Potential Novel Rat Model for Depression/Anxiety Disorders

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Introduction: The leading hypothesis regards major depression and anxiety disorders as an interaction between stressful life events and numerous susceptibility genes of minor effect. To mimic gene-environmental interaction etiological hypothesis in rats, we suggest transiently manipulating the expression of multiple genes at a critical period of brain development, and later in life exposing them to a stressful environment.

Methods: The manipulation of gene expression was performed by a brief interference with Sp family binding to its consensus DNA GC-rich sequence with mithramycin. Environmental insult was induced by exposing rats to chronic variable mild stress. Rats were treated with mithramycin 0.1 mg/kg/day or saline from the 7th to 10th postnatal day (PND). Half of the rats from each group were exposed to chronic mild stress at puberty, after which all of them passed through a battery of depression-relevant behavioral tests.

The rats were decapitated at PND 90 and protein levels of relevant gene were analyzed in the frontal cortex, striatum, hippocampus, and cerebellum and compared with their expression on PND11.

Results: Mithramycin at doses of 0.05-0.2mg/Kg/day s.c. and saline was administered to Wistar rats at PND 7 for 4 days. The lethal dose was 0.2mg/Kg and the optimal dose was 0.1mg/Kg according to dose effects on behavioral and molecular measures. Weight gain during mithramycin treatment (PND7-PND 10) was slightly (25%), but still significantly ($P < 0.01$), reduced. This reduction in weight gain was abolished at PND 35. Mithramycin cause a dose dependent increase of Sp1 protein level at the end of the injection period PND11. At PND 60, following the stress period, increased behavioral anxiety and anhedonia were observed in the group of rats that received both mithramycin and stress. In line with the latter, CREB, a hallmark in depression and brain plasticity, was significantly reduced in the prefrontal cortex in these rats. In addition, Sp1 protein levels were not normalized and significant differences were observed in Sp1 regulated mitochondrial related genes.

Conclusions: The present preliminary results support the potential of this treatment paradigm to become a tool to study gene environment interaction in major depression and anxiety.

Citation: RMMJ 2012;3 Suppl:50–51.

Poster #75Hp

The Role of Dlgap2 in Post-Synaptic Density (PSD) Zone Organization: Implication to PTSD

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Introduction: Disks Large-Associated Protein (Dlgap) family is one of the less studied components of the PSD zone. It was proposed to mediate the translocation of the scaffolding protein PSD95 from the cytosol to the membrane and its communication with sub-synaptic molecules. Impaired expression of Dlgap was reported in both schizophrenia and autism. We showed that abnormal Dlgap2 expression is associated with maladaptation to trauma in a PTSD rat model. In this study, the mode of action of Dlgap2 in the PSD zone is investigated.

Methods: Hippocampi dissected from P1 Sprague-Dawley rats were cultured. Glia proliferation was restrained, resulting in about 30% immunoreactive glia. mRNA levels of Dlgap2, PSD95, Neuroligin 2 (NLG2), NMDA receptor subunit 2B (NR2B), neuronal β3-Tubulin, glial GFAP and the reference genes RSB3K, CypB and β-actin were assessed by qRT-PCR during 4-29 DIV. Intracellular location of Dlgap2 and related proteins was analyzed by immunohistochemistry. In addition, Dlgap2 was silenced by lentivirus-delivered shRNA at 8 and 9 DIV.

Results: Higher Dlgap2 mRNA levels were associated with reduced glia content, suggesting that Dlgap2 is expressed mostly in neuronal cells. Time-dependent Dlgap2 expression showed a bell shaped curve and was positively correlated with that of PSD95 levels. However, the increase in PSD95 expression was delayed by 2 days as compared to Dlgap2, while corroborated with the enhancement in the expression of PSD-related genes, NLG2 and NR2B. To validate further the role of Dlgap2 hippocampal cells we used shRNA-silencing technique. The efficiency of the lentiviral infection measured by lentivirus-delivered GFP was 70%. Dlgap2 silencing resulted in a reduction of 70 ± 5% in Dlgap2 mRNA levels in infected as compared to control cultures. Interestingly, β3-tubulin expression was increased by 146% in the infected vs. the control cultures. No change was observed in mRNA levels of additional members of the PSD zone KaMK2, NLG2 and NR2B.

Conclusions: Our preliminary data show that changes in Dlgap2 in hippocampal neurons are associated with changes in PSD-95. This together with morphological changes suggests a role for Dlgap2 and PSD-related genes in neuronal sprouting. We believe that this study will unravel a role for Dlgap2 in PSD zone, which may be of relevance to postsynaptic function, which is believed to be impaired in PTSD.

Citation: RMMJ 2012;3 Suppl:51.

Poster #76Hp

Opioid-Degrading Enzymes in Individual Reactivity to Traumatic Stress

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Introduction: Reactivity to traumatic stress varies between individuals. The endogenous opioid system has been extensively implicated in anxiety and stress management, but its specific alterations in individual reactivity to traumatic stress are yet to be delineated. We investigated in rats the role of the opioid-degrading enzymes, specifically insulin degrading enzyme (IDE), which degrades β-endorphin, in vulnerability/ resilience to acute traumatic stress.

Materials and Methods: Rats were exposed to traumatic foot-shock stress and categorized according to their behavioral responses to responders—showing extreme anxiety, and non-responders—not differing from the non-stressed rats. Blood levels of β-endorphin and corticosterone, as well as brain levels and activity of opioid-degrading enzymes were estimated. Effects of slowing down β-endorphin degradation following exposure to stress on behaveioral and hormonal responses were tested as well. To that end, we exposed rats to elevated-platform stress, and after categorization to responders or non-responders, exposed them to foot-shock stress, while they received intra-amygdalar insulin or saline prior to foot-shock. Reduced β-endorphin degradation by insulin was verified *in vitro*.

Results: Pre- and post-trauma levels of serum corticosterone, and post-stress plasma β-endorphin concentration differentiated between responders and non-responders. Liquid Chromatography-Tandem Mass Spectrometry analysis of hippocampal and amygdalar β-endorphin degradation rates suggested enhanced activity of IDE in responders. Brain metabolism of β-endorphin correlated with anxiety, whilst the peripheral measures correlated with locomotion. Amygdalar β-endorphin degradation rate was reduced after exposing the amygdala to insulin. Insulin application to the amygdala prior to exposure to traumatic stress reduced post-stress anxiety and serum corticosterone levels specifically in the responders.

Conclusions: Slowing down β-endorphin degradation rate may constitute an integral part of the normal stress-response, upon a failure of which an extreme anxiety develops. IDE and insulin may thus present potential novel targets for pharmacotherapy intervention in stress-related disorders.

Citation: RMMJ 2012;3 Suppl:52.

Poster #77Hp

Differential Expression of Genes Encoding Neuronal Ion Channel Subunits in Major Depression, Bipolar Disorder and Schizophrenia: Implications to Pathophysiology

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Introduction: Evidence concerning ion channels abnormalities in the pathophysiology of common psychiatric disorders is still limited. Given the significance of ion channels in neuronal activity, neurotransmission, and neuronal plasticity, we hypothesized that the expression patterns of genes encoding different ion channels may be altered in schizophrenia, bipolar and unipolar disorders.

Methods: Frozen samples of striatum including the nucleus accumbens (STR-NAC) and the lateral cerebellar hemisphere of 60 brains from depressed (MDD), bipolar (BD), schizophrenic

and normal subjects ($n = 15$ in each group), obtained from the Stanley Foundation Brain Collection, were assayed. The mRNA of 72 different ion channel subunits were determined using Human Neuroscience Ion Channels and Transporter RT²Profiler™ q-PCR Array. The alterations observed in four of the genes were verified by immunoblotting.

Results: In the STR-NAC, the prominent change was observed in the MDD group, in which there was a significant up-regulation in genes encoding voltage-gated potassium channels' subunits. However, in the lateral cerebellar hemisphere (cerebellum), the main change was observed in schizophrenia specimens, as multiple genes encoding various ion channel subunits were significantly down regulated. Alterations in protein levels of four genes grossly matched the changes in their mRNA expression, strengthening the validity of the gene array findings. The impaired expression of genes encoding ion channels demonstrates a disease-related neuroanatomical pattern.

Conclusions: The alterations observed in STR-NAC of MDD may imply electrical hypo-activity of this region that could be of relevance to MDD symptoms and treatment, specifically for deep brain stimulation. The robust unidirectional alteration of both excitatory and inhibitory ion channels in the cerebellum may suggests cerebellar general hypo-transcriptional activity in schizophrenia.

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Poster #78Hp

Perturbation in Mitochondrial Network Dynamics and in Complex I Dependent Cellular Respiration in Schizophrenia

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Background: It has been suggested that mitochondria are involved in the pathology of bipolar disorder (BD) and schizophrenia. However, the mechanism underlying mitochondrial dysfunction is unclear. Mitochondrial network dynamics, which reflects cellular metabolic state, is important for embryonic development, synapse formation, and neurodegeneration. This study aimed to investigate mitochondrial network dynamics and its plausible association with abnormal cellular oxygen consumption in schizophrenia.

Methods: Viable EBV-transformed lymphocytes (lymphoblastoids) from DSM-IV diagnosed patients with schizophrenia ($n = 17$), BD ($n = 15$) and healthy controls ($n = 15$) were assessed for mitochondrial respiration, mitochondrial dynamics and relevant protein levels by oxygraph, confocal microscopy and immunoblotting, respectively.

Results: Respiration of schizophrenia-derived lymphoblastoids was significantly lower as compared to controls, and was twice as much sensitive to dopamine (DA)-induced inhibition. Both impairments were due to complex I dysfunction. Unlike DA, the antipsychotic drug haloperidol, inhibited complex I driven respiration to a similar extent in both schizophrenia and the control cells. Our data show that both drugs interact with complex I, yet at different sites. At the DA interaction site, we found alterations in protein levels of three subunits of complex I, *NDUFVI*, *NDUFVII* and *NDUFSI,* both in brain and in blood cells in schizophrenia. In addition, we observed structural and connectivity perturbations in the mitochondrial network, associated with alterations in the pro-fusion protein OPA1 in schizophrenia derived lymphoblastoids, which was similarly reduced in schizophrenia prefrontal cortex specimens. None of these alterations were observed in the BD cells, which did not differ from the control cells.

Conclusions: We show impaired mitochondrial network dynamics associated with reduced cellular respiration and complex I abnormalities in schizophrenia, but not in BD. If these findings represent disease-specific alterations, they may become an endophenotype biomarker for schizophrenia.

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Poster #105H

Is There Really a Bystander Effect? Injury Markers and Indirect Nerve Injury

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Introduction: The understanding of neuropathic pain has been greatly advanced by experimental models of nerve injury. Most widely used models of neuropathic pain involve injuries that produce an admixture of intact and degenerating axons in close juxtaposition. It is hypothesized that this mixing of injured and intact axons is essential to the development of neuropathic pain. How these various components contribute to neuropathic pain is not completely understood. The purpose of this study was to examine whether markers of nerve injury are up-regulated in nerve that is exposed to degenerating nerve explants, to the exclusion of direct nerve injury.

Methods: Laboratory rats were randomized to one of five surgical procedures: sham surgery (skin incision only) nerve-tie control (nerve-exposure and elevation onto nerve tie), long sciatic nerve fenestration, degenerating nerve explant over long sciatic nerve fenestration (DNE), and nerve transection. Dorsal root ganglia from L5 were harvested at one week post-operative survival and stained for markers of nerve injury, especially activating transcription factor 3 (ATF-3). Sciatic nerve sections were stained for routine histology and macrophages.

Results: Histological sections confirmed the close juxtaposition of intact and degenerating nerve fibers in the DNE model animals. Both DNE and long sciatic nerve fenestration resulted in an increased number of macrophages in the sciatic nerve at one week post-op. Sham surgery was not associated with increased nerve injury markers in the dorsal root ganglion, by contrast, sciatic nerve transection resulted in a dramatic up-regulation of injury markers. Nerve tie-control animals demonstrated a very small but measurable increase in ATF-3 staining. Long sciatic nerve fenestration and DNE manipulations resulted in small but measurable increases in nerve injury markers that were not statistically distinguishable.

Conclusions: Exposure of intact nerve to degenerating nerve factors by means of nerve explant is does not induce an up-regulation of nerve injury markers in transplant-tolerant Lewis rats. The extent to which indirect injury in response to neuro-degeneration as an independent mechanism of neuropathic pain merits additional study.

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Poster #106H

Computational Modeling of the Two-Axon C-Fiber

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Introduction: Despite the critical role of C-fibers in the initiation and transmission of nociceptive signals, little is known about the nature and extent of electrochemical interactions between axons and Schwann cells, and axons and axons, within the C-fiber (Remak) bundle. Axons and Schwann cells within the C-fiber exhibit electrochemical properties that are distinctly different from those of myelinated axons. Yet, much of what is known about axonal signal transmission is based on properties particular to myelinated axons, e.g. saltatory conduction, highly focal ionic fluxes, appraisal of energetic requirements, and pathological alterations such as demyelination. The purpose of this study is to exam the electrochemical properties of non-myelinated axons in more detail.

Materials and Methods: In collaboration with the National Resource for Cell Analysis and Modeling at the University of Connecticut, we have established a computationally intensive model of the two-axon/single-Schwann cell C-fiber bundle. This model incorporates elements of sodium and potassium channels that have distinct

features in axons and Schwann cells, as well as functioning Na-K-ATPases in axon and Schwann cell membranes. In order to establish realistic dimensions for the C-fiber unit, the current model is based on a scanned cross-sectional electron micrograph of a two-axon/single Schwann cell Remak bundle taken from rat nerve.

Results: The model is computationally represented as existing within an interstitial bath of 4 by 2 microns, and contains two axons, each approximately 800 nanometers in diameter. A major computational challenge is the representation of the peri-axonal space, which has significantly smaller dimensions, i.e. 11 nanometers. Preliminary results from this model indicate the dimensions of the peri-axonal space have a profound impact on the concentration shifts of extra-axonal potassium ions as well as sodium ions during action potential propagation. The dramatic shifts in potassium ion concentrations in the peri-axonal space are observed within the model to have a significant effect on the membrane potential of the nearby Schwann cell membrane, leading to depolarization.

Conclusions: We conclude that models of unmyelinated axon-Schwann cell systems are useful for understanding the unique electrochemistry of C-fibers and that further study is needed.

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Poster #113Hp

Psychological Distress among Sisters of Young Females with Eating Disorders: The Mediating Role of Negative Sibling Relationships and Sense of Coherence

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Introduction: Few studies have examined sibling relationships in families that have a child with an eating disorder (ED). The aim of this study was to explore the mediating role of sibling relationships and sense of coherence for the psychological state of the sister without the ED.

Method: Participants were 60 females, aged 13-31 years old, including 30 who had a sister with an ED (study group) and 30 without (controls). The participants completed self-report questionnaires on demographic attributes, depression, psychological distress, sibling relationships, and sense of coherence.

Results: Results showed that the sisters in the study group had higher levels of depression and negative sibling relationships than those in the control group, with a significant correlation found between them. A significant negative correlation was also found between sense of coherence and depresssion. A negative relationship with the sister who had an ED was found to be a mediating variable for the depression level of the sister without the ED.

Conclusions: When compared to controls, young females whose sisters have an ED may present with elements that are more psychopathological. Considering the effect of relationship quality, it may be that the higher depression and the lower coherence are a result of constant interaction with the sick sister. However, it may also represent a shared component (maybe genetic) in the family.

Citation: RMMJ 2012;3 Suppl:55.

Poster #114Hp

Personality and Neuropsychological Measures in Women with Eating Disorders, Their Healthy Sisters, and Normal Controls

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Introduction: The goal of this study was to test whether different lateralization patterns can be

used as markers for eating disorders (ED). We examined lateralization patterns for neutral stimuli—a verbal task (lexical decision) which results in a left hemisphere (LH) advantage and a spatial task (bar graphs) which results in a right hemisphere (RH) advantage. Since ED tend to "run in the family" we tested healthy sisters of women with ED and unrelated healthy controls.

Method: Five groups of right handed women participated in the experiment: Anorexia Nervosa restricting type (AN-R); Anorexia Nervosa binge/purge type (AN-B/P); Bulimia Nervosa binge/purge type; healthy controls; healthy women, who had a sister with ED (sisters). All participants performed a computerized lexical task and a spatial task on a split visual field paradigm, which was designed to test each hemisphere function separately. They have also completed several self-report questionnaires.

Results: All groups show opposing laterality patterns in the two tasks. Sisters of ED women show patterns that are similar to the patient groups, and different from the non-ED control group. The sisters group, who were similar to the ED groups on the lateralization task, had a self-character report that was normal and similar to the control group. In the Bar-Graphs task, findings in the AN-R group are generally worse in comparison to all other groups.

Conclusions: This suggests the likelihood of a familial pattern of faulty information processing mechanisms in EDs. The results of the Bar-Graph tasks revealed that restricting anorexics (AN-R) performed most poorly on this spatial task suggesting difficulty in spatial processing on neutral stimuli. This result cannot be reflecting the effects of low BMI, as BMI equivalent purging anorexics (AN-B/P) do not show this pattern. This bias in size evaluation of stimuli that is not ED related in ANR may hint to a specific difficulty I spatial ability, which may serve as a factor in the development and progressing of the disorder.

Citation: RMMJ 2012;3 Suppl:55–56.

IMMUNODEFICIENCY

Poster #17I

Complete Clinical Remission and Resumption of IL-17 Secretion by GM-CSF Treatment in Chronic Candidiasis

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Background: Chronic mucocutaneous candidiasis (CMC) is a primary immunodeficiency disorder that is characterized by candida infection of skin, nails, and mucous membranes. Type 17 helper T cells (Th17) are crucial for mucosal antifungal immunity. Antigenic or functional deficiency in IL-17 has been implicated in APECED and autosomal recessive subtypes of CMC, whereas in autosomal dominant isolated CMC subtype, most cases are due to gain of function mutation in STAT1,leading to increased secretion of IFNγ which inhibits IL-17 production. This will result in increased susceptibility to fungal infections. Various therapeutic options have failed so far.

Methods: Neutrophil and monocyte functions have been studied by us 17 years ago in a female patient with CMC. Some defects were found (Lancet 1995). Recently, IL-17, IFNγ, IL-2, and TNFα expression (intracellular staining and FACS analysis) and secretion (ELISA) were studied in patient's PBMC, with or without *in vivo* GM-CSF treatment.

Results: Due to myelomonocytic defects, we started with parenteral GM-CSF treatment (300 mg in 0.5-1.0ml, 2-3/week) 17 years ago, and gained full clinical remission. Under this treatment, IL-17 expression and secretion were normal together with other cytokines (see Methods). When we attempted recently to stop GM-CSF treatment, candida infections reappeared within 4 weeks, concordant with undetectable IL-17 expression and secretion. IFNγ secretion was

increased by 50%. No change in IL-2 and TNFα secretion was noticed.

Conclusions: Increased IFNγ secretion with IL-17 deficiency may have resulted in isolated CMC in this patient. GM-CSF treatment may have stimulated IL-23 secretion from dendritic cells resulting in an increase in IL-17 secretion with a decrease in IFNγ. This leads to clinical remission of CMC. Thus, we would suggest trying GM-CSF treatment in cases of isolated CMC.

Citation: RMMJ 2012;3 Suppl:56–57.

PEDIATRIC ONCOLOGY

Poster #18Jo

Cancer Incidence and Survival among Children and Adolescents in Israel during 1998–2007

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Introduction: This study aimed at describing childhood cancer incidence and survival in Israel, and identification of demographic and epidemiologic variations among children and adolescents with cancer.

Methods: We have conducted a wide retrospective epidemiological study using data from the Israel National Cancer Registry to examine the incidence and survival of pediatric cancer of Israeli children aged 0 to 19 diagnosed between the years 1998-2007. Cases were grouped by the international classification of childhood cancer third edition and analyzed according to gender, age, ethnicity, and geographic region. Comparison age-standardized incidence rates various patient's group was performed by Pearson chi-square test. Survival probabilities were estimated by Kaplan-Meyer method (comparing by log-rank test).

Results: Among the 4,255 cases of childhood cancer, there was a total age-adjusted incidence rate of 172.4 per million for children aged 0-19 and 153.4 per million for children aged 0-14. The incidence rate for boys was higher than for girls (192.5 and 153.3 respectively). The incidence cancer rate for Jewish children was higher than for Arabs (177.6 and 156.8 respectively). The largest diagnosed groups were Leukemias (22%), Lymphomas (20.2%), and CNS tumors (17.4%). The number of new cases rose each year but the incidence rate remained steady. Survival probability updated to December 2008 was estimated and 5-year survival was calculated for the new cases to the end of 2003. Overall survival at 5 years was 80.8%, with 72.8% for the Arabic population and 83.2% for the Jewish. The 5-year survival depended upon diagnosis: leukemia, 77.3%; lymphoma, 89.6%; CNS tumors, 70.4%; neuroblastoma, 77.2%; retinoblastoma, 92%; renal tumors, 85.2%; hepatic tumors, 39.1%; bone sarcoma, 70.8%; soft tissue sarcoma, 80.1%; germ-cell neoplasms, 95%, and other epithelial neoplasms, 93.1%.

Conclusions: Incidence and survival in childhood cancer in Israel is in the same medium level compared to other parts of the world and the relative frequencies of various cancers is comparable. This study may set the basis for investigating the genetic and environmental factors, which cause pediatric cancer in Israel delineating the genetic basis for the origin disparities in survival.

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Poster #24Jo

Medical Clowns in the Pediatric Hemato-Oncology Department

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Introduction: Medical Clowns were instituted as a form of therapy by Patch Adams. In the last 10 years, they increased their involvement in medical care mainly with children admitted for care in general hospitals. Medical clowns are considered part of the multi-disciplinary team who care for

sick children. The most frequent objectives of medical clowns are distraction of attention, blocking distress reactions, mitigating side effects of medical interventions, reducing fear of the unknown, and promoting cooperation with medical procedures. The aim of this study was to investigate how the presence of medical clowns in a Pediatric Hemato-Oncology department is considered by the department personnel, the children's parents, and the children by themselves.

Material and Methods: Thirty-five admitted children suffering from different malignant diseases (age ranged from 5-22 years old), 55 parents, and 36 medical personnel were included. All answered an open-ended questionnaire submitted in a face-to-face manner. The instrument used was made up of a 1-3 answer ruler. Young children were helped to complete the questionnaire by their parents. Questionnaire analysis was performed applying the SPSS-12 program.

Results: Children, parents and medical personnel answered that a medical clown makes children laugh in 95%, 95%, and 96% of the cases, respectively. Parents answered that a medical clown made them laugh in 85% of the cases and the medical personnel laugh in 75% of the cases. Children, parents, and medical personnel answered that a medical clown with his/her intervention helps decrease pain suffering in 52%, 60%, and 76%, respectively. A more specific measure of children's reaction towards the clowns before and after surgical and invasive procedures was compared among different age groups. Children between 5–10 (68%) years and between 11–14 (61%) years seemed to react more favorably to clown interventions than adolescents from 15-22 (33%). The general integrated mood in the Hemato-Oncology department improved due to medical clown interventions in 88% (children), 95% (parents), and 88% (medical personnel), respectively.

Conclusions: Interventions by Medical clowns improved the general mood in the Hemato-Oncology department; pain reduction was appreciated better by medical personnel in comparison to parents and children by themselves. Overall, there seems to be a consensus by parents and medical personnel that medical clowns should be present as part of the care team on a daily basis.

Citation: RMMJ 2012;3 Suppl:57–58.

Poster #37Jo

Serum Galactomannan Screening for the Diagnosis of Invasive Pulmonary Aspergillosis in Children after Haematopoietic Stem Cell Transplantation and High Risk Leukemia

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Introduction: Invasive Fungal Infections (IFI) constitutes a substantial source of morbidity and mortality among immunocompromised patients. Morbidity and mortality among patients following HSCT is high. Rapid diagnosis and early treatment of IFI are crucial, yet, limited by other complications of HSCT and the need for invasive procedures mainly to identify invasive pulmonary Aspergillosis (IPA). Our study was designed to investigate the impact of serial Serum Galactomannan Assay (GMA) on the diagnosis of IPA.

Methods: Children with high-risk leukemia or following HSCT were included. Serum samples for GMA (Platela, Aspergillus EIA, Biorad, France) were taken twice weekly from patients at high risk for IFI over 10 months (February–November 2010). Results over 0.5 were considered positive. Patients suspected of having IPA were stratified as possible, probable, and definite according to recent consensus (Clinical Infectious Diseases 2008; 46:1813–21).

Results: There were 27 patients in the study: median age was 11 (range 1-21 years) and 306 samples were processed. Of 22 HSCT children, 15 were after allogeneic, and 7 patients after autologous bone marrow transplantation. Five patients had high-risk leukemia and 20 patients had a prolonged period of screening from 1 to 7 months. In 7 children, only 1–3 samples were obtained.

Serum Galactomannan Assay was negative in 14 patients; none was suspected to have IPA. Thirteen patients had 1–4 positive GMA. Four of

these 13 children (30%) had criteria of possible IPA; due to positive GMA results, they were upgraded to the category of probable IPA and started on early antifungal treatment. However, in 9/13 (70%) of patients the test was considered false positive without any sign of IA. In our group, 6 of 13 patients (60%) showed positive Galactomannan index during high dose chemotherapy or irradiation as well as during infusion of stem cells; another 40% had positive index during Piperacillin-tazobactam treatment, engraftment period and other viral infection (EBV and HHV-6).

Conclusions: Serum Galactomannan Assay may have an important role in the follow up for high-risk patients and support early evaluation and treatment for IA. Negative predictive value is high among children. False positive rate is high. The cost benefit of early detection versus over diagnosis, and performing more specific tests in children should be further evaluated.

Citation: RMMJ 2012;3 Suppl:58–59.

PEDIATRICS

Poster #35J

Should External Laryngeal Manipulation be used in Difficult Pediatric Intubation? A Randomized Controlled Manikin Study

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Introduction: Securing the airway is of major importance in pediatric resuscitation. In injured children, inability to establish and/or maintain a patent airway is the most common cause of cardiac arrest. Due to the unique anatomy of the child, endotracheal intubations may be difficult to perform especially in the pre-hospital setting. However, evidence for children's management of difficult airways is limited. External Laryngeal Manipulation (ELM) is a technique used in cases of poor glottic view in direct laryngoscopy. This technique has been used in anesthesia for many years; however, emergency physicians usually do not utilize it. Studies investigating ELM in the pediatric population are lacking. The objective of this study was to examine if the ELM technique could be helpful in the pediatric age group. We hypothesized that in conditions of poor glottic view in direct laryngoscopy, utilizing ELM technique will improve the chance for successful intubation and would result in shorter intubation time.

Methods: We conducted a randomized, controlled, manikin study, comparing intubation, using ELM (study subjects) with standard intubation (controls). Study participants were emergency medical technicians undergoing training for paramedic status. Each participant performed one intubation attempt on three different pediatric airway manikins, independently. The procedure started with direct laryngoscopy. If an optimal Cormack-Lehane glottic view (CLGV) of more than 2 has been obtained, study subjects were instructed to perform the intubation using ELM; controls were instructed to continue with the intubation. Outcome measures were one-attempt intubation success rate, pre-intubation CLGV, and duration of intubation.

Results: Study group included 13 subjects who performed 39 intubations. In 19 intubations, CLGV of more than 2 had been obtained and ELM was used. The control group included 14 subjects on whom 42 intubations were performed. In 20 intubations, a CLGV of more than 2 was obtained. The mean CLGV score improved from 3.47 ± 0.61 before ELM to 2.16 ± 1.01 when ELM was used. However, no difference was found between the groups in intubation success rate (10/19 vs. 14/20, $p = 0.43$). The duration of intubation was significantly shorter in controls (25.8 seconds vs. 37.8 seconds, $P < 0.007$).

Conclusions: In this pediatric manikin study, ELM performed by novice intubators improved laryngeal view but lengthened the duration of intubation, and did not improve the intubation success rate.

Citation: RMMJ 2012;3 Suppl:59.

Poster #71J

Calprotectin Levels at Diagnosis in Untreated Pediatric Crohn's Disease

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Introduction: Fecal Calprotectin (FC) is a validated marker and a useful screening test of intestinal inflammation in Crohn's disease (CD). The objective of the study was to evaluate prospectively the limitations of FC for identifying CD in newly diagnosed untreated pediatric patients and to assess the association of FC levels with disease location and serum inflammatory markers.

Methods: Consecutive children under age 18 with new onset untreated CD participating in the ongoing ESPGHAN *GROWTH CD* study, were evaluated at diagnosis for PCDAI, extent of disease, C-reactive Protein (CRP), and FC.

Results: Sixty children met the inclusion criteria (mean age 12.6 ± 4.6 years, 38 (63%) males). Disease activity was evenly distributed, 25 (42%) with mild disease, 17 (28%) with moderate disease, and 18 (30%) with severe disease, as judged by physician global assessment of disease activity (PGA). Twenty-seven (45%) had small bowel only, six (10%) had only colonic disease, and the others were combined. Median FC levels were 1862 (range 30-2400 mcg/ gram). Four children (6.6%) had normal calprotectin levels < 50. There was no correlation between calprotectin levels and either PCDAI (r = -0.11; P = 0.94), PGA (r = 0.09; P = 0.53) or disease activity categories). In a multivariate regression analysis, none of the measured variables were associated with calprotectin values (including age (P = 0.86), small bowel disease only (P = 0.2), CRP value (P = 0.22) and gender (P = 0.33).

Conclusions: Calprotectin levels at diagnosis do not correlate with disease activity indices, CRP, or site of disease. Patients with low FC had a trend towards low levels of inflammatory markers as well.

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Poster #72J

The Value of Integrated Pulmonary Index (IPI) Monitoring during Endoscopies in Children

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Introduction: Pulse oximetry has become the standard of care for the detection of hypoxemia during endoscopic procedures, despite the fact that significant alveolar hypoventilation may be undetected. CO_2 monitoring should therefore be considered for all patients receiving moderate or deep sedation.

The "Integrated Pulmonary Index" (IPI) is a software tool that constitutes a representation of four parameters: EtCO2, RR, SpO2, and PR, already displayed on a monitor, in the form of a single index value ranging from 1 to 10 with trend information. The IPI index has been validated for adults and for children over 1 year of age.

In this study, we aimed to study the value of IPI monitoring using Capnostream20® during pediatric endoscopic procedures under general anesthesia (GA) and conscious sedation (CS). We specifically aimed to assess whether 1) IPI monitoring improves patient safety in the pediatric GI suite by reducing hypoxemia and respiratory depression events compared to regular monitoring with oxygen saturation and 2) to assess the safety net of different sedative medications as to adverse respiratory events.

Methods: The IPI signal was monitored and analyzed in order to detect IPI changes due to various parameters changes such as drug dosage

per weight, drug type, and the presence of an anesthetist.

Results: Our data consisted of 124 measurements of 109 patients undergoing different procedures (upper endoscopy 84 patients, colonoscopy 6 patients, both 9 patients). The data was divided into three groups based on the drug type used: Group 1: Propofol only, 5 patients; Group 2: Propofol and midazolam, 89 patients; Group 3: Propofol, midazolam and Fentanyl, 15 patients. Patients in Groups 2 and 3 had significantly higher IPI levels than Group 1. A significantly lower IPI values were found between ages 4-6y compared to 7-12y years old. High midazolam dose was associated with lower IPI levels during the procedure. No significant differences were found for propofol doses. Patients who had an anesthetist present had lower IPI levels during the procedure compared to those who did not. No differences were noted between the different procedures. IPI alerted all apnea episodes (58 events, IPI = 1) and hypoxia (26 events, IPI ≤ 3) episodes, whereas, pulse oximetry captured only the hypoxia episodes (IPI sensitivity = 1, specificity 0.98, positive predictive value 0.95).

Conclusions: Younger patient age, use of propofol alone, higher midazolam doses, and presence of anesthetist are all associated with lower IPI levels. IPI monitoring adds to patient safety during endoscopic procedures.

Citation: RMMJ 2012;3 Suppl:61–62.

Poster #85J

Streptokinase Fibrinolysis Protocol: The Advantages of a Non-Operative Treatment for Stage II Pediatric Empyema Patients

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Introduction: Pediatric empyema necessitates prompt resolution and discharge with minimal morbidity. However, the most effective treatment approach is still indefinite. The current study assessed the efficacy of an intrapleural streptokinase washing protocol as a non-operative treatment for stage-II pediatric empyema compared to operative decortication via number of pediatric intensive-care unit (PICU) admissions, length of PICU stay and hospitalization duration.

Materials and Methods: Seventy-five consecutive pediatric empyema cases were retrospectively evaluated from January 2006 to December 2009. Since July 2007, we used repeated streptokinase-based pleural washing for stage-II patients who did not improve with chest drainage.

Results: Before July 2007, 17 out of 23 stage-II empyema patients underwent decortication, while after July 2007 only one out of 21 underwent decortication. Compared to the operated children, the non-operated ones (i) were admitted to the PICU less frequently (83% vs. 31%; $P = 0.0006$); (ii) spent shorter durations in the PICU (2.56 ± 1.92 vs. 1.04 ± 1.9 days; $P = 0.0148$); and (iii) were not hospitalized for longer durations (13.33 ± 3.69 vs. 11.70 ± 5.74 days; $P = 0.301$).

Conclusions: Using intrapleural streptokinase washing as a non-operative treatment for stage-II pediatric empyema has comparable success rates to the operative approach, with clinically pertinent advantages.

Citation: RMMJ 2012;3 Suppl:61.

CELL THERAPY

Poster #26K

Extra-Cortical Vertical Bone Augmentation by Progenitor/Stem Cells to Allow Rehabilitation of Severely Atrophic Alveolar Bone

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Introduction: Alveolar bone atrophy presents a major clinical problem in periodontology and implant dentistry. In order to install dental implant a minimum of 10 mm vertical bone height is required. Surgical techniques available for vertical and horizontal bone augmentation are

unpredictable, limited to 1-3 mm, and thus not sufficient for dental implant placement. One of the most popular techniques for vertical bone augmentation is Guided Bone Regeneration (GBR). The idea of GBR is to create a space by a rigid barrier to allow new bone formation. The barrier excludes epithelial and connective tissue cells. Mesenchymal stem cells (MSC) participate in bone formation. These cells can differentiate into osteobltasts and secrete molecules that have paracrine effects on other cell populations. Angiogenesis plays a key factor in bone formation. Endothelial progenitor cells (EPC) participate in angiogenesis and in bone regeneration. Our goal is to augment extra cortical vertical bone by combining GBR, MSC, and/or EPC. We expect this novel technique to be predictable and promote the rate of vertical bone formation.

Materials and Methods: Peripheral blood derived EPC and bone marrow derived MSC were isolated from inbred Lewis rats, cultured, and characterized. The MSC were osteogenic transformed (otMSC). Rigid gold capsules (GBR) filled with 0.2 gr fibronectin coated TCP scaffold mixed with cells ($5x10^5$ EPC ($n = 3$), MSC ($n = 5$), or otMSC ($n = 7$)) were fixed to exposed Lewis rats' calvaria. Capsules that were filled with TCP alone served as control (C). Rats were sacrificed after three months and the content of capsules were processed for histology, and stained with HE and Picro Sirius Red. Histomorphometric analyses were performed to determine vertical bone formation and bone area.

Results: New hard augmented tissue filled the space under the capsule in all rats. Augmented tissue was composed of bone, residual TCP, and connective tissue. Mean maximal vertical bone height was approximately doubled following addition of cells to GBR: EPC 4.02 ± 0.29 mm, MSC 4.1 ± 0.54 mm, otMSC 4.1 ± 0.32 mm, compared with (C) group: 2.3 ± 0.25 mm. Bone area was significantly increased in the MSC and otMSC compared with (C) (27.1 ± 2.6 mm^2 $p \leq 0.002$, 33.9 ± 2.4 mm^2 $p \leq 0.014$, 17 ± 4.5 mm^2, respectively).

Conclusions: This feasibility study shows that cell-based therapy combining GBR with MSC or EPC has the potential to promote vertical bone formation. Additional research is required to establish these results. Success of this suggested technology will pave the way to treat bone defects, and open new horizons in periodontology and implant dentistry.

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GASTROENTEROLOGY

Poster #28L

Accuracy and Quality Assessment of EUS-FNA in a Single-Center Large Cohort

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Introduction: Endoscopic Ultrasound-guided fine needle aspiration (EUS-FNA) has variable accuracy. Controversies also persist as to its indications. Therefore, quality assurance (QA) and improvement for EUS-FNA are critical to optimizing its effectiveness. Quality assurance is the systematic monitoring and evaluation of the various aspects of a project. Its key principles are "fit for purpose" and "right first time."

Methods: This work retrospectively thoroughly investigated all patient files from 2008-2010 (with IRB formal approval) for all patients undergoing EUS-FNA. QA study assessed for accuracy and effectiveness of FNA with emphasis on the impact on diagnosis and case management.

Results: Two hundred and sixty-eight consecutive EUS-FNA procedures were evaluated. EUS-FNA cytology helped establish an accurate diagnosis in 86.9% (233/268) of patients with sensitivity, specificity, PPV, NPV, and accuracy of 83%, 100%, 100%, 91.6%, and 94%, respectively. Specific needle used and number of passes was often low or undocumented. Pancreas was the most common site biopsied, (68%). FNA was found most successful (13/13 = 100%) for esophageal lesions, 87% for pancreas, and least informative (67%) for nodes. Eight FNA results were essentially false negatives (including sampling errors) from non-informative specimens. In 11.5%, definitive diagnosis was still lacking after the FNA.

Conclusions: The diagnostic accuracy of EUS-FNA might be further enhanced by 1) taking more FNA passes from suspicious lesions, 2) optimizing needle selections, especially for tougher sites (e.g. uncinate), and 3) having an experienced echo-endoscopist present during examinations performed by trainees during their learning curve. Quality control identified some relatively weak but easily remediable areas, especially in documentation. Electronic files have been appropriately reworked as a result of this quality assessment, so that now "forced fields" require physicians to deliver more thorough documentation in the EUS-FNA reports. The results from Rambam compare favorably to those of many published studies from major centers around the world, but room remains for improvement. Follow-up and quality control efforts may augment the effectiveness and accuracy of EUS-FNA.

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Poster #29L

Comparison of Quality of Colonoscopy in Hospital vs. In Community

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Introduction: Differences in venues might have an impact on quality of colonoscopy procedures. Quality assurance is important both to curtail costs and to maximize efficiency.

Objective: This IRB-approved study aimed to assess and compare the quality of colonoscopies performed in one teaching hospital to those performed at one community service.

Methods: Documentation of the presence or absence of standardized quality indicators (QIs) were tabulated from 700 colonoscopy reports from the academic center, vs. 824 from the community endoscopy service, all for patients over age 40. The American Society for Gastrointestinal Endoscopy (ASGE) quality indicators (QIs) were used as benchmarks.

Results: There was no statistically significant difference between the colonoscopy results from the hospital vs. community endoscopy services regarding patients' demographics (age, gender ratio), depth of exam (92.4% vs. 94.1% complete), polyp detection rate (29.1% vs. 26.8%) and biopsies in patients with diarrhea (75% vs. 67%). Indications for colonoscopy differed: gastrointestinal bleeding was more common at Rambam hospital, screening was more commonly listed as the indication for colonoscopy in the community. Premedication varied: more fentanyl and dormicum and less propofol were used in the community. Good bowel preparation was more frequently reported in the community (68.8% vs. 47.2% in hospital, $P < 0.0001$). Follow-up recommendations were more often documented in the community (74% vs. 53% in hospital, $P < 0.0001$). The range for many QIs varied greatly amongst physicians.

Conclusions: Remediation of weaknesses in the quality of colonoscopies seems plausible through upgrading electronic medical records and increasing awareness of QIs. Colonoscopies performed in both hospital and community services were of good quality compared to the relevant literature, with significant variations in some QIs. Vigilance seems worthwhile to assure quality of colonoscopies.

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Poster #88L

Polymorphisms in the Rac1 and Other Apoptotic Genes: Do They Alter Clinical Response to Azathioprine in Patients with Inflammatory Bowel Disease?

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Introduction: Thiopurines are valuable drugs in the treatment of inflammatory bowel disease. The

precise molecular mechanism of action of these drugs remains unclear despite more than 50 years of use. Recently, azathioprine and its metabolites were found to control T cell apoptosis by modulation of Rac1 activation.

Aim: Assess whether polymorphisms in Rac1 gene and other apoptosis genes predict the response to azathioprine and whether they interact with clinical predictors.

Methods: Cohort of 187 patients treated with azathioprine for Crohn's disease (CD) (n = 156) or ulcerative colitis (UC) (n = 31) was genotyped for 7 single nucleotide polymorphisms (SNPs) in Rac1 gene, as well as for Fas ligand 843 T > C, Caspase-9 93 C > T, AOX1 3404 A > G. Real-time PCR was conducted using TaqMan SNP genotyping assays. Clinical data was obtained retrospectively by reviewing medical records.

Results: The overall rate of remission induction with azathioprine was 74% for Crohn's disease and 71% for UC. After median follow-up of 7 years, 75% of CD and 81% of UC patients remained in remission. Among Rac1 SNPs, in our cohort heterogeneity was found only in Rac1 690T > C: response rates were similar for both genotypes (P = 0.52) but all the patients with TC genotypes (n = 10) retained remission compared to 76% (n = 123) with TT genotype (P = 0.12). Patients with Fas ligand 843 TT genotype responded in 85%, while with CT/CC only in 70% (P = 0.05). Analysis of clinical data revealed that patients with inflammatory (85%, P = 0.02) and ileal Crohn's (85%, P = 0.05) disease responded better to the treatment. Women remained in remission in higher rates than men (84% vs. 68%, P = 0.05).

Conclusions: We observed association between Fas ligand 843 TT genotype and a better response to thiopurines. Further studies in different populations are needed.

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Poster #112L

Early Histological Findings Quantified by Histomorphometry Allow Prediction of Clinical Phenotype in Crohn's Colitis

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Background: The clinical course of Crohn's disease (CD) is variable and relevant for treatment selection. Early aggressive treatment may change disease course, but should be balanced with safety considerations. Diagnostic tools for prediction of disease course are lacking. Histomorphometric analysis allows for quantitative measurements of size, shapes, and orientation of cells and structures in tissues. The aim of the study is to evaluate the histomorphometric features of early colonic biopsies from patients with Crohn's disease and their relationship to evolving clinical phenotypes.

Methods: Colonic biopsies from fifty CD colitis patients classified according to the Montreal classification with at least 5 years post biopsy follow up were analyzed using histomorphometry. The quantitative results were used to predict post biopsy clinical phenotypes and outcomes. Data analysis was performed using statistical and Neural Network (NNET) models.

Results: Differences were observed between clinical phenotypes in the number of inflammatory cells (P = 0.003), lymphocyte aggregates (P = 0.005) and optical density of mature and young collagen (P = 0.008, P = 0.01 respectively). A crypt area of more than 1.8 mm² was associated with phenotype B3 (P = 0.03, OR-3.9). A count of 23 eosinophils or less per field was associated with B2 phenotype (P = 0.03, OR-5.5). Smokers differed from non-smokers in the average crypt area, number of inflammatory cells and fractal dimensions (P = 0.03, P = 0.03, P = 0.01 respectively). Multivariate analysis successfully differentiated between B1 and B2 phenotypes with a sensitivity of 90% and a specificity of 95%; between B2 and B3 phenotypes, with a sensitivity of 89% and a specificity of 70%; and between B1 and B3 phenotypes, with a sensitivity of 47% and a specificity of 95%. We also successfully predicted surgery with a sensitivity of 86% and a specificity of 80%. Finally, a neural network model correctly predicted clinical phenotypes with an accuracy of 94%.

Conclusions: To our knowledge, this is the first study that applied histomorphometry on early

biopsies in order to predict the clinical phenotypes in Crohn's colitis. Measurements allowed differentiation and prediction of clinical phenotypes and outcomes such as surgery. This novel approach in combination with other biologic variables and clinical predictors may significantly increase the ability to classify and predict the clinical course of CD colitis patients, thus improving their management. Prospective validation on larger cohorts is still needed.

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CLINICAL PHARMACOLOGY

Poster #30M

The Economic Benefit of Oral Formulation of Nimodipine Over Intravenous Formulation

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Introduction: Nimodipine is nifedipine analogue. It differs from other Calcium channel blockers by its ability to dilate cerebral vessels to a greater extent than cardiovascular vessels. Its only FDA approved indication is subarachnoid hemorrhage, from ruptured intracranial berry aneurysm.

The drug is available as both, intravenous and oral formulations. The oral bioavailability of the oral formulations is approximately 30%; hence, the oral dosage is 7-fold the intravenous dosage. No clinical difference was observed between the administration of intravenous and oral formulations.

Methods: At mid of 2009, a new strategy was initiated. Oral capsules were used instead of the intravenous formulation when possible. The aim of the study was to evaluate the economic benefit of the formulation switch

Results: The expense per 100 days of admitted patients in the neurosurgery department for both oral and intravenous formulations were calculated. Year 2008 was compared with 2010. The expense of 100 days of admitted patients for year 2008 was 240 dollars, and for year 2010 was 85 dollars.

Conclusions: The usage of the oral formulation had a substantially economic benefit. The formulation switch reduced the expense by 2.8-fold. The oral formulation should be considered in every case possible instead of the intravenous formulation.

Citation: RMMJ 2012;3 Suppl:65.

Poster #31M

Prospective Evaluation of the Dosing Regimen of Vancomycin in Children of Different Weights

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Introduction: Limited data is available regarding the pharmacokinetics (PK), pharmacodynamics, and optimal dosing of most antimicrobials for obese patients. Estimation of volume of distribution (V_d) and clearance (CL) is essential for determining appropriate dosing. Higher trough levels of vancomycin (Vn) are suggested for better outcomes and resistance control. Our prospective study evaluated the adherence to guidelines, among obese (O), normal (N) and underweight (U) children.

Patients and Methods: Children receiving Vn, (20 mg/kg BID), between March 2010 and February 2011 were included. Patients were divided into three groups, (O, N, and U). Adequacy was defined as for adults e.g. trough level beyond 10mg/L and AUC/MIC > 400. The optimal dosage was calculated based on individual PK parameters.

Results: Eighty pairs of levels (trough and peak) were taken from 53 children. Trough range for the standard regimen was 0.24-12.62mg/L, peak range 5.75-45.66mg/L. Mean trough for all children 3.47 ± 2.61mg/L. Only 3% of the trough levels were in the therapeutic range (8% of group U, 3% of group N and none (0%) of group O**).**

Mean value of AUC/MIC was 308 ± 195; only 3 children had a value above 400. Mean elimination $t_{1/2}$ was 3.41 ± 1.25 hours. Mean CL was 0.16 ± 0.08L/hr/kg. Mean V_d was 0.73 ± 0.37L/kg. In order to reach trough levels beyond 10mg/L, a dosing regimen of 11 mg/kg QOD, as a 1 hour infusion, is needed.

Conclusions: Based on pharmacokinetic parameters the dosing regimen should be reevaluated. Children of all weight groups need more frequent and higher dosing of Vn in order to achieve optimal blood levels. Personalized medicine is the ideal way to achieve desired outcomes.

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Poster #110M

Human Intravenous Immunoglobulin Therapy: Benefits, Prescription and Interventions to Cost Management

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Introduction: In Israel according to MOH registration, the intravenous Immunoglobulin-IVIG- therapy has the following indications: Idiopathic Thrombocytopenia Purpura-ITP, Kawasaki Disease, Primary Immunodeficiency syndromes, and Chronic Lymphocytic Leukemia. IVIG is also used for other indications such as Bone Marrow Transplantation and Guillain Barre Syndrome. In the past, those indications were not legally authorized and filling out a special form was required by law in order to dispense this medication (G29 form). In recent years, the price of IVIG has varied. Up to 2005, the price of 1 gram of IVIG was $26.30. From 2005–2007 the price has risen, reaching $55 per gram. As of 2011, the price is $60.0 dollars per gram.

Methods: From 2002–2006, a Retrospective Analysis was performed in order to evaluate the consumption of the drug under a regular intervention circumstances. On the other hand, a Prospective Analysis conducted between 2007–2011 evaluated the consumption of the drug under an aggressive intervention circumstances.

Results: During the regular intervention in the years 2002-2004, there was a decrease of usage and cost of IVIG reaching 76.6%. In 2005 and 2006 the prices of IVIG has doubled nationwide. The amount of IVIG used in Rambam Medical Center in 2005 had reached 10,734 grams and the cost was $590,370. In 2006, the amount was 10,459 gr and the cost was $575,245. In contrast, during the aggressive intervention circumstances that started out in 01/07, the usage amounts were the following: In 2007, the consumption of IVIG was 8,980 grams and the cost was $493,900. In 2008, the consumption was 7,598 grams and the cost was $417,890. In 2009, the consumption was 8,040 grams and the cost was $442,200. In 2010, the consumption was 5,388 grams and the cost was $296,340. In 2011, until today, the consumption had reached 4,492 grams and the cost is $247,060.

Conclusions: Therefore, we recommend a plan that can offer numerous solutions to manage consumption and cost of IVIG without having a negative effect on the clinical results. An Intelligent policy includes an active intervention of experts and a backup of the administration can play a key role that offers a better management of resources, reduce unnecessary cost, and avoids the use of the drug in cases of unproven medical benefits.

Citation: RMMJ 2012;3 Suppl:66.

ORTHOPEDICS

Poster #97N

Determination of Symptomatic Subacromial Calcification in Shoulder by Isometric Strength Measurements of Rotator Cuff Muscles

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Introduction: One of the most prevalent groups of shoulder's disorders is related to subacromial calcification. This pathology is considered one of

the most common illnesses causing intense pain and subsequent weakness of the shoulder. These calcifications are frequently located in the tendon of the supraspinatous muscle, close to its insertion into the greater tuberosity. The diagnosis of subacromial calcification is based on x rays, showing these calcifications, in patients complaining of shoulder pain, usually without prior trauma. Occasionally these calcifications are small and cannot be detected on x rays, but by sonography. Sonography is also used to rule out other shoulder pathologies such as rotator cuff tears and impingement syndrome. We hypothesize that subacromial calcifications might be identified by measurement of the isometric strengths of rotator cuff muscles, which might be a ready available diagnostic modality.

Materials and Methods: Twenty consecutive patients (mean age 46 years) with shoulder pain due to subacromial calcifications, without evidence of rotator cuff tears or impingement syndrome, were evaluated by recording the torque-time isometric curves of the supraspinatus, infraspinatus and subscupularis muscles. The measurements were performed at standardized measurement configuration for each muscle, by using a specially designed dynamometer (measurement rate of 1200 readings/ sec, resolution 0.04N). The tested torque (normalized to lean body mass)-time curves were compared to the curves of mean values in normal population, to patients with rotator cuff tears, and with impingement syndrome obtained in our previous studies. The statistical comparison was by the Friedman repeated measures analysis and Tukey post hoc test, according to the distribution of the values.

Results: We found that the isometric torque-time curves of the three tested muscles in the patients with subacromial calcifications had a significantly lower profile in comparison to the values of the normal population ($P < .01$). In addition, the curves of the calcification group differed significantly from the curves of all three muscles in the impingement group ($P < .01$). When compared to the rotator cuff tear group, the curves of the calcification group differed significantly in the measurements of the infraspinatous and subscapularis muscles ($P < .05$), but not from the supraspinatous curves.

Conclusions: We conclude that subacromial calcifications may be efficiently detected and distinguished from the subacromial impingement syndrome by the standardized isometric force measurements. However, this torque-time profile is similar to the supraspinatus tears indicating on a similar muscular intrinsic pathology.

Citation: RMMJ 2012;3 Suppl:66–67.

IMAGING

Poster #320

Percutaneous Transluminal Angioplasty - The Other Way: US Guided SAFARI Technique

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Introduction: To describe the benefits of Ultrasound (US) guided Subintimal Arterial Flossing Antegrade-Retrograde Intervention (SAFARI) when antegrade Percutaneous Transluminal Angioplasty (PTA) fails.

Materials and Methods: We retrospectively analyzed patients who were treated with the SAFARI technique due to failure of classical antegrade PTA to recanalize occluded femoral and tibial arteries. Between 2009 and 2011, 226 patients underwent 263 PTA procedures in our hospital for treatment of limb ischemia. We used the SAFARI technique on 16 patients in whom antegrade PTA failed to provide direct flow to the ischemic site. In all patients, diagnostic angiography was performed in order to determine arterial patency and in all patients, the retrograde puncture was performed under US guidance. In 15 (93.7%) patients, the ensuing puncture site was in the Dorsalis Pedis (DP) artery; in one patient, we punctured the Tibialis Anterior (TA) artery. The guide wire was pushed in a retrograde manner through the previously inserted antegrade catheter, while no snare was needed. In 8 patients (50%), the balloon dilatation was performed retrogradely through the distal sheath; in the rest of the patients, the balloon dilatation was done using both puncture sites.

Results: In all 16 (100%) patients, the US guided puncture of a distal artery was successful.

Combined antegrade and retrograde (SAFARI technique) PTA was successful in 14 (87.5%) of the patients in which the antegrade PTA alone did not provide satisfactory recanalization and was considered failed. In one patient, we successfully passed the occluded vessels but repeated balloon inflations did not provide a good flow. As a minor complication, temporary DP artery spasm was seen in 2 (12.5%) of the cases. No major complications occurred.

Conclusions: The SAFARI technique is usually used when the classic antegrade PTA fails. This procedure necessitates a patent distal artery, very skilled angiographists with ultrasonographic skills and it is time consuming. However, it provides a good last alternative in patients in which the antegrade PTA has failed.

Citation: RMMJ 2012;3 Suppl:67–68.

Poster #34O

Asymptomatic Deep Vein Thrombosis in Advanced Cancer Patients: The Value of Venous Sonography

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Introduction: Although guidelines for venous thromboembolism prevention are available, the implementation of anticoagulant prophylaxis in patients with advanced cancer has yet to be more clearly defined. We aim to determine the incidence of lower extremity deep vein thrombosis (DVT) diagnosed by Ultrasound-Doppler (USD) in asymptomatic non-ambulatory patients with advanced cancer.

Materials and Methods: In a prospective study, 44 non-ambulatory cancer patients with grade 3-4 World Health Organization (WHO) performance status, asymptomatic for lower extremity DVT, underwent bilateral venous USD studies of the lower extremities. Different risk factors and laboratory data were registered and correlated with the incidence of DVT.

Results: Asymptomatic DVT was detected in 15 of 44 patients (34%, 95% CI, 0.21 > 0.34 < 0.49). Twenty three percent of all patients had isolated deep calf vein thrombi and 11% of all patients had thrombi in the proximal veins. The only significant risk factor was the number of metastatic sites. DVT was found in 4 out of 23 (17.4%) patients with one metastatic site as opposed to 11out of 21 (52.3%) with two or more sites ($P < 0.001$).

Conclusion: Ultrasound Doppler of the lower extremities detected asymptomatic DVT in 34% of advanced non-ambulatory cancer patients; USD may serve as an additional tool when considering anticoagulant therapy for this specific population.

Citation: RMMJ 2012;3 Suppl:68.

Poster #39O

Improvement of Intracranial Hemorrhage Imaging with a Novel 3D Image Reconstruction Algorithm

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Objectives: Prospective assessment of a novel three-dimensional (3D) image reconstruction algorithm for image quality enhancement of intracranial hemorrhage in reduced dose head computed tomography (CT).

Methods: Patients admitted with head trauma, who had been diagnosed with intracranial hemorrhage, were prospectively recruited to this IRB-approved study. All patients underwent an initial full dose CT scan of the head. A clinically indicated follow up reduced dose CT study (35-50% dose reduction) was thereafter conducted within the following 48 hours. All full dose head CTs were obtained using a 16 or 64 slice multidetector row CT scanner (MDCT). Reduced dose head CTs were obtained with 64 slice MDCT and post-processed using a novel 3D non-linear noise reduction algorithm (MedicVision, Tirat Carmel, Israel). All CT studies were examined in a blinded fashion by two experienced neuroradiologists. The post-processed reduced dose study was

reviewed side by side on an imaging workstation with both the unprocessed reduced dose study and the unprocessed high dose study. Studies were evaluated on a grading scale for visual accuracy of anatomic structures, pathologic findings, and subjective image quality.

Results: The study group included 55 adult patients suffering from intracranial hemorrhage; 51 intracranial extra-axial hemorrhages were identified and evaluated. Twenty-one parenchymal hematomas and cortical contusions were also evaluated. All low dose studies were of diagnostic quality. All hemorrhages were identifiable on both unprocessed and processed reduced dose images. Processed reduced dose image quality was markedly improved when compared to the unprocessed images. There was no significant difference in visualization of hemorrhages between regular dose head CT and reduced dose head CT processed with the 3D non-linear noise reduction algorithm.

Conclusions: Visualization of intracranial hemorrhages was improved in reduced dose CT imaging when post-processed with a novel 3D non-linear noise reduction algorithm. Diagnostic quality of reduced dose head CT is comparable to that of regular dose CT when processed with a 3D non-linear noise reduction algorithm. Routine use of this novel algorithm holds the potential of decreasing patient radiation exposure from computed tomography.

Citation: RMMJ 2012;3 Suppl:68–69.

Poster #40O

Enhancement of Signal-to-Noise Ratio and Low Contrast Detectability in Low-Dose CT Images using Non-Linear Post-Processing

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Introduction: It has been postulated that image reconstruction algorithms that increase the signal-to-noise ratio (SNR) of low-dose CT images will reduce Low Contrast Detectability (LCD). This research evaluates a novel image reconstruction algorithm, showing improved LCD in low-dose SNR-enhanced images.

Methods: Two CT performance phantoms (the American College of Radiology (ACR) CT accreditation and Catphan 600), containing 2.0-15.0 mm (diameter) low-contrast targets at 0.3-1.0% contrast levels, were scanned on the 64-slice GE Discovery 690 and Philips Brilliance 64 CT scanners, respectively. 32 thin-slice datasets were acquired in axial or helical scanning modes at dose levels of 8-50 mGy, with parameter combinations simulating typical acquisitions. An additional 32 corresponding datasets were generated by applying 3D non-linear post-processing (SafeCT from Medic Vision Imaging Solutions) to the original datasets, using default abdomen processing parameters. All datasets were reformatted to slice thicknesses of 0.625-5.0 mm. Two slices were extracted from each dataset for review. The 128 images were presented in random order to five experienced CT readers (three radiologists and two physicists) who were requested to specify the smallest detectable low contrast targets.

Results: All processed images showed a decrease of at least 70% in image noise relative to their corresponding original images. The related-samples Wilcoxon signed rank test was performed, showing that LCD was significantly higher in the processed images ($p < 0.01$ for the ACR and $p < 0.0001$ for the Catphan phantoms) than in the original images. Highest LCD improvements were observed at low-dose levels (200%, $p < 0.0001$ for 100 mAs) and at low-contrast levels (150%, $p < 0.0001$ for 0.3% contrast level). In some cases, processed images showed higher LCD compared to the original images acquired at double the dose.

Conclusions: Three dimensional non-linear post-processing may improve not only the SNR of the CT image, but also the LCD. This was confirmed over a wide range of CT parameters and conditions, suggesting significant potential for CT dose reduction.

Clinical Relevance—Application: Image quality and radiation dose are of prime concern in CT imaging today. This study demonstrates improved quality of low-dose images in terms of SNR and LCD using a novel post-processing algorithm.

Citation: RMMJ 2012;3 Suppl:69.

Poster #41O

The Utility of Tablet Computer Technology for the On-Call Interpretation of Brain CT

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Objectives: This is an initial evaluation of an image interpretation application optimized for the tablet computer technology. The aim of the study was to determine the diagnostic accuracy of interpreting brain CT examinations with the use of tablet technology.

Methods: We identified 134 consecutive brain CT examinations performed in our Emergency Department during the course of one week. These exams were reviewed by three experienced Neuro-radiologists using an iPad tablet computer (Apple) and a web-based image viewer optimized for tablet technology (Light-Viewer, Carestream Health). The radiologists reviewed on average 34 different exams each and completed a worksheet containing questions regarding acute, sub-acute, and chronic findings as well as questions about the reading time and the radiologist's confidence in the findings. All major and minor findings were then compared to the original interpretations, which were performed on a regular PACS workstation. Discrepancies between findings were reviewed by all three radiologists and the final diagnosis was determined by consensus.

Results: Eighty-two exams were found to be normal (61%). Acute findings included seven acute intracranial hemorrhages (5%), four new fractures without hemorrhage (3%), five acute strokes (4%), and three new tumors (2%). Thirty-three patients had mentionable chronic ischemic changes including old strokes (25%). All acute findings were correctly interpreted by the radiologists using the tablet computer. Some differences in minor and incidental findings existed but were not considered relevant to the immediate patient management. Reading time using an iPad was found to be longer when compared to reading time using the PACS workstation.

Conclusions: Mobile wireless devices such as an iPad can provide on-call attending physicians the ability to perform accurate image interpretation of Emergency Department brain CT, thus enabling them to offer their professional advice, from any location where wireless communication can be achieved.

Citation: RMMJ 2012;3 Suppl:70.

Poster #46O

FDG-PET/CT Imaging in the Diagnosis of Osteomyelitis in the Diabetic Foot

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Introduction: Osteomyelitis, the most serious complication of diabetic foot, occurs in about 20% of patients. Early diagnosis is crucial. Appropriate treatment will prevent or decrease the rate of amputation. The objective of this study is to assess the value of FDG-PET/CT in diabetic patients with clinically suspected osteomyelitis.

Materials and Methods: Prospectively enrolled 39 consecutive diabetic patients (29 men, age range 28-71 years) with 46 suspected sites of foot infection. Thirty-eight patients had type 2 and one patient had type 1 diabetes for duration of 4-25 years. Twenty-eight patients were treated with insulin. FDG-PET/CT was interpreted for the presence, intensity (SUVmax) and localization of increased FDG foci. Final diagnosis was based on histopathology and bacteriology of surgical samples, or clinical and imaging follow-up.

Results: Osteomyelitis was correctly diagnosed in 18 sites, and excluded in 21 sites. Two of 20 lesions with focal bone FDG uptake were false positive with no further evidence of osteomyelitis. Five sites of diffuse FDG uptake of mild intensity involving more than one bone on CT were correctly diagnosed as diabetic osteoarthropathy. SUVmax in osteomyelitis was higher as compared to soft tissue infection ($P < 0.05$). Elevated glucose serum levels were measured in 60% patients at the time of study but with no false negative results. FDG-PET/CT had a sensitivity of 100%, specificity 93%, and accuracy 96% for diagnosis of osteomyelitis in diabetic foot.

Conclusions: FDG-PET/CT has high performance indices for evaluation of the diabetic foot. The PET component identifies FDG-avid foci in

sites of acute infection precisely localized by fused PET/CT images in order to differentiate correctly between osteomyelitis and soft tissue infection.

Citation: RMMJ 2012;3 Suppl:70–71.

Poster #53O

The Utility of Tablet Computer Technology for On-Call CT Interpretation

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Objective: Initial evaluation of an image interpretation application optimized for the tablet computer technology. The aim of the study was to determine the diagnostic accuracy of interpreting CT examinations of the body with the use of tablet technology.

Methods: Fifty CT exams were chosen from our PACS archive data for the study, including 25 chest and 25 abdominal CT's. For each category, we chose seven or eight exams that were previously reviewed and found to contain an acute pathology and 17-18 normal exams. The chest exam pathologies included cases of pulmonary emboli, acute lobar pneumonia, lung cancer, and aortic dissection. The abdominal exam pathologies included cases of acute appendicitis, urinary tract stones, small bowel obstruction, and colonic masses. These exams were reviewed by three experienced radiologists using an iPad tablet computer (Apple) and a web based image viewer optimized for tablet technology (Light-Viewer, Carestream Health). The reviewing radiologists were blinded to the number and types of pathologies included. The exams were reviewed and the radiologist completed a worksheet containing questions regarding acute, sub-acute, and chronic findings as well as questions about the reading time and the radiologist's confidence in the findings. All major and minor findings were then compared to the original interpretations that were performed on a regular PACS workstation. Discrepancies between findings were reviewed by all three radiologists and the final diagnosis was determined by consensus.

Results: All acute findings were correctly interpreted by the radiologists using the tablet computer. Some differences in minor and incidental findings existed, but were not considered relevant to the immediate patient management. Reading time using an iPad was found to be longer when compared to reading time using a PACS workstation.

Conclusions: Interpretation of body CT exams using mobile wireless devices such as an iPad is a very promising tool for on-call attending physicians. It provides the ability to perform accurate image interpretation of CT exams from any location where wireless communication can be achieved.

Citation: RMMJ 2012;3 Suppl:71.

Poster #107O

Mass and Mass-Like Lesions of the Temporo-Mandibular Joint

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Introduction: Mass lesions involving the Temporo-Mandibular Join (TMJ) are not commonly encountered. Their prompt diagnosis and treatment are essential for appropriate patient care. Those lesions may grow from either the joint space, or the temporal or the mandibular component of the joint. The purpose of this review is to cover the imaging findings of a variety of mass lesions of the TMJ, with emphasis on the radiological differential diagnosis.

***Materials and Methods*:** Cases of mass lesions involving the TMJ were collected from our clinical database and teaching files.

***Results*:** The results were as follows.

Developmental: Condylar hyperplasia is mostly idiopathic and unilateral with slowly progressive enlargement of one side of the mandible. On imaging, asymmetrical condylar enlargement is depicted.

Infection: Septic arthritis is most commonly a result of direct extension from adjacent infectious

focus, or might be a part of a systemic blood born process. Usually, diagnosis is easily made based on clinical presentation; however, in chronic conditions with destructive changes, an infectious lesion might be misdiagnosed as a neoplasm. Osteomyelitis may rarely preferentially affect the bones adjacent to the joint.

Inflammation: Various inflammatory conditions that affect synovial joints may also involve the TMJ. Those include Rheumatic arthritis, seronegative arthritis, and collagen-vascular disease. Identifying the lesion as centered in the joint space is key for diagnosis.

Benign neoplasm: Neoplastic lesions affecting the TMJ are rare. Determining the origin of the mass lesion whether it arises from the bones, disc space, or adjacent soft tissues is a key for appropriate differential diagnosis. Benign neoplasms are usually recognizable due to bony remodeling and possible secondary degenerative changes that affect the other TMJ. Possible lesions are: Synovial chondromatosis, pigmented villonodular synovitis, giant cell tumor, osteoma, chondroma, etc.

Malignant neoplasm: Those are characterized by bony destruction and aggressive behavior. The TMJ may also be secondarily affected by metastases. Differential diagnosis includes: Ewing's sarcoma, rhabdomyo-sarcoma, eosinophilic granuloma, multiple myeloma, etc.

Conclusions: A differential diagnostic approach to mass lesions affecting the TMJ should start with identifying whether the mass is arising from the mandible, temporal bone, or joint space. In addition, looking for features of benign versus malignant behavior, soft tissue involvement, and changes in the other TMJ may assist in making the diagnosis.

Citation: RMMJ 2012;3 Suppl:71–72.

Poster #111O

Imaging the Formation of Blood Vessels from Endothelial Cells *In Vivo*

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Introduction: Abnormal vessel growth and function are characteristic of, and contribute to, the progression of cancer as well as ischemic and inflammatory diseases. Understanding how endothelial cells communicate with each other and with their environment to form a branched functional vascular network can help develop more pro- and antiangiogenic drugs. The aim of this study is to observe the process of blood vessel formation from endothelial cells *in vivo*, and to assess quantitatively this formation in order to elucidate the role of the physical surroundings and of specific molecules on the different stages of the process: sprouting, branching, tube formation, pruning, remodeling, and perfusion.

Methods: Human umbilical vein endothelial cells (HUVECs) were virally infected to express GFP and implanted as spheroids in a semi-solid plug in a dorsal skin-fold window chamber of a nude mouse. The fate of the cells was observed by periodical *in vivo* imaging using fluorescent microscopy over a period of up to 4 weeks.

Results: The HUVEC spheroids undergo sprouting, form structures containing typical tip cells and stalk cells, and with time produce an unorganized network of vessels. The process of vessel formation is dependent on the constituents of the plug.

Conclusions: Implantation of HUVEC spheroids into a dorsal skin-skin window chamber can be used to assess factors influencing blood vessel formation.

Citation: RMMJ 2012;3 Suppl:72.

Poster #116O

Diagnosing Acute Appendicitis in Adults: Accuracy of Color Doppler Sonography and MDCT Compared with Surgery and Clinical Follow-Up

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Introduction: The objective of our study was to evaluate the accuracy of color Doppler sonography and contrast-enhanced MDCT in the diagnosis of acute appendicitis in adults, and their utility as a triage tool in lower abdominal pain.

Methods: We reviewed the medical records of 420 consecutive adult patients, 271 women and 149 men, 18 years old or older, referred from the emergency department to sonography examination for clinically suspected acute appendicitis between January 2003 and June 2006. Patients underwent sonography of the right upper abdomen and pelvis followed by graded compression and color Doppler sonography of the right lower quadrant. Computed tomography (CT) was performed in 132 patients due to inconclusive sonography findings or a discrepancy between the clinical diagnosis and the sonography diagnosis. Sonography and CT reports were compared with surgery or clinical follow-up as the reference standard. Statistical analyses were performed by Pearson's chi-square test and cross-tabulation software.

Results: Sonography and CT correctly diagnosed acute appendicitis in 66 of 75 patients and in 38 of 39 patients, respectively, and correctly denied acute appendicitis in 312 of 326 and in 92 of 92 patients. Sonography was inconclusive in 17 of 418 cases and CT, in one of 132 cases. Sonography and CT allowed alternative diagnoses in 82 and 42 patients, respectively. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for sonography were 74.2%, 97%, 88%, 93%, and 92%, respectively, and for CT, 100%, 98.9%, 97.4%, 100%, and 99%, respectively.

Conclusions: Sonography should be the first imaging technique in adult patients for the diagnosis of acute appendicitis and triage of acute abdominal pain. Computed tomography should be used as a complementary study for selected cases.

Citation: RMMJ 2012;3 Suppl:72–73.

Poster #117O

Color-Coded Duplex Sonography Compared to MDCT for the Diagnosis of Crohn's Disease Relapse and Complications

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Introduction: To evaluate the accuracy of color-coded duplex sonography (CCDS) for the diagnosis of Crohn's disease relapse and complications compared to multidetector computed tomography (MDCT).

Methods: The Institutional Review Board approved the protocol research and written consent forms were obtained. Patients with diagnosis of Crohn's disease presenting with symptoms compatible to relapse or complications (54 patients, 27 female, ages 9-80, mean 34.6) were enrolled. Patients underwent CCDS and MDCT examinations, within two weeks of each other. The study standard of reference was MDCT. Location and extent of diseased bowel, wall thickness, stenosis, hyperemia, mesenteric fat thickening, lymphadenopathy, abscess, fistula, peritoneal fluid, were examined for signs of hepatobiliary disease.

Results: Upwards of 80% of the patients had terminal ileal involvement and 55% had disease confined to the ileum. Significant correlation between the two modalities was found regarding wall thickness, abscess, and fistula. CCDS demonstrated sensitivity and specificity of 88 and 53%, respectively, for diagnosis of luminal stenosis. Hyperemia was more commonly diagnosed on CCDS. CCDS demonstrated sensitivity and specificity of 84% and 83%, respectively, for diagnosis of mesenteric fat thickening and lymphadenopathy and 66 and 86%, for peritoneal fluid. Fatty liver was found in 18%, and gallstone disease in 6%.

Conclusions: Color-coded duplex sonography was accurate in diagnosing disease location, wall

thickness, and extra-intestinal inflammatory findings associated with Crohn's disease, potentially placing CCDS as the first-line imaging modality for the diagnosis of Crohn's disease relapse and complications.

Citation: RMMJ 2012;3 Suppl:73–74.

NURSING

Poster #36P

Changes in Nurses' Attitudes towards Physicians Strikes in 1998 vs. 2011

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Introduction: Political, economic, social, and organizational changes within a society may have some impact on the attitudes of professionals in the workplace. The purpose of this survey was to examine the change in nurse attitudes towards physician strikes over time.

Material and Methods: An anonymous questionnaire was filled out by nurses twice: first in 1998 ($N = 106$), and for the second time in 2011 ($n = 175$). Each survey was taken during the time of prolonged physician strikes in the Israeli health care system. The questionnaire included identical questions as to their attitudes to the strike, particularly involving ethical issues. In 1998, the questionnaires were handed out on paper via head nurses; in 2011, the questionnaires were sent out by e-mail. In both cases, the surveys were conducted while the strike was in progress for just over 110 days. Statistical comparisons of the results were made using SPSS 17th version.

Results: Compared to 1998, there was a statistically significant rise in 2011 in the percentage of nurses who replied that striking by physicians is a legitimate weapon for physicians to use ($P < 0.005$); in the number of nurses who would strike under the same circumstances if they were physicians ($P < 0.005$); and in the number who reported that physicians took into consideration the nurses' opinions as to whom to treat during/despite the strike ($P = 0.04$). There was a statistical trend towards an increasing number of nurses who said that the suffering of patients due to the strike is somewhat or fully justified ($P = 0.06$). Yet, most of the nurses faced a difficult dilemma involving loyalty to physician colleagues vs. loyalty to patients. Many nurses reported in open questions that they had found ways to mitigate the suffering of patients resulting from the strike.

Conclusions: The changing trends of the Israeli societal values regarding the legitimacy of striking as a protest tool have filtered into the health care system. Nurses face professional and personal conflicts during any physicians' strike.

Citation: RMMJ 2012;3 Suppl:74.

BASIC RESEARCH

Poster #43Q

Reprogramming of Telomeric Regions during the Generation of Human Induced Pluripotent Stem Cells and Subsequent Differentiation into Fibroblast-Like Derivatives

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Introduction: Human induced pluripotent stem (hiPS) cells provide therapeutic promises, as well as a potent *in vitro* model for studying biological processes that take place during human embryonic development and subsequent differentiation in normal and disease states. The epigenetic characteristics of iPS cells are reprogrammed to the embryonic state at which they acquire pluripotency. In addition, telomeres in hiPS cell must elongate sufficiently to provide the necessary replicative potential. Recent studies have demonstrated that the epigenetic characteristics of telomeric and subtelomeric regions are pivotal in regulating telomere length.

Material and Methods: We studied telomere length, subtelomeric DNA methylation, and telomeric-repeat-containing RNA (TERRA) expression in several hiPS cell clones derived from normal neonatal foreskin fibroblasts.

Results: We found that telomeres lengthen significantly in hiPS cells in comparison to the parental fibroblast source, and progressively shorten after differentiation back into fibroblast-like cells, concomitantly with telomerase activation and down-regulation, respectively.

Subtelomeres in hiPS cells were found to be generally hypermethylated in comparison to the parental source. However, bisulfite analysis revealed that at several subtelomeres examined, methylation levels differed between hiPS clones and that both *de novo* methylation and demethylation processes occurred during telomere reprogramming. Notably, although subtelomeres were in general very highly methylated, TERRA levels were elevated in hiPS cells, albeit to different degrees in the various clones.

Conclusions: Elevation of TERRA may reflect enhanced stability or impaired degradation in hiPS cells, and/or alternatively, increased transcription from the hypomethylated subtelomeres. We suggest that TERRA may play a role in regulation of appropriate telomere function and length in hiPS cells.

Citation: RMMJ 2012;3 Suppl:74–75.

Poster #92Q

A Comparison of the Anti-Atherogenic Effects of Reduced Aldosterone versus Specific Blocking of The Mineralocorticoid Receptor in apoE0 Knockout Mice

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Introduction: Elevated levels of the mineralocorticoid, aldosterone, are known to be involved in the pathophysiology of cardiovascular diseases. Eplerenone, a highly selective mineralocorticoid receptor antagonist (MRB), acting by competitively inhibiting binding to MR, has been shown to be protective in experimental atherosclerosis, in association with reduced oxidation and inflammation. However, neither the effects of reduced aldosterone levels nor the aldosterone-independent effects of epleronone on atherosclerosis development were previously determined. Using adrenalectomized atherosclerotic mice, this study will provide an experimental *in vivo* system to test the above questions.

Methods: Male mice, 5 months old, apoE deficient (E0), and prone to spontaneously develop atherosclerosis on a high fat diet, were randomly divided into two groups: control or adrenalectomized (ADX) mice. Each group was further divided into vehicle or eplerenone (100mg/kg/day) treatment in their drinking water for 2 months. The aortas, peritoneal macrophages were harvested.

Results: Adrenalectomy reduced serum aldosterone and corticosterone levels by 75% and 65%, respectively. Serum cholesterol and triglycerides were also significantly reduced in ADX mice by 39% and 58%, respectively. Similarly, reduced levels of serum cholesterol were observed in the eplerenone treated mice. However, a 59% higher capacity to induce cholesterol efflux from macrophages was measured with HDL obtained from eplerenone-treated mice but not from ADX mice. Total peroxides in peritoneal macrophages were significantly reduced by 73% and 63% in both, ADX or eplerenone treated mice, respectively. Inflammatory markers in peritoneal macrophages, ICAM1, MCP1, IL6, and TNFa were markedly reduced to a similar extent in both Epl and ADX treated mice. A significantly reduced aortic atherosclerotic lesion area of 50% was measured only in eplerenone-treated mice. The beneficial antiatherosclerotic effects of ADX and eplerenone alone were lost in the eplerenone-treated adrenalectomized mice, despite the 40% and 49% reduction in serum aldosterone and corticosterone levels.

Conclusions: Although reduced serum levels of adrenal hormones were associated with reduced atherogenicity expressed by inflammation, oxidation and cholesterol, in serum and macrophages, these changes did not result with significant changes in atherosclerotic lesion area. Inhibition of the mineralocorticoid receptor on the other hand was associated with reduced atherosclerosis.

Citation: RMMJ 2012;3 Suppl:75.

DERMATOLOGY

Poster #89R

Clinical and Neuroimaging Findings in Patients with Neurosyphilis

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Introduction: Neurosyphilis is often asymptomatic and the diagnosis depends on cerebrospinal fluid (CSF) findings. Not much is currently known on the role of neuro-imaging in the diagnosis of neurosyphilis. The present study attempted to further to characterize this role.

Material and Methods: Six consecutive patients (pts) with the diagnosis of symptomatic neurosyphilis based on abnormal CSF findings between 2003 and 2010 underwent cranial computerized tomography (CT) and magnetic resonance imaging (MRI). The mean pt age was 39 years; all were males. Detailed histories were taken from all six pts. All pts underwent complete physical examination including a neurological examination, and were asked and examined for vascular risk factors including diabetes mellitus, hyperlipidemia, and hypertension as well as medication histories, toxic exposure, and tobacco use. Baseline routine blood counts and chemistries were also performed. In addition, all six pts were examined for cardiac involvement including electrocardiography (ECG) and cardiac ultrasound. The CSF analysis included protein concentrations, glucose levels, and cell counts. The following tests were performed: Venereal Disease Research Laboratory Test (VDRL) test, rapid plasma regain (RPR) test, and Treponema pallidum hemagglutination (TPHA) test. The latter were performed in both the serum and the CSF samples. HIV serology was performed in all of the pts.

Results: Despite the lack of complaints, the neurological and ophthalmological examination revealed abnormalities in five of the six pts, most commonly cranial nerve involvement (three pts) and hemiparesis (two pts). The CT and the MRI studies revealed abnormalities in four of the six pts, and in all six pts, respectively. The CT and MRI findings were congruent in three pts, showing brain infarcts in two and mild generalized atrophy in one. In two pts, in whom the CT was interpreted to be normal, the MRI showed acute stroke and multiple laccunar infarcts, respectively. The sixth patient showed generalized atrophy on CT and suspected Gummas and infarcts on MRI. In more than half of the pts, especially those with cranial nerve involvement, neuroimaging studies were not congruent with the neurological and ophthalmological findings.

Conclusions: 1) The most common neuroimaging finding in asymptomatic neurosyphilis is vascular occlusion most likely due to meningovascular endarteritis; 2) MRI is more sensitive than CT in this respect; 3) the neuroimaging findings are often not congruent with the neurological findings; and 4) neurosyphilis should always be considered in young pts with unexplained brain infarcts.

Citation: RMMJ 2012;3 Suppl:76.

RESPIRATORY

Poster #61S

Implanted Upper Airway Stimulation Device for Obstructive Sleep Apnea

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Introduction: Previous feasibility studies have shown that electrical stimulation of the hypoglossal nerve can improve obstructive sleep apnea (OSA). The current study examined the safety and preliminary effectiveness of an Upper Airway Stimulation (UAS) system (Inspire Medical Systems, Inc.) and identified baseline predictors for therapy success.

Material and Methods: The UAS systems were implanted in patients with moderate to severe OSA who failed or were intolerant of continuous

positive airway pressure (CPAP). The study was conducted in two parts: In Part 1, patients were enrolled with broad selection criteria. Apnea hypopnea index (AHI) was collected using lab-based polysomnography at pre- and post-implant visits. Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) were also collected. In Part 2, patients were enrolled using selection criteria derived from the experience in Part 1.

Results: In Part 1, 20 of 22 enrolled patients (2 exited the study) were examined for factors predictive of therapy response. Responders had both a BMI ≤ 32 and AHI ≤ 50 ($P < 0.05$) and did not have complete concentric retropalatal collapse. Part 2 patients ($n = 8$) were selected using responder criteria and showed an improvement of AHI from baseline 38.9 ± 9.8 to 10.0 ± 11.0 ($P < 0.01$) at 6 months post-implant. Both ESS and FOSQ improved significantly in Part 1 and Part 2 subjects.

Conclusions: The current study has demonstrated that therapy with upper airway stimulation is safe and efficacious in a select group of patients with moderate to severe OSA who cannot or will not use CPAP as primary treatment.

Citation: RMMJ 2012;3 Suppl:76–77.

INTERNAL MEDICINE

Poster #81T

Consumption of Pomegranate Decreases Serum Oxidative Stress and Reduces Disease Activity in Patients with Active Rheumatoid Arthritis

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Background: Oxidative stress is involved in the pathogenesis of joint inflammation in Rheumatoid arthritis (RA). Serum HDL-associated paraoxonase 1 (PON1) is a native potential antioxidant that hydrolyzes specific oxidized lipids in lipoproteins and macrophages. Pomegranate extract (POMx) is a rich source of dietary antioxidants (polyphenols) that increases PON1 activity. A POMx rich diet reduced the incidence and severity of joint inflammation in mice with collagen-induced arthritis.

Aims: We investigated the efficacy of 12 weeks POMx on disease activity in RA patients (pts), and its influence on their serum oxidative status.

Methods: Eight RA pts with inadequate response to DMARDs (mean age/disease duration 62.7 yrs, disease duration 7.7 yrs) with active RA (inclusion criteria DAS28 > 4.5) were recruited. Six patients consumed POMx (5 ml/bid) during 12 weeks. Smoking, diabetes mellitus, daily prednisone dose > 10 mg, recent (< 1 month) parenteral steroids, and previous or concomitant biological therapy were exclusion criteria. Treatment efficacy was assessed using DAS28 (ESR) and HAQ-DI at weeks 0 and 12.

Results: POMx reduced DAS28 by 17% ($P < 0.02$). This could be mostly related to a significant reduction (62%) in number of tender joints ($P < 0.05$). POMx consumption was also associated with a significant reduction in serum oxidative stress, measured as lipid peroxides ($P < 0.02$), and by a significant increase in serum HDL-associated PON1 activity ($P < 0.02$). Addition of POMx to serum from RA patients reduced AAPH-induced lipid peroxidation by up to 25% compared to age-matched healthy controls (18%).

Conclusions: Consumption of POMx reduces disease activity in RA patients. This effect could be related to its antioxidative capacity and raised activity of PON1. Thus, dietary supplementation of POMs may be a useful additive strategy to attenuate clinical symptoms in active RA and reduce cardio-vascular risk. Further studies regarding POMs influence on RA activity on large patient's cohort is warranted.

Citation: RMMJ 2012;3 Suppl:77.

Poster #83T

Ultrasound Assessment of Enthesis Thickening in Psoriatic Arthritis Patients Treated with Adalimumab Compared to Methotrexate

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Background: Main signs of Psoriatic arthropathy (PsA) are arthritis, tendinitis, enthesitis, and spinal involvement. Musculoskeletal ultrasound (MSUS) has become the gold standard for examination of tendons; it has already been proven in monitoring synovitis in rheumatoid arthritis (RA) patients (pts).

Objectives: This study assesses the effect of adalimumab (ADA) compared to methotrexate (MTX) on the thickness of tendons and enthesis in PsA pts.

Methods: Thirty-two pts with active PsA were included. Group 1: 21 PsA pts starting ADA treatment; 14 women, 7 men, mean age 51.9 ± 9.5 years. Group 2: 11 PsA pts beginning MTX; 5 women, 6 men, mean age 45.1 ± 14.3 years. Disease activity was assessed by the number of tender (TJ) and swollen joints (SJ), inflamed enthesitis (IE), pain assessment (PA), patient (PDA) and physician (PGDAI) disease activity evaluation by visual analogue scale (VAS). The MSUS assessment and thickness measurement of the extensor (ET) and flexor tendons (FT) of the second and third fingers of both hands, plantar fascia (PF) and Achilles tendon (AT) bilaterally were performed before initiating the therapy, 6 and 12 weeks (wks) after.

Results: In Group 1, all disease activity parameters improved at visit three, and reached statistical significance for the number of TJ (10.38 vs. 6.06, $P = 0.0071$), SJ (8.19 vs. 4.94, $P = 0.04$), PF (71.52 vs. 43.44, $P = 0.006$), and PGDAI (70.45 vs. 40.95, $P = 0.0014$). Decreased thickness was observed for AT bilaterally, and was significant on the left (Lt) side (0.38 vs. 0.33, $P = 0.02$), and for Lt PF (0.13 vs. 0.10, $P = 0.01$). A statistically significant positive correlation was found between the decrease of thickness of the ETs and the number of TJ and IE, PGAD, PGA.

In Group 2, parameters of IE ($P = 0.04$), PGA ($P = 0.017$), and PGDA ($P = 0.05$) decreased significantly, while the number of TJ and SJ did not change. No changes were observed in the thickness of both AT and PF, FT and ET tendons of hands after 12 wks. Six wks after initiating ADA, thickness of Lt AT, the second Rt FT and the number of TJ, SJ, PF, and PGA were significantly decreased in comparison to the MTX group ($P = 0.007$; $P = 0.05$ $P = 0.032$; $P = 0.001$; $P = 0.034$ and $P = 0.003$, respectively).

Conclusion: In pts with PsA, treatment with ADA, compared to MTX, significantly improved signs of disease activity as well as MSUS parameters of enthesis such as AT and PF. The MSUS monitoring of enthesis is a useful tool for monitoring PsA enthesopathy.

Citation: RMMJ 2012;3 Suppl:78.

Poster #93T

Medication Reconciliation in the Geriatric In-patients

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Introduction: Medication errors and medication related problems are one of the leading causes of morbidity and mortality among the geriatric patients, both in the outpatient and the inpatient environment. A large percentage of medication errors occur at hospitalization and transition from different departments. These medication errors can be avoided by managing a comprehensive and consecutive process of "Medication Reconciliation." It is a formal process of obtaining and documenting a complete and accurate list of the patient's current medications upon admission and comparing this list to the physician's admission, transfer, and\or discharge orders, to identify and resolve discrepancies and errors in medication list.

Methods: The process of medication reconciliation will be conducted for elderly patients (age > 65) at the internal medicine wards. Inclusion criteria: age > 65 years, on more than five medications. (1) Designing a personalized Med Rec worksheet (2) advanced communication between the health care providers. (3) When the patient is admitted to the internal medicine ward, the pharmacist collects an accurate and complete medication history using a predesigned Med Rec worksheet (the verification step), the same process is repeated when the patient is transited to a different department. If any discrepancies are identified, the physician is notified (the clarification step), the error is corrected by the treating physician (the reconciliation step). When discharged, the patient meets with the pharmacist for education and consultation, and outpatient follow up is conducted when possible.

Expected Results: The expected number of patients is 30 in duration of 2 months. As observed in previous similar studies, we expect decreased medication related problems, and increased patient awareness and adherence.

Expected Conclusion: Unintentional medication discrepancies are common at interfaces between the health care transitions, due to insufficient communication and inaccurate medication reconciliation, which can lead to serious drug related problems. A comprehensive and consecutive Med Rec process must be carried out for bridging the gaps in continuity of care, therefore providing safety and efficacy of health for patients during transitions in care. The pharmacist's involvement is essentially important at various points in the Med Rec process, by identifying, solving, and preventing drug-related problems. The shared responsibility of health care providers (physicians, nurses and pharmacist), is the key to a successful Med Rec process.

Citation: RMMJ 2012;3 Suppl:78–79.

SURGERY

Poster #87U

A Modified Thoracotomy Technique Reduces the Intensity of Acute Postoperative Pain

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Introduction: The standard posterolateral thoracotomy is associated with substantial morbidity, and is rated as one of the procedures inducing the most intense pain. Since enhanced pain experienced during the acute postoperative phase is a major predisposing factor for the development of chronic pain, attenuating acute postoperative pain (APOP) following thoracotomy has become an especially relevant need in the clinical arena. Accordingly, this study aimed at revealing whether a modified thoracotomy technique, which less invasively and more gradually accessed the chest cavity, would be associated with the attenuation of pain intensity during the acute postoperative phase.

Materials and Methods: Eighty-four patients (Group 1) have undergone the standard posterolateral thoracotomy, while forty-five patients (Group 2) have been operated according to a modified technique, mainly guided by a lower degree of invasiveness and a gradual ribs expansion. APOP was measured both at rest ($APOP_{rest}$) and during physical activity ($APOP_{provoked}$) of hand elevation and cough within 5 days after surgery. The effect of pain catastrophization in response to experimental pain applied before surgery on APOP intensity was also explored.

Results: A linear regression analysis revealed that lower $APOP_{provoked}$ scores were significantly associated with the modified thoracotomy technique ($P < 0.001$), with no effect of individual pain catastrophization levels, age or gender. $APOP_{rest}$ was comparable in both groups.

Conclusions: These observations (i) point to the importance of the modified surgical technique, allowing the attenuation of APOP while achieving the primary surgical goals, and (ii) emphasize the complexity of APOP as a composition of distinct processes of the pain system.

Citation: RMMJ 2012;3 Suppl:79–80.

Poster #91U

Renal Dysfunction Associated with Increased Intra-Abdominal Pressure in Experimental Heart Failure: Nephroprotective Effects of Phosphodiesterase-5 Inhibition

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Introduction: The deleterious effects of elevated intra-abdominal pressure (IAP) on the kidneys are widely recognized in abdominal compartment syndrome, visceral edema, and laparoscopic surgery. Previously, we demonstrated that rats with congestive heart failure (CHF) exhibited exaggerated sensitivity to the adverse renal effects of elevated IAP compared with sham controls. In the present study, we tested whether IAP induces acute kidney injury (AKI), and whether phosphodiesterase-5 (PDE5) inhibition ameliorates the adverse renal effects of elevated IAP in rats with CHF.

Methods: Following a baseline period, rats with high- and low-output CHF induced by the placement of aorto-caval fistula or LAD ligation, respectively, and sham-controls were subjected to consecutive IAPs of 7, 10, or 14 mmHg for 45 min each by CO_2 insufflation. Urine flow (V), Na+ excretion (UNaV), glomerular filtration rate (GFR), renal plasma flow (RPF) and NGAL excretion were determined. The effects of pretreatment with Tadalafil (10 mg/day, PO) on the adverse renal effects of elevated IAP were examined in these rats.

Results: While IAP of 7 mmHg in sham-controls did not affect V, UNaV, GFR and RPF, IAPs of 10 and 14 mmHg produced dose-dependent reductions in these parameters. Basal kidney function and renal hemodynamics were lower in both low- and high-output CHF rats. When subjected to 10 and 14 mmHg, CHF rats exhibited exaggerated declines in V, UNaV, GFR, RPF, and increased NGAL excretion compared to sham controls. Pretreatment with Tadalafil ameliorated the deleterious renal effects of high IAP in both CHF models.

Conclusions: Rats with CHF are vulnerable to the adverse renal effects of pneumoperitoneum. Tadalafil abolishes renal dysfunction and AKI induced by high IAP, supporting a therapeutic role for PDE5 inhibition in laparoscopic surgery in CHF states.

Citation: RMMJ 2012;3 Suppl:80.

NEPHROLOGY

Poster #90V

Effects of Everolimus on Proteinuria and Expression of Glomerular Slit Diaphragm Proteins in Experimental Nephrotic Syndrome

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Introduction: Everolimus, an mTOR inhibitor, is used as a potent immunosuppressant in renal transplantation. Although various serious side effects of Everolimus have been described, including renal injury and proteinuria, other studies have demonstrated beneficial renal effects of the drug. Therefore, the aim of this study was to examine the effects of different doses of Everolimus given as either early or late treatment on proteinuria and slit diaphragm proteins in adriamycin (ADR)-induced experimental nephrotic syndrome (NS).

Methods: Low or high dose of Everolimus (20 or 100 mg/L via drinking water) was administered to NS rats, beginning either 3 days prior to NS induc-

tion (early treatment) or 2 weeks after the induction of NS (late treatment). Daily and cumulative urinary protein excretion (UprV) was determined throughout the treatment period, which lasted 6 weeks. Moreover, the effects of Everolimus on GFR and key slit diaphragm proteins, namely nephrin and podocin, were assessed at the end of the study.

Results: While the low dose of Everolimus resulted in therapeutic plasma concentration of 4.9 ± 0.6, the high dose yielded supra-pharmacological plasma level of 21.3 ± 4.4 ng/ml. As expected, ADR administration induced gradual significant increase in daily and cumulative UprV, in association with glomerular injury as presented by decrease in nephrin and podocin abundance. Low dose of Everolimus as early, and to a lesser extent as late treatment, reduced UprV and increased plasma albumin levels. These beneficial effects of low dose Everolimus were associated with improvement in GFR and substantial preservation of glomerular podocin and nephrin immunoreactivities. In contrast, high dose of Everolimus aggravated renal dysfunction and did not preserve nephrin/podocin expression. However, protein excretion in NS rats treated with the high Everolimus dose was eventually reduced secondarily to its deleterious effects on GFR.

Conclusion: Our study indicates that Everolimus possesses antiproteinuric effect at a therapeutic dose, whereas at a high dose it aggravates pre-existing glomerular injury.

Citation: RMMJ 2012;3 Suppl:80–81.

NUTRITION

Poster #102W

Standardized versus Individualized Total Parenteral Nutrition in Very-Low-Birth-Weight Infants: A Comparative Study

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Introduction: Parenteral nutrition (PN) improves growth and outcome of very-low-birth-weight (VLBW) infants. Optimal PN composition, standard (STD-PN) or individualized (IND-PN), is still controversial. The aim of this study was to compare IND-PN and STD-PN as to nutritional and growth parameters, complications and cost.

Material and Methods: A total of 140 VLBW infants were studied. Each of the 70 neonates from the IND-PN group was matched with a neonate of similar gestational age (GA) (± 4 days) on STD-PN. Data collection included demographic, maternal, intrapartum, neonatal, interventional, growth, and nutritional data.

Results: Compared to STD-PN infants, IND-PN infants had a significantly lower mean birth weight, greater need for resuscitation at birth and interventions thereafter. Nevertheless, IND-PN infants showed significantly greater weight-gain during the first week ($P = 0.036$) and the first month of life ($P = 0.0004$), and higher discharge-weight ($P = 0.012$) and head-circumference ($P = 0.006$). IND-PN infants received higher mean daily caloric intake. They also had significantly shorter duration of exclusive PN and needed less electrolyte corrections.

Conclusions: Compared to STD-PN infants, IND-PN infants achieved significantly better growth without added clinical or laboratory complications had shorter period of exclusive PN and less electrolyte corrections. Individualized PN, in accordance with the current more aggressive nutritional approach, appears to be the optimal PN for VLBW infants. Yet, STD-PN with adequate composition is an appropriate alternative.

Citation: RMMJ 2012;3 Suppl:81.

Poster #103W

Nutritional Parameters as Predictors of Transplant Outcome

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Introduction: Patients undergoing bone marrow transplant (BMT) are at high risk for

malnutrition due to mucositis, vomiting and diarrhea. Decline in nutritional status is presumed to be a negative prognostic indicator for BMT outcome. The aim of the study was evaluating nutritional parameters in patients prior to and during allogeneic BMT.

Material and Methods: A total of 43 allogeneic BMT patients receiving total parenteral nutrition (TPN) were enrolled; 24 patients underwent an allogeneic transplant from matched related donors, 15 from matched unrelated donors, and 5 haploidentical BMT. Thirty-two patients received myeloablative conditioning, and in 12, reduced-intensity conditioning was used. Median age was 35.5 years (17–72). Nutritional status (NS) (determined by body mass index (BMI), total cholesterol (TC), and albumin (Alb) levels) was correlated with rate of infection, survival and engraftment.

Results: *Nutritional status and prognosis*: Admission levels: Higher TC levels were associated with a lower infection rate during hospitalization ($P = 0.019$). Mortality rate was higher among patients with a lower NS ($P = 0.04$). The BMI < 20/ > 30 vs. normal BMI was associated with delayed engraftment and increased mortality (NS). During hospitalization lower Alb and TC levels were inversely related to the number of infections ($P = 0.026$, $P = 0.006$, respectively), which was directly associated with mortality. Mean Alb levels among survivors were higher compared with patients who died ($P = 0.001$). Among patients who survived, mean TC level was 240.9 ± 66.9mg/dl vs. 199.28 ± 58mg/dl among those who succumbed ($P = 0.031$). *Alimentation* Average duration of TPN feeding was 22.08 ± 15.1 days. 59.5% of patients receiving TPN failed to fully attain the planned nutritional goal, the most common cause (40.5%) being hypertriglyceridemia. Average min. Alb in patients who did not attain their nutritional goal was lower (2.03 ± 0.5g/dl vs. 2.46 ± 0.5g/dl) than in those who did ($P = 0.014$). Survival rate was higher in patients who achieved their nutritional goal (82.4% vs. 56%, $P = 0.075$).

Conclusions: The nutritional status of patients before and during transplant has a crucial impact on the risk of complications and survival. Total parenteral nutrition remains the most successful method for feeding patients after allogeneic transplantation, despite known complications. Therefore, individually tailored feeding plans adjusting to the changing conditions of each patient are warranted. A pre-hospitalization feeding plan might be beneficial for this patient group.

Citation: RMMJ 2012;3 Suppl:81–82.

Poster #104TPN

A Tailored Nutritional Screening Tool for Rapid Identification of Malnutrition in an Acute Care Hospital Setting

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Introduction: Malnutrition is extremely prevalent in hospitalized patients, associated with high rates of morbidity and mortality. Limited resources may prevent the proper evaluation of patients by nutrition experts. Our work validates specificity and sensitivity of an electronic-automatic, tailored Computer Option Screening Tool (COST) compared to the Malnutrition Universal Screening Tool (MUST), also used in our facility.

Methods: The COST system combines laboratory data, anthropometric parameters, medical diagnosis, history, and social and functional parameters to give immediate information on nutritional risk. Fifty randomized patients from internal and surgical wards were assigned to this study. Each patient was screened by both screening tools; COST was correlated with Length of Stay (LOS) and MUST, as well as expert clinical dietitian evaluation.

Results: According to the MUST, 16% of the patients were at high risk of malnutrition (score ≥ 2) and LOS was 13 ± 9 days, which was significantly higher than patients with MUST score of < 1 ($P = 0.01$). According to the COST, 40% of the patients were at high risk of malnutrition (score ≥ 6) and LOS of 8.8 ± 4.75 days, which was significantly higher than patients with COST score of < 5 ($P = 0.01$).When comparing patients identified as high risk for malnutrition by MUST we found a 100%

correlation to COST. The COST also identified 11 high-risk patients who were under-diagnosed by the MUST and needed nutritional support, as verified by the independent expert case review.

Conclusions: The goal of this research was to validate reliability of a new user-friendly electronic screening tool, developed in our medical center. Reliability for high risk of malnutrition compared to MUST was 100% in our pilot. We believe this novel time saving method maximizes efficiency and is an effective method in detecting patients who are in need of nutritional support or surveillance.

Citation: RMMJ 2012;3 Suppl:82–83.

HUMAN GENETICS

Poster #109Y

Deciphering the Genetic Defect behind Kohlschutter-Tonz Syndrome

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Background: Kohlschutter–Tonz syndrome (KTS) (MIM 22675) is a rare autosomal recessive neurodegenerative disorder, characterized by progressive dementia, spasticity, and epilepsy. The disease is marked by a generalized enamel defect known as amelogenesis imperfecta (AI). The syndrome was first reported in families originating from Switzerland and Sicily. Affected children develop normally until the onset of seizures around one year of age, followed by mental deterioration. All children show the same enamel defect known as amelogenesis imperfecta. Zlotogora (1993) reported on a boy and a girl with KTS born to first cousins-once removed, of Druze origin from Northern Israel. Only 21 patients with KTS have been reported to date worldwide. Recently, several additional KTS cases ($n = 13$) were identified by us in the same Druze township of Northern Israel. This study seeks to identify the genetic defect and the pathogenesis underlying KTS.

Methods: Following signed informed consent (self and parental), blood samples were drawn for DNA extraction, from all available KTS patients ($n = 13$) and relevant family members pertaining to three separate kindred. Although all families were from the same, close knit, Druze village, we were unable to relate all participants to one pedigree. Clinical, neurological, and developmental assessments were undertaken in selected patients. Whole genome linkage analysis using Affymetrix 250K SNP array (Biological Services Unit at the Weizmann Institute) was undertaken using five DNA samples from affected individuals. The 6000 SNPs array platform by Illumina (BioRap Technologies Ltd. at the Rappaport Institute was used to analyze 12 additional samples).

Results: A Candidate locus of 0.8 Mb was identified. Using SUPERLINK online, linkage analysis of families 1–3 generated two-point LOD score of 6.4 at chr16:4.67 with a maximum multipoint LOD score of 7.70. Sequence analysis of candidate genes ($n = 10$) was performed using primers designed by us. A newly identified, uncharacterized gene (namely *kts1*) of 11 coding exons, encoding 287 amino acids, was found to harbor a nonsense mutation, resulting in a premature stop codon at Arginine 157. All KTS family members, both affected and healthy, were screened for the mutation RFLP analysis. Family members segregated as expected. After screening 45 DNA samples from randomly selected healthy individuals from the Druze village, four heterozygotes were identified.

Conclusions: A heretofore-uncharacterized gene, *kts1*, was recently identified by us. Public databases regarding the *kts1* gene retrieved very little information. It has been reported as a "leucine zipper domain" protein that "may act as a positive regulator of cell proliferation."

Citation: RMMJ 2012;3 Suppl:83.

Poster #115Y

Two Distinct Phenotypes in 11 Individuals, Demonstrating Alternate Unbalanced Recombinants Derived from a Cryptic Paternal Balanced Translocation between Chromosomes 10 and 14

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Background: Two syndromes, each characterized by a distinct cluster of clinical features, were segregated in 11 individuals from one kindred. All affected children were the products of non-consanguineous mating. However, all affected individuals shared a common progenitor. The diagnosis of unbalanced chromosomal abnormalities was sought. Yet, cytogenetic studies were reported to be normal. Molecular cytogenetics tools were undertaken to investigate further this prototype of abnormalities.

Methods: Following signed informed consent (parental), blood samples were drawn, for DNA extraction, from all available patients (n = 10) and parents (n = 6), pertaining to three nuclear families, from one kindred. Clinical, neurological, and developmental assessments were undertaken in selected patients. Two distinct phenotypes, A and B were delineated, marked by mental retardation, either moderate or severe, respectively, and salient dysmorphic features associated with early scenescence (phenotype B). Whole genome SNP array analysis using the "HumanCytoSNP-12v2.1 DNA Analysis BeadChip Kit (Illumina)" was undertaken on two affected individuals demonstrating distinct phenotypes.

Results: Whole genome SNP array analysis identified an unbalanced cryptic translocation involving a terminal 5 Mb deletion (100273988-106353482) of 14q32.2-14Q32.3 and a terminal 5 Mb duplication (125708-5329074) of 10p15.3-10P15.1 in patients with phenotype A. An alternate unbalanced recombinant, namely terminal 5 Mb deletion (125708-5329074) of 10p15.3-10p15 and terminal 5 Mb duplication (100273988-106353482) of 14q32.2-14q32.3, was shown in patients with phenotype B.

Conclusions: Investigations of apparently balanced chromosomal rearrangements in patients with abnormal phenotype by molecular cytogenetics tools, especially by array CGH, have become the gold standard for deciphering cryptic chromosomal abnormalities.

Citation: RMMJ 2012;3 Suppl:84.