תקצירים
כנס המחקר
המרכז הרפואי שערי צדק

18.5.2016

Abstracts
Research Conference
Shaare Zedek Medical Center

מדעית שערי צדק
SHAARE ZEDEK SCIENTIFIC

המרכז הרפואי שערי צדק
SHAARE ZEDEK MEDICAL CENTER

Yissum

האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

Conference Schedule

7:30-8:00 Registration and Coffee

8:00-8:15 Welcoming Remarks

Prof. Jonathan Halevy, Director General, Shaare Zedek Medical Center
Prof. David Lichtstein, Dean of the Faculty of Medicine, The Hebrew University of Jerusalem
Prof. Shy Arkin, Vice President for Research and Development, The Hebrew University of Jerusalem
MK Rabbi Yakov Litzman, Minister of Health

8:15-9:30 First Session

Chairs: Prof. Dan Turner and Dr. Ariella Shitrit

Best Abstract: Auditory responses to stimulation at soft tissue sites before and after fixation of mobilecomponents of the middle ear
Dr. Ronen Perez, Cahtia Adelman, Jean-Yves Sichel, Haim Sohmer

Invited Lecture: Parkinson in patients and carriers of Gaucher disease: From Clinical observation in single cases to drug development
Prof. Ari Zimran

Best Abstract: Single Cell Testing versus Amniocentesis and NIPT: Ultra-high Resolution Preimplantation Screening for Microduplication-Microdeletion Syndromes
Dr. David Zeevi, Tal Dror, Efrat Burak, Sophie Kirshberg, Elinor Hakam-Spektor, Dina Kort, Elina Farhi, Merav Ben Shlomo, Sharon Zeligson, Rachel Beeri, Talia Eldar-Geva, Ephrat Levy-Lahad, Gheona Altarescu

The Best of OBGYN
Prof. Uzi Beller

Invited Lecture: Meet RedCap - a data managing software for research, available for all at SZMC
Ms. Gili Focht

The Best of Internal Medicine
Prof. Amos Yinnon

Best Abstract: Shift Handover in the Intensive Care Unit
Ms. Chaya Broyer

Invited Lecture: Cytomegalovirus infection in pregnancy: studies of maternal immune system in relation to fetal infection
Prof. Yechiel Schlesinger

9:30-10:15 Poster Viewing and Coffee Break

10:15-10:45 State of the Art Guest Lecture

Drug treatment for disease prevention - an illustrative case in Alzheimer's disease
Prof. Marta Weinstock-Rosin, Faculty of Medicine, The Hebrew University of Jerusalem

10:45-11:45 Second Session

Chairs: Prof. Jacob Rowe and Dr. Floris Levy-Khademi

Best Abstract: Co-encapsulation of Alendronate and Doxorubicin in Pegylated Liposomes: A novel formulation for chemo-immunotherapy of cancer
Dr. Hilary Shmeeda, Yasmine Amitay, Stephan T. Stern, Yechezkel Barenholz, Alberto Gabizon

Invited Lecture: The next genetic revolution: Gene Editing
Prof. Ephrat Levy-Lahad

Best Abstract: Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section, and adverse maternal and neonatal outcomes
Dr. Lior Drukker, Yael Hants, Rivka Farkash, Rosa Ruchlemer, Arnon Samueloff, Sorina Grisaru-Granovsky

The Best of Pediatrics
Prof. Yechiel Schlesinger

Best Abstract: Can Dual Energy CT Predict the Need for Surgery in Crohn's Disease
Dr. Naama Bogot, Ruth Cytter-Quint, Tomer Adar, Roy Biron, Irith Hadas, Dov Wengover, Eran Goldin

Best Abstract: Loss-of-function of PCDH12 underlies recessive microcephaly mimicking intrauterine infection
Dr. Adi Aran, Nuphar Rosenfeld, Ranit Jaron, Paul Renbaum, Shachar Zuckerman, Hila Fridman, Sharon Zeligson, Reeval Segel, Yoav Kohn, Lara Kamal, Moien Kannan, Yoram Segev, Eyal Mazaki, Ron Rabinowitz, Ori Shen, Ming K. Lee, Tom Walsh, Mary-Claire King, Suleyman Gulsuner, Ephrat Levy-Lahad

The Best of Surgery
Prof. Petachia Reissman

11:45-12:00 Awards for Outstanding Research Projects

Advanced Researchers Category
Medical Students, Interns and Residents Category

12:00 Closing Remarks

Prof. Dan Turner

12:00-13:00 Lunch & Poster Viewing

Round Table Discussions 4th floor Patio
In collaboration with The Hebrew University of Jerusalem's IMRIC Research Hubs

שלום רב,

עיסוק במחקר בסיסי וקליני לצד שרות קליני והוראה הם נשמת אפו של כל בית חולים ובוודאי של בית חולים אוניברסיטאי בעל סינוף אוניברסיטאי מלא לפקולטה לרפואה.

בשנים האחרונות הוקמה רשות מחקר, נחתם הסכם עם חברת יישום של האוניברסיטה העברית ("יישום"), הושגו מענקי מחקר רבים, התרחב שיתוף הפעולה עם תעשיית התרופות לניהול מחקרים ביוזמת החוקרים או החברות ונבחנו רעיונות רבים של חברי סגל בית החולים לקראת יישום ורישום פטנט.

כתוצאה מפעילות ברוכה זו, קבלה הפעילות המחקרית במוסדנו תנופה רבה, מתפרסמים מדי שנה למעלה מ-300 מחקרים בספרות המקצועית, חלקם בעיתונות מן השורה הראשונה.

לעונג לי לקדם בברכה את כנס המחקר הראשון בשערי צדק במסגרתו יוצגו לצבור עובדי בית החולים ולמבקרים מבחוץ מפירות התנובה המחקרית שלנו.

ההיענות לפניית רשות המחקר הייתה גבוהה ומרגשת והניבה כ-180 תקצירי עבודות מחקר המוצגות בפניכם במסגרת יום מחקר זה.

ברכותיי למארגנים, בייחוד לדר' רננה אופן ונתניה בר כוכבא, ואיחוליי ליום מחקר פורה במהלכו ניווכח כולנו בתרומתו המשמעותית של שערי צדק למחקר הרפואי, ובכך כמובן לרווחת החולים בארץ ובעולם.

פרופ' יונתן הלוי
מנכ"ל המרכז הרפואי

שלום רב,

רופאים וחוקרים יקרים,

אין חולק על העוצמה הקלינית של המרכז הרפואי שערי צדק. גדלנו, התפתחנו והוספנו שירותים חדשים. הציבור מצביע ברגליים ומספר הפונים לקבל אצלנו טיפול הולך ועולה.

אבל זה לא כל הסיפור. בד בבד למגמה זו, כמעט בהיחבא, אנו עדים למהפכה אמיתית בארגון המחקר והפיתוח בשערי צדק. מאז 2011 הוקמה הרשות למחקר ופיתוח ובעקבותיה גם חברת מדעית שע"צ למסחור ידע, נחתם הסכם שיתוף פעולה אסטרטגי עם חברת יישום של האוניברסיטה העברית, הוקמו קרנות פנימיות לתמיכה משמעותית במחקר עצמאי, הוקצו משאבים לפיתוח פטנטים וקידום רעיונות מסחריים, הוסדרו נהלים, ושונו סדרי עדיפויות. דרך הרשות למו"פ וחברת מדעית אנו חותמים על למעלה מ-170 חוזי מחקר וייעוץ כל שנה ומנהלים גרנטים אקדמיים בהיקף של מליוני שקלים. במקביל, מנוהלים במדעית מספר לא מבוטל של פרוייקטים למסחור, פטנטים, הסכמי שירות וייעוץ.

כנס מחקר זה, הראשון בתולדות שערי צדק, מביא באחת לחזית את העשייה המחקרית הענפה במוסד. 180 התקצירים הכלולים בספר זה משקפים עוצמה מחקרית מרשימה בהיקפה ואיכותה. מרשים לא פחות הייצוג המכובד לכל המחלקות והיחידות הרפואיות, כולל הסיעוד והמקצועות הפרא-רפואיים. רופאי וחוקרי שערי צדק מפרסמים למעלה מ 300 מאמרים כל שנה, ומספר הפרסומים עולה בשנים האחרונות בקצב של כ 5-10% לשנה.

אל לנו לנוח על זרי הדפנה כי מלאכה רבה עוד לפנינו. פיתוח המדע הבסיסי כולל בניית מעבדות חדשות, עידוד רופאים להגיש גרנטים אקדמיים חיצוניים, שילוב חוקרי ורופאי שערי צדק ברשתות מחקר ארציות ובינלאומיות, קידום פטנטים ורעיונות יישומיים והגדלת נפח המחקר עם חברות התרופות.

כנס זה הוא חגיגת מחקר בראש ובראשונה לחוקרים עצמם שמשקיעים מעבר לדרישות הקליניות של התפקיד מתוך אמונה שמחקר חשוב לרפואה ולמטופלים.

תודה מיוחדת לנתניה בר כוכבא, ד"ר רננה אופן, טלי כץ וקטרינה אלירז על מסירות רבה ועבודה יומיומית מקצועית ליצירת תנאים מיטביים לעשייה מחקרית ויזמית.

תודה גדולה גם לוועדת הלסינקי המוסדית בראשות ד"ר ואן דייק על עבודה אינטנסיבית וברמה הגבוהה ביותר לשמירת גבולות האתיקה של המחקר.

ביום חג זה אני מברך את כולנו להמשך עשייה מחקרית פוריה ומועילה לטובת החולים והרפואה.

פרופ' דן טרנר
עוזר מנכ"ל למו"פ

Table of Contents

SZMC Research Conference 2016

Gastric Embolization Trial for Morbid Obesity (GETMO Trial)

Adam Farkas, MD. Senior Physician, Vascular and Interventional Radiology, Shaare Zedek Medical Center.

Ram Shapira, MD. Senior Physician, Surgery, Shaare Zedek Medical Center. Anthony Verstandig, ***MD. Gabi Munter, MD. Menachem Schechter, MD.*** Senior Physicians in Vascular and Interventioanl Radiology (AV), Endocrinology (GM), and Gastroenterology (MS)

Background/Aims: To evaluate the safety and efficacy of gastric artery embolization as a minimally-invasive option to induce weight loss in the morbidly obese.

Morbid obesity has reached global epidemic proportions and continues to rise in prevalence. It is associated with a myriad of health problems, including gallstones, type 2 diabetes, high blood pressure, high cholesterol and triglycerides, coronary artery disease (CAD), stroke, some cancers, and sleep apnea, among other conditions. Diet and exercise are ineffective in inducing sufficient weight loss in many morbidly obese patients. Bariatric surgery carries potential for obesity recurrence and serious complications. A safe and effective, minimally-invasive alternative, is thus an attractive additional treatment option.

There are dozens of known hormones that lead to satiety and thus limit food intake. Ghrelin, however, is the only known orexigen, or appetite stimulating hormone. Moreover, ghrelin is heavily and disproportionately concentrated within the gastric fundus.

In several recent animal studies, gastric artery embolization of the branches supplying the gastric fundus resulted in short term reduction in ghrelin levels, as well as short term weight loss. Longer term data are not available.

Methods: The procedure will be initially performed on two patients with a body mass index of 40 or above, as a proof-of-concept model. Patients' ghrelin levels and weight loss will be monitored for a period of one year after embolization. Secondary endpoints will include resolution of co-morbidities such as type 2 diabetes and hypercholesterolemia.

In this procedure, selective blood vessels to the stomach are blocked ("embolized") by injecting tiny particles through a small catheter, into the arteries that supply the gastric fundus. A standard angiographic catheter is placed via the common femoral artery into the celiac artery and angiograms are performed. The brach arteries (specifically left gastric artery) supplying the gastric fundus are then selectively catheterized and embolized to stasis.

Results: Results of the initial proof-of-concept model are pending.

Conclusion: We hope to show that gastric embolization is a safe and effective, minimally-invasive alternative to surgery, for the treatment of morbid obesity.

Can Dual Energy CT Predict the Need for Surgery in Crohn's Disease?

Bogot NR, Cytter-Quint R, Adar T, Biron R, Hadas I, Wengrower D, Goldin E

PURPOSE: Dual energy CT (DECT) is sensitive for detection and quantification of iodine in tissue. We aimed to evaluate the correlation between iodine uptake in the inflamed bowel wall in Crohn's disease (CD) and the need for surgery and create an inflammtory index.

METHOD AND MATERIALS: IRB approved prospective double-blind study. 36 patients (mean age 38.6 years, 20 males) with Crohn's disease (CD) underwent a DECT (Somaton Flash) for acute abdominal symptoms. Study protocol: abdominal-pelvic CT using DE mode (100 and 140kV), IV contrast and negative oral contrast contrast. The DECT was interpreted by a radiologist blinded to the clinical outcome. The referring physicians were blinded to DECT interpretation. Studies were interpreted by a radiologist on dedicated software (syngo.CT dual energy, singo.via). Enhancement (HU) was measured for each bowel lesion in both low and mixed images. Inflammatory enhancement index (IEI) was defined as the ratio between the inflamed segment and the stomach (HU on mixed images). Patients were followed for 3 months for an outcome of surgery.

RESULTS: A total of 63 intestinal lesions were demonstrated (1-3 per patient). Eleven patients underwent surgery, 7 within 3 months after the CT and 4 within 1 month after the CT. Higher attenuation on 100kV and mixed images correlated with increased risk of surgery within 3 month: 92.2 vs. 66.6 for 100kV ($p=0.01$) 82.7 vs. 59.5 for mixed images ($p=0.01$) as well as for surgery within 1 month 105.2 vs. 67.04 ($p=0.05$) and 93.8 vs. 59.7 for the mixed images ($p<0.05$). AUROC analysis for the IEI achieved negative predictive value of 98% for the need for surgery.

CONCLUSION: DECT is a reliable tool in assessment of inflammation in patients with CD and can predict the need for surgery. The IEI has a high negative predictive value.

CLINICAL RELEVANCE/APPLICATION: Our study demonstrates that DECT is possible novel decision making tool (surgery vs. conservative surgery) applicable also to acute settings.

Meckel's diverticulum - radiologic appearance in symptomatic and asymptomatic patients with pathologic correlation: review of 50 cases

Nadin Abu Ata, Dept. of Radiology

Background: Meckel's diverticulum (MD) is the most common congenital anomaly of the gastrointestinal tract, with approximate prevalence of 2%. It is a true diverticulum that results from failure of omphalomesenteric duct regression. It is mostly asymptomatic. However - symptoms may be related to: ectopic mucosal tissue (GI bleeding), mechanical complications -such as small bowel obstruction (SBO), inflammation or perforation.

Purpose: To describe the different radiologic appearances of MD in various imaging modalities (US, CT, MR) and correlate between the radiologic appearance and the pathology specimen.

Material and methods: A retrospective review of all cases of MD that were diagnosed between 1/2004-4/ 2015 in Shaare Zedek Medical Center was undertaken. Only patients with relevant imaging studies were included. Patient's demographics, clinical information, imaging findings, operative and pathologic reports were collected for all cases. Imaging appearance was compared to the pathologic specimen.

Results: Fifty patients' files were reviewed, 33 males, mean age 29±23.1 (5wk- 83y). Thirty patients (60%) were symptomatic. In this group, mean age was 30±22.9 (9m-83y). Twenty one patients (70%) presented with abdominal pain, 4 with SBO, 3 with GI bleeding and 2 with anemia. Radiologic diagnosis was made in 11 cases of the symptomatic patients (37%) and 1 case from the asymptomatic patients (5%). Ten cases were diagnosed by CT, 5 by US and 1 by MRI. Meckel's scan was diagnostic in 3 cases. Videocapsule assisted in diagnosis was diagnostic in 1 case.

Radiologic manifestations were SBO (n= 9), inflammation/perforation (n= 8) and inverted MD (n=2). In 3 cases of SBO the MD presented with bezoar. Prominent tissue was seen in 1 case and appearance of gastric folds was noted in 1 case. In one case, MD was incorrectly diagnosed pre and postnatally as duplication cyst.

In all asymptomatic cases, MD had the appearance of non dilated fluid filled small bowel loop.

Conclusions: MD has variety of clinical presentations and radiologic appearances. Familiarity with its different manifestations on different imaging modalities is crucial for early and accurate diagnosis.

Asymptomatic MD is hard to identify on abdominal CT even in a retrospective review of imaging and despite large size MD.

Ultrasound As A Primary Imaging Modality For Follow Up Of Crohn's Disease In Pregnant Women: Initial Results

Y. Fraenkel-Wandel[(1)], ***R. Cytter-Kuint***[(1)], ***A. Keinan***[(2)], ***A. Shitrit***[(3)]
[(1)]Radiology, [(2)]Surgery, [(3)]Gastroenterology, Shaare Zedek Medical Center, Jerusalem

Purpose: Imaging pregnant women with Crohn's disease is very challenging. The use of CT and MRI is restricted due to radiation or the inability to inject gadolinium.

Lack of radiation makes the ultrasound (US) imaging the study of choice for many medical conditions in pregnancy. However, especially in advanced stages of pregnancy, the bowel is pushed by the uterus and the normal anatomy is altered, which makes the scanning more difficult. Our purpose is to evaluate the accuracy of ultrasound in the assessment of Crohn's disease in pregnant women with comparison to post-partum MR/CT enterography.

Materials and methods: In this prospective study (still ongoing), pregnant women with known or suspected Crohn's disease, were referred from the IBD-MOM clinic for sonographic assessment of abdominal symptoms (pain, bloating, etc.). The study was approved by the institutional review board with waiver of informed consent.

Patient's demographics, clinical information and imaging findings were collected for all cases. Radiologic findings included: abdominal wall thickness, bowel wall thickness, mucosal irregularity, bowel wall hyperemia and strictures. Mesenteric changes and extra-luminal findings were evaluated as well. US studies were compared with post-partum MR/CT enterography.

Results: 19 patients enrolled in the study. Three of them were scanned more than once. Mean age was 30±5.8 (range 20-39y). Pregnancy week ranged from 8-32 weeks. 14 patients had known CD. Bowel wall changes were noted in 15 patients and changes in the mesentery in 6 patients. The terminal ileum was detected in 15 patients. No correlation was found between the abdominal wall thickness or the week of pregnancy to the quality of the imaging of the terminal ileum (p=0.23 and p=0.93, respectively).

Till now, 7 women had post-partum MR/CT enterography. In 6 women, the findings correlated with the US findings. In one case, an entero-enteric fistula was missed by the US (5 women will have their MR enterography in the next 2 months).

Conclusions: These initial results are indicative of the potential of US as a primary tool for follow up of CD in pregnancy. Meticulous scanning is informative in most women throughout the whole pregnancy period.

CHADS2 and CHA2DS2VASc Predict Short and Long-Term Mortality In Patients With Cardiovascular Diseases Admitted To The Hospital

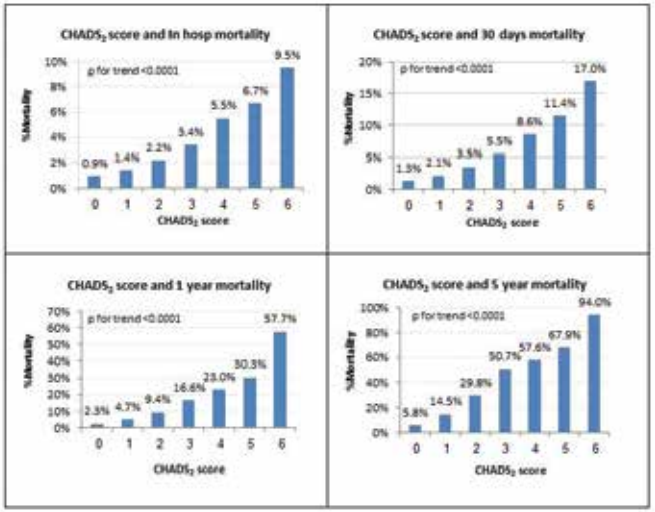
Dratva, Moriel, Klutestein, Balkin, Rosenmann, Hasin, Wolff, Rav-Acha, Medina, Butnaru, Tzivoni, Weisz

Background: CHADS2 and CHA2DS2VASc scores have been extensively studied as predictorsof stroke in patients with atrial fibrillation. The components of these scores including age, gender, heart failure, diabetes mellitus, hypertension, prior TIA/stroke, and vascular disease, are all known as conditions associated with cardiovascular outcomes. We hypothesize that these scores can be used as predictors of outcomes in cardiovascular diseases.

Methods: We reviewed all admissions to the cardiology department in 1992-2015. Only the first admission was included in the analysis. CHADS2 and CHA2DS2VASc scores were calculated by the electronic medical record, and mortality data was extracted from the government civil registry.

Results: Total of 38,603 patients with first hospital admission to the cardiology department were analyzed. CHADS2 score was correlated with in-hospital, 30-day, 1-year and 5-year mortalities (Figure). CHA2DS2VASc score had similar correlation and did not contribute beyond CHADS2.

Conclusion: in patients with cardiovascular diseases admitted to the hospital, CHADS2 and CHA2DS2VASc Scores can be used as predictors of short- and long-term mortality.



The Utility and Outcome Of Multidisciplinary Cardiac Rehabilitation After Myocardial Infarction In The Modern Era

Jacob Klein, Noa Raviv Abeles, Michael Mazar, Ariel Karawan, Allon Kirschner, Zviya Mizrachi, Rachel Aran, Rivka Farkash, Jonathan Balkin, Marc Klutstein, Dan Tzivoni, Giora Weisz

Background: Cardiac Rehabilitation (CR) has been shown to be effective in reducing mortality in the era preceding modern treatment of myocardial infarction (MI), but its benefit was questioned following modern early revascularization. We sought to examine the characteristics and outcomes of MI patients who were eligible and referred for CR.

Methods: Patients with acute MI were referred to an outpatient cardiac Multidisciplinary rehab program. The program included personalized and supervised adjusted physical activity twice weekly for at least 3 months, lifestyle modification interventions, and risk factor control including recommendation for medication adjustment. Patients that could not participate due to orthopedic or cognitive impairments were excluded. We compared the patients who participated in the program to those who elected not to participate in the years 2007-2014. Mortality data was extracted from the government civil registry.

Results: Of 4049 eligible patients who were referred to CR, 2079 (51.3%) participated in the program, and 1970 (48.7%) elected not to participate. Independent predictors to participate in the CR program included STEMI, age <75, male gender, non-DM, non-smoker, no prior CABG, and no PVD.

CR as compared to non-CR patients had lower rates of 1-year hospital readmission (11.9% vs. 22.0%, p<0.001), and mortality (0.5% vs. 1.7%, p=0.027). Multivariate analysis revealed that CR was an independent predictor protecting from mortality (OR 0.53, 95%CI 0.44-0.65, p<0.001). Other predictors of mortality included prior CABG (OR 1.53), DM (OR 1.36), and hypertension (OR1.31), all p<0.01.

Conclusions: Following acute MI, only half of the patients who were referred and eligible for CR elected to participate. Patients who participated in CR program had a significantly lower readmission rates and lower mortality. Participation in CR rehabilitation program should be vigorously encouraged to all patients after MI.

Coronary artery disease among survivors of VT/VF arrest

D. Kiselnik, J. Balkin, M. Ilan, A. Medina, A. Butnaru, D. Rosenmann, M. Moriel, M. Klutstein, R. Wolff, G. Weisz, M. Rav Acha

Cardiology Dept, Shaare Zedek Medical Center, Hebrew University, Jerusalem.

Introduction: Current guidelines recommend coronary angiography to all survivors of sudden cardiac death (SCD) because the dominant cause is coronary artery disease (CAD). However, the need for a routine angiography among SCD survivors who do not have known heart disease, and do not have prodromal clinical symptoms, ECG changes or biomarkers suggestive of CAD is questionable. The aim of this study was to characterized the non-CAD survivors and examine the prevalence of severe CAD among these patients.

Methods: Retrospective study of survivors of out-of-hospital aborted SCD admitted from 1992 to 2015. Patients were characterized according to final major cardiac diagnosis. Coronary angiograms were reviewed.

Results: Of 1470 out-of-hospital survivors admitted to the hospital 104 (7%) had no prior known heart disease and no prodromal clinical symptoms or signs suggestive of CAD on admission. Of these, 69 (66%) had a diagnosis unrelated to CAD: 33 cardiomyopathy; 24 Valvular (severe AS or MR); 9 channelopathies, 2 metabolic disorders, 1 WPW with AF. The remaining group of 35 patients had no overt cardiac diagnosis on admission, hence were called "idiopathic". Mean age of the "idiopathic" group was 54±16, 83% of these were males. Their echocardiography revealed preserved or mild LV dysfunction. Only 16 (45%) of the "idiopathic" group underwent coronary angiography, since the others had either contraindication or severe anoxic brain damage with poor prognosis. Severe CAD was found in only one (6%) patient; non obstructive lesions in 4 (25%), and normal coronaries in 11 (69%) patients.

Conclusions: In patients admitted to the hospital with aborted SCD and no overt symptoms or signs suggestive of CAD, the majority has diagnosis of other heart disease, and only a small minority was found to have CAD. These findings challenge the guidelines recommendation, and warrant a large prospective study.

The management of perforated cardiac device leads: A multicenter study

Rav Acha M[1], Rafael A[2], Keaney J[2], Elitzur Y[3], Rozen G2, Taha L[1], Sechter Y, Ilan M[1], Mela T[2], Medina A[1], Weisz G[1]

[1]Cardiology Dept, Shaare Zedek Medical Center, Hebrew University, Jerusalem [2]Cardiac Arrhythmia Center, Massachusetts General Hospital, Boston [3] Cardiology Dept., Hadassah Hospital, Hebrew University, Jerusalem

Introduction: Perforation of implantable cardiac device leads is a rare but well-known complication of device implants and its management can be controversial. Management strategies are either "conservative", based on patient and lead observation; or lead revision, in which the perforating lead is repositioned or replaced. The aim of the present study was to compare the outcomes of these strategies.

Methods: A multicenter retrospective analysis, inquiring data from clinical F/U notes, TTE and device interrogation reports, and imaging studies of patients with suspected lead perforation during the years 2000-2015. Perforation was defined by suggestive clinical symptoms along with a lead protrusion on imaging or a bloody pericardial effusion (PE) on pericardiocentesis. The primary endpoint was a composite of residual symptoms, re-accumulation of moderate/large PE, and lead dysfunction during 6 month F/U. Fisher exact test was used for comparison between categorical variables.

Results: There were 32 perforations presenting 12±23 days s/p device implant. The presenting symptoms included pleuritic-type chest pain (CP) (62%), dyspnea (28%), hemodynamic shock (21%), and syncope (12.5%). A PE was revealed on TTE/CT studies in 26 cases (81%), and cardiac tamponade diagnosed by clinical or TTE parameters in 20 cases (62%). The perforating leads were RA, RV, CS or unknown in 12, 12, 2, and 6 cases, respectively. A "conservative" strategy was held in 17 cases (53%). Lead revision was performed in 15 cases (47%), including 12 cases with significant lead dysfunction and 3 cases in which CP, PE ± BP drop developed shortly after implant.

The primary endpoint occurred in 7/17 (41%) cases treated "conservatively", including 4 late occurring tamponade cases, 2 cases with persistent CP, PE or lead dysfunction resulting in late lead revision and a case with constrictive pericarditis, compared with 1/15 (6.6%) case of constrictive pericarditis among patients managed via lead revision (p=0.04).

Conclusions: In patients with lead-induced perforation, a "conservative" approach was associated with higher adverse events compared with lead revision strategy. Further prospective studies are needed to establish a more unified management approach to this problem.

A Novel Mapping Annotation Technique to Facilitate Isthmus Detection in Scar-related Atrial Tachycardia Following Atrial Fibrillation Ablation

***M. Rav Acha*[1], *W.J. Kostis*[2], *Guy Rozen*[2], *E.K. Heist*[2], *J.N. Ruskin*[2], *M. Mansour*[2]**

[1]Cardiology Dept., Shaare Zedek Hospital, Hebrew University, Jerusalem

[2]Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston.

Introduction: The common ablation strategy of atrial tachycardia (AT) encountered after AF ablation relies on electroanatomic activation mapping (EAM), using a "conventional" window of interest (WOI) centered on the atrial signal of the CS catheter, in addition to entrainment maneuvers to detect the AT isthmus location. Entrainment can be challenging due to low signal-to-noise ratio, inability to capture scar tissue, and risk of AT termination. We describe a novel EAM annotation, using a WOI starting 40 ms prior to the earliest P wave on the surface 12-lead ECG, to detect the reentrant AT exit site. It is based on the mechanistic similarity between scar-related reentrant AT and scar-related ventricular tachycardia, where pacing from the tachycardia isthmus is characterized by a stimulus to QRS interval > 40 ms, reflecting a "slow conducting channel".

Methods: Patients with non CTI-dependent AT after prior AF ablation were included. The AT EAM was performed with CARTO using our novel annotation. Ablation was considered successful if the AT terminated during the ablation.

Results: 27 patients with 33 non-CTI-dependent AT classified as: mitral annulus (17/33), roof (9/33), anterior/posterior LA wall (5/33), and RA (2/33) AT, were included. A complete EAM was achieved in 31/33 AT, encompassing 94±4.6% of the AT cycle length. A clear "early meets late" line was identified in all 31 AT maps, confirming their reentrant mechanism. Low amplitude pre-P fractionated electrograms were found in 30/31 (97%) AT, occurring at a mean distance of 2 mm from the "early meets late" line. Ablation at these presumed isthmuses resulted in AT termination in 30/31 AT (97%). Notably, 17/31 AT terminated within 1-3 lesions indicating ablation at a critical isthmus.

Conclusion: We propose a novel EAM annotation to allow detection of the critical isthmus of post AF ablation AT easily and without reliance on entrainment. Ablation of these isthmuses results in termination of the AT in the majority of patients.

Excitability of direct reprogrammed murine tail fibroblasts: between wild-type fibroblasts and cardiomyocytes

***Rav Acha M*[1], *Mills R*[2], *Chen JX*[2], *Wu SM*[2], *Milan D*[2]**

[1] Cardiology Dept., Shaare Zedek Hospital, Hebrew University, Jerusalem

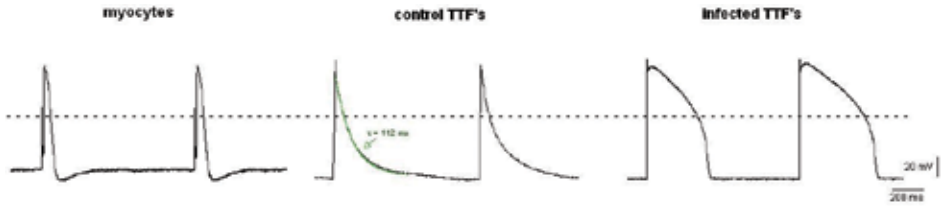
[2] Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston.

Introduction: Limited regenerative capacity of postnatal cardiomyocytes (CM) creates need for alternative regenerative approaches. Cellular rejection, low efficiency differentiation, and tumor formation have presented hurdles for these approaches. Direct reprogramming of fibroblasts into CM using Gata4, Mef2c, Tbx5 (GMT) was recently described to circumvent some of these challenges. We investigated the electrophysiological (EP) changes induced by overexpression of GMT in murine tail fibroblasts (TF).

Methods: Lentiviral overexpression of GMT was induced in TF from multiple lines of transgenic mice carrying different CM lineage reporters. Infected TF exhibited variable expression of CM specific genes and protein profiles. Whole cell current and voltage clamp studies of wild-type (WT) TF (n=30), GMT infected TF (n=32) and control CM (n=26) were performed as previously described.

Results: Isolated CM consistently showed a spontaneous repetitive action potential (AP) activity which did not appear in any of the WT or GMT infected TF. Pacing of CM with variable amplitudes elicited an "all or none" AP response, while all WT and majority (78%) of GMT infected TF showed a passive decay of membrane potential according to the cell's time constant. Nevertheless, minority (22%) of GMT infected TF demonstrated a stimulus dependent response consisting of rapid up-sloping nifedipine-sensitive potential followed by a variable duration (50-500 ms) plateau, suggestive of Ca-dependent Chloride current. Few GMT infected TF could sustain a repetitive low frequency (0.1Hz) membrane oscillatory potential. Voltage clamp recordings revealed a voltage gated calcium current in GMT infected TF but in contrast to CM, no voltage gated sodium current could be detected.

Conclusion: GMT overexpression in fibroblasts results in induction of voltage dependent Ca and Ca-dependent chloride currents. These currents are responsible for some excitable features in the reprogrammed cells. However, these changes fall short of the essential characteristic EP properties of functional CMs.



The importance of trans-thoracic echocardiographic supra-sternal view in the diagnosis and treatment follow up of pulmonary emboli

Rav Acha M,MD[1]; Medina A,MD[1]; Rosenmann D, MD[1] ; Bogot N,MD[2]; Klutstein MW, MD[1]; Butnaru A, MD[1] ; Weisz G MD[1]

[1]Cardiology Dept., Shaare Zedek Medical Center, Hebrew University, Jerusalem

[2]Radiology Dept., Shaare Zedek Medical Center, Hebrew University, Jerusalem

The diagnosis of pulmonary emboli (PE) is not always straightforward and relies heavily on the clinical presentation. Further imaging evaluation depends on the pre-test clinical probability for this diagnosis. We describe here a case presenting with vague symptoms with a low clinical probability for PE. The diagnosis of PE was based on a single TTE supra-sternal view showing a large mobile mass within main pulmonary artery, without the usual and common echogenic signs of RV pressure overload. Furthermore, this supra sternal view enabled evaluation of the efficacy of thrombolytic treatment given, revealing a rapid and efficacious lysis of the pulmonary artery thrombus within 24 hours. This case stresses the importance of a complete TTE examination including a supra-sternal view for PE diagnosis and treatment follow-up.

The association between statin pretreatment and LDL-C levels and the presentation of patients with an ACS: Data from the ACS Israeli survey (ACSIS) 2002-2010.

Kolker Shimon[1] ,Moriel Mady[1] ,Matetzky Shlomi[2] ,Shlomo Ni[2] ,Leitersdorf Eran[3] Goldenberg Ilan[2], Tzivoni Dan[1] ,Weisz Giora[1] ,Gottlieb Shmuel[1,2]

[1]Cardiology Department, Shaare-Zedek Medical Center, Jerusalem

[2]Neufeld Cardiac Research Institute, Sheba Medical Center, Tel-Hashomer, Ramat-Gan,and3Hadassah hospital, Jerusalem, Israel.

Background: Most ST elevation myocardial infarctions(STEMI) usually occur as a result of a vulnerable coronary artery plaque rupture, statins posses hypolipidemia and pleotropic properties and thus may stabilize coronary artery plaque. Aim: To determine the association between LDL-C levels, with or without concurrent statin use and the presentation of patients with an ACS(STEMI vs. NSTEMI).

Methods: Data was drawn from the Acute Coronary Syndrome Israeli Surveys(ACSIS), a biennial survey collecting data on all ACS patients hospitalized in each of the 26 public CCU/Cardiology departments in Israel. Data from the years 2002-2010 was used. The incidence of STEMI presentation was calculated according to LDL-C levels(mg/dl), (<50, 50-69, 70-100, 101-130 and >130) on admission and the use of statins prior to the index ACS event.

Results: Among 6790 patients, 2760(41%) were statin treated and 4030(59%) were statin naïve before the index ACS event. The proportion of STEMI at presentation was significantly lower among statin treated vs. statin naïve patients(36% vs. 57%, p<0.0001). At each LDL-C level, the proportion of STEMI was significantly lower among statin treated patients(figure, p<0.0001 for all comparisons). LDL-C<70mg/dl was associated with a lower proportion of STEMI presentation only among statin treated patients, but not among statin naïve patients (33% vs. 57%, p<0.0001). Multivariate analysis adjusting for the propensity score for statin use(including baseline pertinent variables), revealed that statin use was independently associated with lower STEMI presentation(OR=0.73, p<0.007), but not LDL-C<70mg/dl (OR=1.13, p=0.33). Similar results were obtained when the analyses were done separately among patients with or without prior cardiovascular disease.

Comparison of Free Breathing Cardiac MRI Radial technique to the Standard Multi breath-hold cine SSFP CMR technique for the assessment of LV Volumes and Function

Shimon Kolker, Giora Weisz, Irit Hadas Halpern, Naama Bogot, Arik Wolak

Cardiology Dept., Radiology Dept., Shaare Zedek Medical Center

Background: Cardiac MRI (CMRI) is generally accepted as the gold standard for left ventricular (LV) volumes and function assessment. Standard cine SSFP sequences require prolonged, repeated breath holds and therefore may be challenging, particularly for debilitated, pediatric and elderly patients. The compressed sensing, Radial cine (RC) k-space acquisition technique can provide a good image quality without the need for breath holding. The purpose of this study was to compare volume and function results between free breathing RC technique and the standard multi-breath-hold cine SSFP technique.

	LV EDV ml	LV ESV ml	LV EF %	LV Mass gram	RV EDV ml	RV ESV ml	RV EF ml
Mean ± SD (SSFP technique)	162.7±66.4	70.8±53.3	60.4±15.5	123.9±44.2	156.6±42.5	83.1±33.4	47.6±11.4
Mean ± SD (RC technique)	160.7±66.5	69.6±52.6	60.6±15.2	124.3±45.9	156.5±43.3	83.6±33.3	46.7±11.2
Mean ± SD (both techniques)	161.8±66	70.2±52.9	60.5±15.3	124.1±44	156.6±42.5	83.3±33	42.5±11.2
Range	66.6-300.2	15.3-222.6	18.6 - 86.5	49.9-192.3	69.5-238.6	33.6-178.4	13.5-68.6
Limits of agreement	(-8.2) - 12.2	(-6.4) - 8.8	(-3.4) - 3.2	(-34) - 33.4	(-7.5) - 7.6	(-7.5) - 6.7	(-3.2) - 3.9
Bias	1.98	1.19	-0.13	-0.3	0.05	-0.43	0.34
Correlation	0.99	0.99	0.99	0.93	-0.2	0.05	0.24

Methods: 24 patients who underwent clinically indicated cardiac MRI (CMRI) were included in the study. In all patients both standard cine and radial cine sequences were performed. The images were analyzed using CMR42 semiautomatic tool of the CVI42 software, version 5.0.0 for both LV and RV end diastolic volume (EDV), end systolic volume (ESV) and ejection fraction (EF) and myocardial mass for LV. The RC and the standard breath-hold SSFP techniques were compared using Pearson correlation and Bland-Altman analyses. Values of $p < 0.05$ were considered statistically significant.

Results: The average age was 45.7±18, there were 15 males and 9 females. Results of Pearson correlations and Bland-Altman analyses (P values for all correlations were <0.05) are summarized in the table below.

Conclusions: The results demonstrate the feasibility of applying the RC compressed sensing strategy to evaluate LV and RV volume and function with high accuracy in a variety of patients, without the need for breath holding, in considerably shorter scan times.

Trends in statin use and lipid profile among patients presenting with an ACS between the years 2002-2013, in Israel

Kolker Shimon[1], Weisz Giora[1], Moriel Mady[1], Matetzky Shlomi[2], Shlomo Nir[2], Segev Amit[2], Goldenberg Ilan[2], Tzivoni Dan[1], Gottlieb Shmuel[1,2]

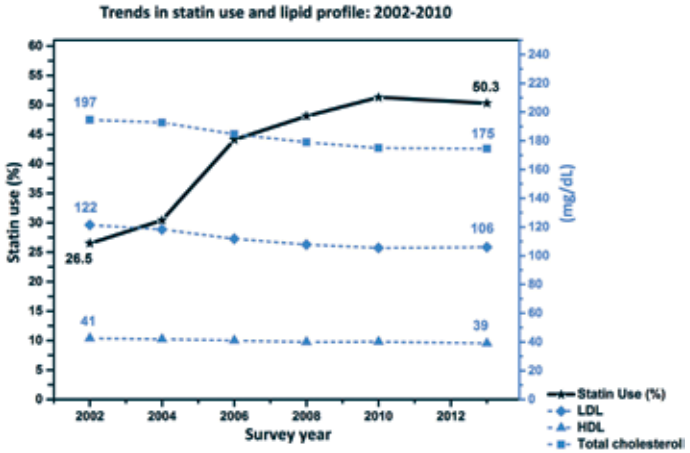
[1]Cardiology Department, Shaare Zedek Medical Center, Jerusalem,[2]Neufeld Cardiac Research Institute, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel.

Background: Dyslipidemia is an independent major risk factor for the development of coronary artery disease (CAD). Statins are the cornerstone for primary and secondary prevention of CAD.

Aim: To describe trends in lipid profile and statin use between the years 2002-2013 in a large cohort of patients admitted with an acute coronary syndrome (ACS).

Methods: Data was drawn from 6 consecutive ACS Israeli surveys (ACSIS), performed between the years 2002-2013 in Israel. Lipid profile on admission(total cholesterol [TC], LDL-C and HDL-C) and use of statins prior to the index hospitalization were determined for the total cohort and for subgroups with or without prior CAD.

Results: From 2002 to 2013, use of statins prior to the index ACS event steadily increased and was paralleled by decline in TC, LDL-C and HDL-C (Figure, p for trend<0.0001).Among patients with CAD,TC declined from 192mg/dl in 2002 to 160 mg/dl in 2013,and LDL-C declined from 116mg/dl to 93 mg/dl (respectively, p for trend<0.0001).Among patients without CAD,TC declined from 199.9 mg/dl in 2002 to 183mg/dl in 2013, andLDL-C declined from 125 mg/dl to 114 mg/dl (respectively, p for trend <0.0001).



Conclusions: Among patients admitted with ACS during the last decade, better adherence to guidelines with increasing use of statinsprior to the index event was paralleled by an improvement in lipid profile. These findingshave relevance for primary and secondary prevention.

QRS prolongation in patients with left ventricular dysfunction not fulfilling criteria for resynchronization therapy

Tal Hasin, Moshe Rav-acha, Aharon Medina, Natali Shaltiel, Michael Ilan, Marc Klutstein, Adi Butnaru, David Rosenmann, Rivka Farkash, Mady Moriel, Tatyana Weitsman, Giora Weisz

Background: Cardiac Resynchronization Therapy (CRT) improves and prolongs life in patients with heart failure, reduced ejection fraction, and prolonged QRS. Patients not meeting QRS criteria are usually excluded from this therapy. However, QRS may prolong over time, and patients may become eligible to CRT. The purpose of this work is to study QRS prolongation among patients with reduced EF and narrow QRS

Methods: We screened our 2005-2014 database for adult patients with echocardiographic EF<35% and narrow QRS (≤120 msec) on baseline ECG done within 90 days of TTE and a follow-up ECG at least 90 days later. Patients with pacing devices were excluded. The follow-up ECGs were screened for prolonged QRS (≥130 msec).

Results: Total of 191 patients fulfilled inclusion/exclusion criteria. Patients were followed for median of 788 days with 3.2±1.3 ECGs. In 34 patients (18%) QRS widened above 130msec (to 145±15msec) during follow up, and their characteristics are shown in the Table. In patients with newly-developed wide QRS, the QRS morphology was LBBB in 29%, RBBB in 44% and non-specific in 27%. Among 20 patients without pacing and with additional subsequent ECG (at median of 598 days later) the QRS remained ≥130msec in 13 (65%).

Conclusions: In patients with reduced ejection fraction and baseline narrow QRS duration, 18% prolonged their QRS during follow-up. Patients who prolonged their QRS were characterized by larger left ventricle and atrial sizes and relatively wider initial QRS. Periodic reevaluation of ECG criteria in patient with congestive heart failure is recommended in order to identify patients who may be eligible and benefit from CRT.

Table: Characteristics of patients with versus without prolonged QRS at follow-up.

	All (n=191)	QRS ≥130msec ((n=34	QRS <130msec ((n=157	P value
Age (year) mean±SD	67±15	71±12	66±15	0.055
Male (%)	76%	88%	74%	0.074
Baseline QRS (msec) mean±SD	95±14	106±11	92±14	<0.001
Change in QRS (msec) median[IQR]	8 [2-20]	38 [22-50]	4 [-2-12]	<0.001
Left ventricle diastolic diameter (cm)	5.9±0.9 (n=174)	6.41.1±	5.8±0.8	0.001
Fractional shortening (%)	18±7 (n=123)	185±	18±8	0.443
Left atrial diameter (cm)	4.60.8± (n=172)	4.8±0.7	4.50.7±	0.023

Improvement in functional mitral regurgitation after coronary catheterization with and without percutaneous coronary intervention

Tal Hasin, David Rosenmann, Tatyana Weitsman, Rivka Farkash, Adi Butnaru, Liat Alper-Suissa, Zahi Khouri, Marc Klutstein, Giora Weisz

Background: Functional mitral regurgitation (FMR) occurs in patients with left ventricular (LV) dysfunction and anatomically normal mitral valve. Recent observation suggested improvement in FMR post percutaneous coronary intervention (PCI).

Methods: This is a retrospective single-center analysis of patients with significant FMR (≥moderate mitral regurgitation associated with ≥moderate LV dysfunction; without mitral deformity) that underwent coronary catheterization within 6 months after echocardiography and a follow-up echocardiogram 2 to 24 months after catheterization. Patients that underwent surgery or cardiac resynchronization after catheterization and before follow-up echocardiogram were excluded. MR was graded 0-6 and LV function 0-5. Change in FMR between pre and post catheterization echocardiograms was recorded. The impact of PCI on this change was determined.

Results: One hundred and one patients were included in the study. Mean age was 67±13 yr and 30% were females. Forty patients (40%) underwent PCI that included Cx/marginal in 19, RCA in 20, left main/LAD in 10 and graft in 5 vessels; 61 patients (52% with ischemic heart disease) had diagnostic catheterization only. There was no significant difference in age, gender, hypertension, diabetes, hyperlipidemia, smoking, LV function or MR severity at baseline between PCI/non-PCI patients. At follow-up MR improved by 1 grade in 62 patients (61.4%) and by ≥2 grades in 41(40.6%). Significant correlations (Spearman) were found between improved MR and improved LV end diastolic diameter, left atrial diameter, estimated pulmonary pressure, fractional shortening and LV function ($p<0.01$ for all). Baseline characteristics or echocardiographic variables did not predict the improvement in MR. Improvement in MR was observed in 24 (60%) PCI patients and in 38 (62%) non-PCI patients ($p=0.817$). Target PCI vessel did not influence MR improvement.

Conclusion: In patients referred for coronary catheterization, functional mitral regurgitation improvement is associated with improved ventricular dimensions and function. Percutaneous intervention has no effect on FMR improvement.

Prevalence of Left Heart Disease among Patients with Echocardiographically Determined Pulmonary Hypertension

***Authors:** T. Weitsman, G. Weisz, R. Farkash, D. Meerkin, M. Klutstein, A. Butnaru, D. Rosenmann, T. Hasin. Cardiology department, Shaare Zedek Medical Center*

Background: Group II pulmonary hypertension (PH secondary to left heart disease) is considered by far the most prevalent group among patient with PH, but only space data is available [1]. Trans-thoracic echocardiography (TTE) is the best initial screening test and increased tricuspid regurgitation gradients (TIG) are frequently used as surrogates of pulmonary pressure. Utilizing echocardiography studies have shown the prevalence of PH among patients with left heart disease is between 25-100% [2]. One population study reported PH in 9.1% of the cohort, with 79% classified as group II [3]. More data on the true prevalence of group II among patients with PH, the prevalence of the specific causes and trends of these distributions over time is lacking.

Methods: All transthoracic echocardiograms (TTE) performed from 1991 to 2014 at our center were analyzed. Adult patients, with significantly elevated tricuspid incompetence gradient (TIG) ≥50 mmHg were chosen and evaluated for features of left heart disease. These were divided into four groups: (1) Left ventricle (LV) systolic dysfunction (≥moderate), (2) Significant mitral or aortic valve disease (≥ moderate-severe MR, AS, AR or ≥ moderate MS),(3) Combined LV systolic and valve dysfunction , (4) HFpEF defined as diastolic dysfunction ≥ grade II by echo Doppler or combination of left atrial enlargement (≥4.5cm) with thickened interventricular septum (≥1.4cm) in patients without LV systolic dysfunction or valve disease [3]. Data was represented as mean±SD or median and interquartile range as appropriate. Comparisons were made using Chi-Square Tests.

Results: Of TTEs in 63,150 patients, after exclusion prosthetic tricuspid valve (5) and pulmonic stenosis (23) 5687 (9%) had elevated TIG. Mean age was 75±13 years, 55% were females. Of these 4154 (73%) had group II characteristics. Median TIG was 56mmHg (IQR 52, 63), without difference between group II and non-group II patients. The proportion of group II PH and the above defined sub-groups is illustrated in figure 1. Specific causes of left heart disease were LV systolic dysfunction in 8%, mitral regurgitation in 55%, mitral stenosis in 6%, aortic regurgitation in 3%, aortic stenosis in 12%, combination LV systolic dysfunction and valve disease 18% and diastolic dysfunction in 20%. There were 4585 patients referred to TTE during hospitalization and 1102 ambulatory TTEs. There was no difference in prevalence of group II PH between hospitalized and ambulatory patients. Clinical characteristics of patients with PH group II and non-group II PH are presented in table 1. Prevalence group II PH is illustrated in figure 2. This did not significantly change during more than 20 years. The proportion of diastolic dysfunction increased through the years from 6.9% to almost 20% and the proportion of valve disease increased slightly. However, the proportion of LV systolic dysfunction decreased from 10.7% to 3.0% as well as the combination LV systolic dysfunction with valve disease.

Conclusions and implications: Pulmonary hypertension (defined as TIG≥50) occurs in 9% of patients referred for transthoracic echocardiography. Left heart disease accounts for the majority (73%) of pulmonary hypertension. Of those patients with group II PH, half have significant valve abnormalities with mitral regurgitation being the most prevalent. Over the span of 20 years, the proportion of patients with group II PH remains but its causes change; HFpEF increased while systolic dysfunction decreased (possibly due to improvement in treatment for systolic dysfunction). The most prevalent cause of PH is left heart disease. More research is needed to characterize and develop specific treatment strategies for this group.

Risk factors for low quality bowel cleansing in hospitalized and ambulatory patients undergoing colonoscopy, a large retrospective study.

Dan M. Livovsky, *Anat Horesh, Yael Milgrom, Benjamin Koslowsky, Eran Goldin, Ahuva Spitz, Dov Wengrower

The Digestive Diseases Institute, Shaare Zedek Medical Center, Jerusalem

Background/Aims: The diagnostic yield, therapeutic efficacy and safety of colonoscopy depend on adequate bowel visibility. The quality of bowel preparation in hospitalized patients is often poor, requiring further preparation and additional colonoscopies; exposing patients to unnecessary risks and potential adverse effects. The aims of this study were to compare the quality of bowel cleansing of inpatients compared to outpatients, to identify risk factors for inadequate preparation and to calculate the number and cost of colonoscopies that could have been avoided.

Methods: A retrospective study of more than 11000 colonoscopies that were performed at Share Zedek Medical Center during years 2014-2015. Risk factors for poor or inadequate preparation were calculated by logistic regression.

Results: Out of a total of 11825 colonoscopies, data about visibility was available for 9654 (81.6%), 9204 (95.3%) of them were outpatients. Inpatients were more commonly male (58% vs. 51% p < 0.01), significantly elder (56.29 (95%CI 55.97 - 56.61) vs. 66.5 (95%CI 65.04 to 67.96) years old, p <0.0001), and more frequently received preparation with polyethylene glycol (PEG) (63% vs 25% p< 0.001). Visibility was qualified by the endoscopists as excellent/good, fair, poor or inadequate in 22.7 vs. 32.6%, 26.1 vs. 44.3%, 25.6 vs.17.8% and 25.6 vs 5.3% in inpatients vs. outpatients respectively (p<0.0001). On unadjusted logistic regression, age (OR 1.007 (1.004-1.01) per increment in one year), inpatient status (OR 3.49 (2.8-4.2)) and using a picosulaphate preparation (OR 2.02 (1.84-2.22)) were associated with inadequate preparation. Female gender (OR 0.676 (0.615-0.742)) and using a PEG preparation (OR 0.498 (0.451-0.549)) were protective. Interestingly when adjusting for age, gender, inpatient status and preparation, only male gender (OR 1.43 (1.29-1.58)) and using picosulphate (OR 1.52 (1.26-1.84)) remained as risk factors, while the association of inpatient status and inadequate preparation was inverted with an OR of 0.38 (0.17-0.84). Using a strict pre-specified definition, by manual revision we found 69 “unnecessary” procedures that were performed in inpatients; this translates into 75900-113850 NIS, according to the Ministry of Health price list.

Conclusions: Inadequate bowel cleansing is a common problem in hospitalized patients, leading to repeated procedures and significant costs. However, it seems that the quality of preparation depends on the patient himself and not on the inpatient status. Yet, we advocate that it’s possible and necessary to improve bowel visibility in hospitalized patient undergoing colonoscopy.

* These authors contributed equally to the manuscript

Fecal Calprotectin and Lactoferrin as Biomarkers in Patients Undergoing Capsule Endoscopy

Ariella Bar-Gil Shitrit, Benjamin Koslowsky, Sam Adler, Kalman Paz, Eran Goldin

Digestive Diseases Institute Shaare Zedek Medical Center

Background: Capsule endoscopy (CE) is often used to investigate small bowel Crohn's disease (CD). However, it is time-consuming, expensive and results depend on operator skills. We assessed the predictive value of fecal calprotectin and lactoferrin in patients undergoing CE.

Patients and Methods: All patients had normal colonoscopy and gastroscopy prior to CE. Stool specimens from 68 patients were measured for calprotectin and 38 patients for lactoferrin and correlated with CE results and other blood parameters. ROC curve analysis was used to determine the predictive value of fecal markers for abnormal findings and for CD.

Results: CE results included 37 abnormal findings (21 CD, 11 bleeding angiodysplasias and 5 other pathologies). Fecal calprotectin and lactoferrin were higher in patients with abnormal CE (p=0.005 and p=0.04, respectively). Mean calprotectin level in CD (257±452 µg/ml) was higher than in other patients (144±190 µg/ml; p=0.006). Mean lactoferrin level in CD was 26±51 mg/kg compared to 5.4±7.8 mg/kg in others (p=0.04). The area under the curve was 0.767 for calprotectin and 0.70 for lactoferrin. Fecal calprotectin of 100 g/ml had a sensitivity of 77%, specificity of 60%, positive predictive value (PPV) of 50%, and negative predictive value (NPV) of 84% in predicting CE findings of CD. Fecal lactoferrin of 1.5 g/ml had 73% sensitivity, 65% specificity, 50% PPV, and 84% NPV in predicting CE findings of CD.

Conclusions: Fecal markers can be simple, noninvasive surrogates for abnormal CE findings. Fecal markers can help determine which patients should be referred for CE.

Serum Chitinase 3-like-1 (CHI3L1) and fecal calprotectin levels for non-invasive disease activity assessment in IBD patients during pregnancy

Hagai Schweistein[1], ***Benjamin Koslowsky***[2], ***Tomer Adar***[2], ***Shimon Shteingart***[2], ***Adi Rave***[1], ***Sorina Grisaru-Granovsky***[3], ***Eran Goldin***[2], ***Ariella Bar-Gil Shitrit***[2]

[1]The Hebrew University Medical School, [2]Digestive Diseases Institute, [3]Obstetrics and Gynecology department

Background: Noninvasive evaluation of disease activity in inflammatory bowel disease (IBD) may be challenging. Doing so during pregnancy is even more so.

Chitinase 3-like-1 (CHI3L1) protein, also known as YKL-40, is associated with increased pathogen adherence and intestinal inflammation. Increased levels of CHI3L1 have been previously described in IBD patients,

Aim: To evaluate the use of serum CHI3L1 levels as biomarker for disease activity in pregnant IBD patients.

Methods: Consecutive consenting pregnant IBD patients were recruited from our multidisciplinary IBD-MOM referral clinic to this IRB-approved prospective observational study. During an elective clinic visit, blood tests were for CHI3L1 levels and inflammatory markers (CRP and ESR). Stool was collected for calprotectin levels and disease activity was determined using the Crohn's disease activity index (CDAI) and partial Mayo score for Crohn's disease (CD) and ulcerative colitis (UC) patients respectively. Each patient's visit has been classified as a Distinctive sample.

CHI3l1 was then correlated with other inflammatory and disease activity parameters. In CD, the correlation was also assessed in the subset of patients with inflammatory presentation.

Results: A total of 84 samples from 57 pregnant IBD patients were recruited to this study, including 64 samples from 45 CD patients and 20 samples from 12 UC. Participants' average age and mean Gestational age at enrollment were 30.67±5.99 years and 20.77±9.58 weeks respectively. 25,33 and 26 samples were drawn during first, second and third pregnancy trimesters.

Disease activity in CD patients measured mild-moderate and moderate to severe in 14(21.9%) and 7(10.9%) patients respectively. CRP, ESR and fecal calprotectin levels were 1.48±2.66 (n=62), 30.40±20.83 (n=50) and 1070.9±1170.47 (n=20) respectively. CDAI score weakly correlated to ESR (r=0.32) and CRP(r=0.45) in CD group. However for those with inflammatory presentation the correlation became more significant: ESR (r=0.51), CRP (r=0.619). Stool calprotectin level positively correlated CDAI (r=0.60). CDAI weakly correlated to CHI3L1(r=0.257, P=0.07)

In UC samples, 20% and 10% were of patients with moderate and severe disease respectively. CRP, ESR and fecal calprotectin levels were 1.06±0.81 (N=20), 22.33±14.11 (N=18) and 1810.5±1368 (N=6) respectively. Fecal calprotectin positively correlated the partial Mayo score (r=0.77).

CHI3L1 and the partial Mayo score were significantly correlated in UC group.

(r=0.587, P=0.008, N=19)

Conclusions: In this prospective study, with over 80 samples from pregnant IBD patients, fecal calprotectin and serum CHI3L1 levels proved to correlate non-invasive disease activity score in CD and UC respectively. Our findings mark these parameters as potential valuable decision making tools in managing IBD during pregnancy pending further validation.

First year results of the use of vedolizumab for inflammatory bowel disease: A single center experience

Benjamin Koslowsky, Ariella Bar-Gil Shitrit, Betty Mazuz, Dan Livovsky, Eran Goldin

Digestive disease institute, Shaare-Zedek Medical center, Jerusalem, Israel

Introduction: Crohn's disease (CD) and ulcerative colitis (UC) are increasing over the past years. New biological treatments, namely anti-TNFs were introduced during the past decade. Still, many patients are refractory or lose response to these therapies. Vedolizumab is an anti-integrin of b7, uniquely encountered in the gastrointestinal system. It was approved for use in Israel in March 2015.

Aim: To report the real life results of vedolizumab given in a large single referral medical center over the past year

Methods: All patients receiving vedolizumab in Shaare-Zedek Medical Center from March 2015 to March 2016 were included. All participants had a full demographic and clinical assessment at initiation. All had a disease activity scoring and completed an adverse event evaluation before treatment introduction, at week 6, and every 8 weeks since until 52 weeks.

Results: Altogether 47 patients were followed. 24 (51%) had CD and 19 had UC (40%), 1 had undetermined IBD and 3 had pouchitis. 22 (47 %) were men, median age was 37 [range 22 to 76]. Median years of disease prior to treatment was 11 [range 1 to 50]. 43 patients (92%) had received a prior anti TNF (12 [25%] only infliximab, 7 [16%] only adalimumab and 24 [51%] both anti TNF's) before receiving vedolizumab. Only 4 (8%) patients were naïve to any previous biological treatment. 23 (49%) patients were receiving concomitant treatments (8 steroids, 6 5-ASA, 4 immunomodulators, 3 antibiotics and two a concomitant anti TNF). 45 (96%) patients completed the induction phase until week 6 and 15 (32%) patients were analyzed up to week 52. Mean HBI of the whole cohort was 7.6 at induction and then 6.2, 6.3, 5, 5.1 and 4.6 at weeks 6, 14, 22, 30, and 52, respectively ($p<0.001$ for comparison of the initial result to all weeks). The partial Mayo score was 6.1 at induction and then 4.9, 4.8, 4.9, 4.5, and 2 at weeks 6, 14, 22, 30, and 52, respectively ($p<0.001$ for comparison of the initial result to all weeks). The average CRP went down from 3.3 at induction to 1.7, 1.9 and 1.9 at weeks 22, 30 and 52, respectively ($p=0.004$ comparing the initial result to week 52). Ten patients stopped the treatment, 1 due to side effects, three underwent IBD surgery due to inadequate response and 6 others did not respond to the medication. No patients in our cohort experienced a secondary loss of response.

Conclusions: Vedolizumab was newly introduced into the IBD therapy armamentarium. The medication was given safely, with a very low level of adverse events. It seems like there is an overall positive effect on both clinical and inflammatory markers. Long term follow up on more patients is needed.

Pregnancy - Onset Ibd Is Not Associated With Adverse Maternal Or Neonatal Pregnancy Outcomes

Benjamin Koslowsky[1], Dan Meir Livovsky[1], Eran Goldin[1], Sorina Grisaru-Granovsky[1], Ariella Bar-Gil Shitrit[1]

Digestive Diseases Institute1 ,Fetal-Maternal Medicine, Shaare-Zedek Medical Center, Jerusalem, Israel

Background: Inflammatory bowel diseases (IBD), mainly Crohn's disease (CD) and ulcerative colitis (UC), may affect female patients during their childbearing years. In some cases, IBD may first manifest during pregnancy (pregnancy-onset IBD [PO-IBD]). Immune-tolerance is noted during pregnancy, and may have a role on disease severity of pregnant patients with IBD. The outcomes of PO-IBD have not been previously studied. In our center, a dedicated IBD-MOM clinic, comprised of a multidisciplinary team, manages the diagnosis and treatment of IBD patients prior, throughout and after pregnancy.

Aim: To evaluate the pregnancy and neonatal outcomes of female patients with PO-IBD.

Methods: During years 2011-2014, 81 IBD patients were followed at our IBD-MOM clinic. Patients with PO-IBD were compared to a control group of female patients with IBD, diagnosed prior to pregnancy [non PO-IBD]. Both maternal and neonatal outcomes were compared. Diagnosis of UC during pregnancy was performed by flexible sigmoidoscopy and mucosal biopsies. Diagnosis of CD during pregnancy was achieved by MRE and subsequently confirmed by colonoscopy and ileoscopy with mucosal biopsies post-partum. Statistical analysis was done to assess the profile of these two study populations including characteristics of their IBD and pregnancy outcome variables.

Results: 11 patients with PO-IBD and 70 controls with non PO- IBD were analyzed. The mean age was 28±5 and 29±5 years, for the study and control groups, respectively. Within the PO-IBD, 4 patients (36%) were diagnosed with CD and 7 (64%) with UC compared to 22 (31%), 46 (66%), and 2 (3%) patients with CD, UC and IBD-undetermined, respectively, in the control group. No differences were noted between the two groups in the ethnic origin, type of disease, extent of disease involvement, pattern of IBD, need of steroids or need for hospitalization. Maternal and neonatal results did not differ between the groups. Spontaneous vaginal delivery was achieved in 90% and 73% of the PO-IBD and control group, respectively ($p=0.48$). Mean week of delivery was 39.6±1.3 and 38.3±3, respectively ($p=0.11$). Mean birth weight was 3167±688 and 2942±590 gram, respectively ($p= 0.27$). Normal Apgar scores (9-10) were documented in 100% and 97% of the newborns, respectively ($p= 0.72$). Postpartum exacerbation rate was observed in 33% and 27%, respectively ($p=0.48$).

Conclusion: PO-IBD is not associated with negative impact on maternal or neonatal pregnancy outcomes compared to non PO-IBD.

Hearing loss in patients with inflammatory bowel disease

Dov Wengrower[1]*, Benjamin Koslowsky[1]*, Uri Peleg[2], Betty Mazuz[1], Leore Cohen[3], Menahem Gross[3], Alin Ben David4, Eran Goldin[1], Chanan Shaul[2]

[1]Digestive Diseases Institute, Shaare Zedek Medical Center, Jerusalem, Israel, affiliated with the Hebrew University Medical School, [2]Department of Otolaryngology Head and Neck Surgery, Shaare Zedek Medical Center, Jerusalem, Israel, [3]Department of Otolaryngology Head and Neck Surgery, Hadassah University hospital, Jerusalem, Israel, [4] Department of Gastroenterology, Hadassah University Hospital, Jerusalem, Israel, 1*Dov Wengrower and Benjamin Koslowsky contributed equally to this study

Abstract:

Background: Inflammatory bowel disease (IBD) has many characteristics of autoimmune diseases. Sensorineural hearing loss has been reported in many autoimmune diseases. Little is known about hearing loss in patients with IBD.

Methods: A prospective blinded comparative study was conducted over a 3 year period. IBD patients and controls underwent a complete otorhinolaryngeal examination and eudiometry test.

Results: Altogether 105 participants (76 patients and 29 controls) took part in this study. Mean age was 36, 51% were males and 40% of the patients were presently hospitalized due to IBD exacerbation. Audiometric examination revealed that any hearing loss (mild to severe) was found in 29 (38%) of the IBD population, compared to 4 (14%) of the control group (p=0.02). Extraintestinal manifestation (EIM's) were present in 33/76 (43%) of IBD patients. Any hearing loss and moderate to severe hearing loss was found in 17/33 (52%) and 7/33 (21%) in the EIM-positive group compared to 12/43 (28%) and 4/33 (12%) in the EIM-negative group (p=0.036 and p=0.14, respectively). Out of patients over the age of 40 with other EIM's all 11/11 (100%) of had any hearing loss compared to 8/12 (66%) of patients over the age of 40 without other EIM's, p=0.035.

Conclusions: Hearing loss may be another EIM of IBD. It is found in 38% of IBD patients, and in up to 52% of patients with other EIMs and increases over the age of 40. Early hearing evaluation should be recommended to these high risk IBD patients.

A repeated anorectal manometry 9 months after a 3rd degree obstetric anal sphincter injury (OASIS) may change the recommendation about the preferred mode of delivery in future pregnancies.

Dan M. Livovsky[1], Revital Arbel[2], Yair Edden3, Rila Meyuhas[4], Ariella Bar-Gil Shitrit[1] and Joseph Lysy[1].

[1]The Digestive Disease Institute, [2]The department of Gynecology and Obstetrics, [3]The department of General Surgery and The department of Physiotherapy all at Shaare Zedek Medical Center, affiliated with the Hebrew University, Jerusalem.

Background/Aims: A 3rd or 4th degree OASIS is a significant risk factor for anal sphincterdysfunction and fecal incontinence. Clinical, physiological and anatomical consequences of the tear will determine sphincter function hence the recommended mode of future deliveries. Ano-Rectal Manometry (ARM) and Endo-Anal UltraSound (EAUS) are performed 6 -12 weeks postpartum in order to provide women with a rational recommendation. In a subset of women, ARM at three months showed that the severity of sphincter dysfunction was out of proportion to a mild sphincter injury on EAUS. Assuming that recovery may still be in progress an additional ARM within 6 months was recommended. In the meantime, patients were asked to continue biofeedback physiotherapy. The aim of this study was to investigate if a second ARM after 6 months of biofeedback may influence the recommendation for mode of delivery in the future.

Methods: Retrospective evaluation of women that were evaluated at our multidisciplinary pelvic floor clinic during 2013-2014 and who underwent two ARMs after a 3rd degree OASIS. ARM was performed by using a water-perfusion system.

Results: Out of 114 patients that were evaluated, 12 (10.5%) underwent ARM twice. The mean age at childbirth was 23.8 (SD 2.1) years A 3a, 3b and 3c grade OASIS were diagnosed in 6 (50%), 4 (33%) and 2 (17%) patients respectively. Anal pain was reported by 3 (25%) patients, incontinence to flatus by 2 (17%), and constipation by 1 (8%), six (50%) patients were asymptomatic. Mild (< 30°), moderate (> 30° and <60°) and severe (> 70°) defects at the external anal sphincter (EAS) were observed by EAUS in 3 (25%), 5 (42 %) and 4 (33%) of patients respectively. Nine (75%) women underwent pelvic floor physiotherapy. The first ARM was performed in average 126.8 (SD 29.4) days postpartum and the mean time between manometries was 209.6 (SD 70) days. Anal resting pressure increased from 63 (SD 20.5) to 80.1(SD 17.4) mmHg (p=0.09). Both, maximal absolute anal squeeze pressure and maximum increment in anal squeeze pressure (maximal squeeze pressure - resting pressure) significantly increased from 105.08 (SD 39.4) to 147.5 (SD 44.18) mmHg (p=0.024) and from 40.25 (SD 21.6) to 73.25 (SD 41.5) mmHg p=0.031, correspondingly (Graph 1 & Figure 1). Due to the physiologic improvement observed at the second ARM, in 4 (33%) cases the recommendation of the pelvic floor clinic was changed and vaginal delivery was considered as an acceptable option in subsequent deliveries.

Conclusions: When there is discrepancy between severity of anal weakness as demonstrated on ARM and anatomy based on EAUS findings three months postpartum, a second ARM within 6 months after biofeedback may show significant improvement in external and internal anal sphincter function. This repeated evaluation may alter the decision regarding future deliveries in up to one third of the patients

Fecal microbiota transplantation for recurrent Clostridium difficile infection is highly effective - a retrospective study from two Israeli tertiary centers

Nathaniel Aviv Cohen[1], #Dan M. Livovsky[2], Binyamin Koslowsky[2], Shir Yaakobovitch[3], Merav Ben Yehoyada[3], Ronen Ben Ami[4], Amos Adler[5], Hanan Guzner-Gur[1], Eran Goldin[2], Moshe Erwin Santo[3], Zamir Halpern[3], *Kalman Paz[2], *Nitsan Maharshak[3],[6]

[1]Internal Medicine "B", Tel Aviv Medical Center, [2] The Digestive Diseases Institute, Shaare Zedek Medical Center, Jerusalem, [3]Department of Gastroenterology and Liver Diseases, Tel Aviv Medical Center,[4]Infectious Disease Unit, Tel Aviv Medical Center , [5] Department of Clinical Microbiology, Tel Aviv Medical Center, [6]The Bacteriotherapy Clinic, Department of Gastroenterology and Liver Diseases, Tel Aviv Medical Center

* These authors contributed equally to the manuscript

Background/Aims: Colitis caused by Clostridium difficile (C difficile) is the most common cause of hospital-acquired diarrhea. Fecal microbiota transplantation is proving increasingly successful in treating recurrent C.difficile infection (CDI). The aim of this study was to assess the success rate and side effects of FMT for refractory or recurrent CDI in two different Israeli centers and to evaluate whether using two different protocols for donor selection, FMT preparation and routes of FMT administration affect the results.

Methods: Retrospective analysis of treatment protocols and outcomes from 22 patients with refractory or recurrent CDI receiving FMT at two Israeli centers was performed.

Results: In this series FMT had an overall 2-month cure rate of 89% with no statistically significant difference between the patients cohorts compared.

Conclusions: FMT is a safe and effective treatment for refractory and recurrent CDI. More research is required to assess superiority of the various modes of FMT delivery and efficacy and cost-effectiveness of FMT as first-line therapy for CDI.

Oral Ambroxol for neuronopathic signs and symptoms of Gaucher Disease

Ari Zimran, Deborah Elstein, Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem Israel

Five years ago in this forum we presented the results of a pilot study using oral ambroxol (Zimran et al. Blood Cells Mol Dis. 2013 Feb;50(2):134-7) as a pharmacological chaperone (Maegawa et al. J Biol Chem. 2009 Aug 28;284(35):23502-16) in patients with type 1 Gaucher disease (GD); we monitored hematological and visceral signs. Our conclusions highlighted very specific action points should we intend to employ this modality in GD: [1] it was safe; [2] patients were compliant with a three-times daily regimen; and, importantly, that [3] the dosage used which was the highest approved for over-the-counter (OTC) indications, was insufficient for heavier patients to benefit and hence a higher dosage and one based on body weight would be required. However, the underlying premise of the study was that eventually this drug would be appropriate for neuronopathic GD (Castilla et al. J Med Chem. 2012;55(15):6857-65). In the intervening years, the Japanese group of Ohno and Narita, based on important pre-clinical investigations by others as well (Luan et al, Brain Dev. 2013;35(4):317-22; Bendikov-Bar et al. Blood Cells Mol Dis. 2013;50(2):141-5.Narita et al. Ann Clin Transl Neurol. 2014;1(2):135-40; Castill et al. Eur J Med Chem. 2015;90:258-66), has shown that clinically relevant change in neurological signs of type 3 GD including myoclonic seizures and even supranuclear horizontal gaze palsy, was effected by appropriate doses of ambroxol. In addition, patients and some treating physicians have been galvanized to treat the signs of Parkinson disease (McNeill et al. Brain. 2014;137(Pt 5):1481-95) that are seen in patients with GD. We believe that use of ambroxol for carriers of GD mutations with Parkinson disease also seems plausible as a therapeutic option.

Therefore, we have begun to think about an ambroxol registry to monitor safety and efficacy by reaching out to treating physicians prescribing ambroxol; but this has a retrospective rather than proactive function. We have been talking about ambroxol for nearly 15 years in the hope of acquiring the patented rights to this drug and employing it in clinical trials with patients with type 3 (and possibly 3c) and for those GD patients with Parkinson disease. We believe that too much time has elapsed in discussions and we are hopeful that B4B can make the case in the European Union for funding of a clinical trial at minimum for young adults with type 3 and those patients with GD and Parkinson disease.

Significant And Continuous Improvement In Quantitative Chemical Shift Imaging (Qcsi) In Patients With Gaucher Disease Treated With Taliglucerase Alfa During The Early Access Program

Ari Zimran, MD[1*]; Tama Dinur, PhD[1]; Deborah Elstein, PhD[1]; Erik Akkerman, PhD[2]; Carla E. M. Hollak, MD, PhD[2]; Raul Chertkoff, MD[3]; Mario Maas, MD[2]

[1]Gaucher Clinic and Genetic Unit, Shaare Zedek Medical Center, Jerusalem, Israel, [2]University of Amsterdam, Academic Medical Centre, Amsterdam, the Netherlands, [3]Protalix BioTherapeutics, Carmiel, Israel

Taliglucerase alfa, the first plant-cell-expressed recombinant therapeutic protein FDA-approved for human use, is the third enzyme replacement therapy (ERT) approved for treating Type 1 Gaucher disease (GD).

In trials, efficacy endpoints were organomegaly reduction and hematological parameter improvement; impact on bone was exploratory because of slower skeletal response to other ERTs. Using more sensitive MRI, improvement in bone-marrow infiltration was demonstrable ≤12 months. We report the impact of taliglucerase alfa on bone marrow, assessed by QCSI, in 26 patients treated in the Early Access Program (EAP) after the 2009 imiglucerase shortage.

The investigator-initiated study was designed for patients with fat fraction (FF)≤0.30 and predictive of bony complications when FF<0.23. Of 15 treatment-naive patients (10 female; mean age 50.6 years), 9 had baseline FF≤0.30, 3 discontinued, and 4 with baseline FF≤0.23 and follow-up measurements improved to FF>0.23. Among 11 treatment-switch patients (6 female; mean age 40.5 years; mean imiglucerase exposure 9.5 [range 1-17] years), 8 had baseline FF<0.26, 5 of whom had FF<0.23; 3 improved to FF≥0.29 (1 year) and 1 increased to FF=0.26 (2 years). EAP protocol mandated increasing dosage to 30U/kg EOW; 2 patients at this dosage (17 years' imiglucerase exposure) with baseline FF=0.13 and FF=0.19 increased to FF=0.26 at 1 year, implying a booster effect (possibly due to 100% mannose residues resulting in greater bone uptake vs 40-60% mannose residues for imiglucerase).

Booster effect requires further studies. This report adds to the overall taliglucerase alfa efficacy profile in adult patients with Type 1 GD, emphasizing bone benefit.

Taliglucerase Alfa During Pregnancy For Patients With Type 1 Gaucher Disease

Ari Zimran1*; Deborah Elstein1; Hanna Rosenbaum2; Raul Chertkoff3

[1]Gaucher Clinic and Genetic Unit, Shaare Zedek Medical Center, Jerusalem Israel, [2] Rambam Medical Center, Haifa, Israel, [3] Protalix BioTherapeutics, Carmiel, Israel

Bleeding tendency, organomegaly, and skeletal complications such as osteonecrosis of the hip joints in Gaucher disease (GD) may complicate pregnancy and delivery. Because pregnancy itself may worsen GD by inducing thrombocytopenia, anemia, and at times even bone crises, enzyme replacement therapy (ERT) may have an important role during this major life event. Label warnings with regard to pregnancy, even for the new ERTs with reproductive toxicology included in the drug development program, have led to concerns about the safety of ERT during pregnancy.

Our group was the first to administer ERT in pregnancy and recommend that our female patients conceive with and continue ERT during their pregnancy. We reviewed patient records starting in 2009 for pregnant women receiving taliglucerase alfa from conception through the post-partum period.

In all, 9 patients had 15 pregnancies: 1 patient had 3 pregnancies (1 missed abortion, 2 full-term, healthy infants; similar events were reported with imiglucerase before she switched to taliglucerase alfa); 1 patient had 3 pregnancies (1 missed abortion, 1 therapeutic abortion, 1 full-term, healthy infant); 1 patient had 2 pregnancies (2 full-term, healthy infants); and the remaining 6 patients had 6 viable pregnancies (full-term, healthy infants). Follow-up was up to 6 years.

The overall 86% live birth rate with taliglucerase alfa (excluding the therapeutic abortion) is similar to that for patients with GD treated with imiglucerase or velaglucerase alfa. In fact, the maternal and neonatal outcomes were similar to the general population. These data add to the safety profile for taliglucerase alfa.

Children with type 1 Gaucher disease: changing profiles in the 21st century

Deborah Elstein PhD, Aya Abrahamov MD, Gheona Altarescu MD*, Ari Zimran MD, Gaucher Clinic and Genetics Unit*, Shaare Zedek Medical Center, Jerusalem, Israel

Abstract: Gaucher disease (GD) has a broad clinical spectrum, from a peri-natal lethal neuronopathic form to a chronic, non-neuronopathic form with many patients considered asymptomatic throughout normative life-spans, yet there is only partial correlation with specific genotypes. With increased awareness for GD especially among at-risk populations such as Ashkenazi Jews (AJ) and the availability of relatively cheap and non-invasive diagnosis, there has been a trend to pre-marital and newborn screening that has led to increasing numbers of diagnosed patients. The purpose of this study is assessment of pediatric (<16 years) Israeli AJ patients with GD to ascertain demographics and clinical features at presentation and over time (up to 16 years) because many are products of large-scale screening efforts. 55/67 of our pediatric patients born since 01/01/2000 are AJ with non-neuronopathic GD: 28 are N370S/N370S; 24 are N370S/other; 3 are other/other. 30 children were diagnosed by screening; 10 others have a sibling previously diagnosed by screening. Of 19 children receiving enzyme replacement therapy (ERT), four were by screening, (N370S/N370S; N370S/L444P, N370S/84GG, N370S/IVS2+1); others were diagnosed because of GD symptoms and/or a sibling with symptomatic GD. Four began ERT at <2 years of age; nine at 3-5 years; the rest at 6-12 years. 49% presented with height and weight growth percentiles ≤25%, but group means were not dramatically altered up to 12 years follow-up including in 10 receiving ERT (8 for >5 years). 22% presented with anemia and 20% with thrombocytopenia; at last follow-up 4% and 6%, respectively, remained cytopenic. Thus, we present an entirely new demographic profile for pediatric GD because so many are products of screening and have few GD signs/symptoms at presentation and at long-term follow-up. Nonetheless, early diagnosis is good, especially for non-N370S/mild genotypes. However, the potential advantage of screening would be genotype-specific prognostication and appropriate genetic counseling.

Key words: enzyme replacement therapy; Gaucher disease; large-scale screening

COI: None of the authors have any conflicts of interest to report regarding the contents of this study.

10-Years with Colistin: A Retrospective Case Series

David E. Katz MD MPH[1] and Eli Ben-Chetrit MD[1,2]

[1]Internal Medicine Department and the, [2]Infectious Disease Unit, Shaare Zedek Medical Center, Affiliated with the Hebrew-University Hadassah-Medical School, Jerusalem, Israel

Objective: At the Shaare Zedek Medical Center, we have been using colistimethate sodium (CMS) for empiric as well as pathogen directed treatment. We present our 10-year experience.

Methods: We conducted a retrospective case-series analysis of patients admitted from January 1, 2004 through May 1, 2014 who received at least one dose of CMS. Patient characteristics analyzed for all admission for which patients received CMS, included: age, number of re-admissions, admission ward, renal function, disposition, and microbiology results. Overall trend in defined daily dose (DDD) for CMS and resistant isolates was analyzed.

Results: 5,603 admissions met inclusion criteria. Patients' mean (±SD) age was 80±14 years, 1162 (48%) of the admissions were from a healthcare facility, and 4,367 (78%) of the admissions were to general Internal Medicine wards. The median number of hospital admissions per patient was 5, median admission and discharge creatinine (mg/dl) were 1.05 and 1.01, respectively; 2.3% of admissions required first-time dialysis. The discharge rate from the hospital was 58.4%. Excluding intrinsically CMS-resistant Gram-negative organisms, bloodstream and urine isolates were 98% and 100% susceptible, respectively. CMS use (DDDs) increased during the study (p for trend = 0.04) without significant increase in incidence of multi-drug resistant organisms.

Conclusions: CMS use at our institution has increased during this 10-year period. Nevertheless, there is no increasing trend in CMS-resistant organisms, 58% of the patients were discharged alive, and we did not observe significant nephrotoxicity in patients prescribed CMS. CMS should be reserved for microbiologically confirmed extensively drug resistant Gram-negative infections.

Duration of carriage of carbapenem-resistant Enterobacteriaceae following hospital discharge.

Frederic S. Zimmerman, MD, Amos M. Yinnon, MD and Yonit Wiener-Well, MD
Department of Internal medicine at Shaare Zedek Medical Center.

Background: Patients infected or colonized with carbapenem-resistant Enterobacteriaceae (CRE) are taken cared of under isolation and cohorting, using strict contact precautions. Upon subsequent hospital admission they are placed under the same precautions until surveillance cultures, which are taken upon admission but whose results require 2-3 days, indicate discontinuation of CRE carriage. There are as of yet few studies investigating duration of CRE carriage and defining which populations require precautions upon readmission, This determination is purpose of the current study.

Methods: We conducted a follow-up of patients from whom a clinical or surveillance culture CRE culture was obtained in our hospital during 2009-2010. Patients were followed up both prospectively and retrospectively by rectal swab cultures taken either as part of clinical follow-up or as part of the study.

Results: Out of 346 patients in the initial database, 137 met the inclusion criteria and follow-up cultures were successfully obtained from 97. We calculated an overall mean time from index culture to CRE negativity of 387 days (95% CI: 312-463). At 3 months, 78% of patients were culture positive by Kaplan-Meier survival estimate, at 6 months 65% were positive, and at 1 year 39% were positive. Two factors were found to affect the duration of CRE carriage: repeat hospitalizations and whether the patient had clinical CRE disease ($p<0.001$) or was a CRE carrier ($p<0.002$).

Conclusions: Our data suggest that if a patient was CRE positive during a previous hospitalization and requires readmission, he does not require initial isolation and cohorting if more than one year has passed and he did not require further admissions since the index culture, especially if the initial positive CRE isolation was derived from a surveillance culture. Patients with multiple hospitalizations or those who were diagnosed with clinical CRE disease should be assumed to have a more extended duration of CRE carriage. Thus, this study contributes to better defining the patient populations that require cohorting and isolation, simultaneously preventing the spread of CRE and making the CRE negative patient's hospital stay more comfortable, easing care and reducing the risk of CRE reinfection.

Using a departmental report to reduce the rate of blood cultures contamination: Initial results of a long-term study.

Frederic S. Zimmerman, MD, Amos M. Yinnon, MD and Yonit Wiener-Well, MD
Department of Internal Medicine at Shaare Zedek Medical Center

Background: Blood cultures are an essential part if prompt identification of bloodstream infections. However it is that up to 50% of positive culture represent contaminants, requiring significant additional laboratory resources and resulting in unnecessary treatment and extended hospitalization. Reduction of blood culture contamination has been achieved using venipuncture and phlebotomy teams, as in our institution, as well as by feedback on contamination rates. Thus, the principle object of this study was the determination of baseline blood cultures contamination rates versus contamination rates after initiating a monthly departmental report card focusing on those rates.

Methods: In this prospective uncontrolled trial, a monthly departmental report card was addressed to each department head and reported, in a combined graphic and textual format on a single sheet of paper, on his or her department's blood culture contamination rate. This was compared to the department's contamination rate in previous months and to the overall hospital contamination rate. The report also showed contamination trends for the department and hospital from the beginning of the study period. Lastly, it contained recommendations, based on guidelines, for lowering the contamination rate.

After initiating the report card, we followed rates of blood culture contamination by department for 6 months and compared those rates to blood contamination rates prior to the intervention in order to assess the value of that intervention in reducing contamination.

Results: In the month prior the initiation of the intervention 2831 blood cultures were taken with 129 showing contamination for an overall contamination rate of 4.6%, much higher than the maximum accepted rate of 2.5%. After initiating the intervention contamination rates went steadily down. In the last month studied 3186 blood cultures were taken with 88 showing contamination for an overall contamination rate of 2.8% (p for the trend < 0.001, p for the month prior to the intervention vs. the last month of the intervention < 0.01). These trends were consistent if the divisions of pediatrics, medicine or emergency medicine were evaluated separately (p for the trend < 0.001, 0.001 and 0.002, respectively). However, no trend of reduced contamination was shown in the division of surgery.

As a comparison, in the 6 months prior to the intervention there was a significant increase in overall hospital blood culture contamination. No consistent trends were shown in the separate divisions.

Conclusions: This study shows that initiating a simple, inexpensive intervention - feedback on a departmental level - can significantly reduce the rate blood culture contamination. Further study is needed to determine why this trend was not shown in the division of surgery and if this reduced rate persists over the long-term.

Serum Uric Acid as Short Term Mortality Predictor in the Acute Care Setting

Yuval Schwartz, Gideon Nesher, Gabriel S Breuer

Shaare Zedek Medical Center and the Hadassah Hebrew University School of Medicine.

Background: Many studies have showed that the serum uric acid (SUA) is an independent predictor of adverse cardiovascular events and all-cause mortality, but some studies have yielded conflicting results. Even more contradicted issue is the relationship between SUA and mortality in acutely hospitalized patients. In this context there is scarce data about SUA as an independent predictor of short-come outcome in the hospitalized older patient.

The aim of this study is to determine whether SUA obtained within 48 hours after admission can predict short-term outcome.

Methods: The analysis was conducted in an 850-bed medical center. 860 adult patients were admitted to internal medicine departments between March 1st 2014 and June 30th 2014. We evaluated SUA level drawn within 48 hours after admission as predictor of in-hospital mortality. In addition we collected clinical and epidemiological data.

Results: The mean age of patients was 78±14. The mortality rate was 15.1% (130 patients), and the mean SUA was 6.25 ± 2.70 mg/dl. The most common cause for hospitalization was pulmonary infection (16.8%) followed by congestive heart failure exacerbation (9.3%). The mortality rate was 11% (66 patients out of 562) in the group with SUA ≤ 7.5 in comparison to 27% (64 patients out of 171) in the group with SUA above this level [P < .001]. Moreover, SUA was an independent predictor of mortality in a multivariate regression analysis, with an odds ratio of 2.71 (confidence interval 1.82-4.04 = P < .001).

Table 1: logistic regression analysis

Variables in the Equation	B	S.E.	Wald (df=1)	Exp(B)	95% C.I.for EXP(B)
Gender	0.01	0.2	0.00	1.01	0.69-1.49
Age	0.02	0.01	4.12*	1.02	1-1.03
creatinine	0.13	0.06	4.70*	1.14	1.01-1.29
Uric Acid	0.18	0.04	26.64***	1.2	1.12-1.29
Constant	-4.55	0.72	39.87	0.01	

*p < .05, *** p< .001

Conclusion: SUA level is a strong independent predictor of short-term outcome in elderly patients admitted to internal medicine departments.

Bone Density in Hospital Physicians and Pensioners Over the Age of 65 - a Group at Risk for Vitamin D Deficiency During their Working Years

Futeran Chen, Sylvetsky Noa, Munter Gavriel

Abstract: Hospital physicians are indoor workers with low sun exposure, and are at risk for low levels of serum 25-hydroxyvitamin D, (25(OH)D)., In a previous study carried out at Shaare Zedek Medical Center, the mean serum level of 25(OH)D among hospital physicians was significantly lower than those of community-based physicians. Continuing this line of enquiry, we investigated bone density among hospital physicians. We conducted a prospective study to assess bone density among hospital physicians over the age of 65.

Although vitamin D has an important role in calcium and phosphate homeostasis, the link between low vitamin D levels and osteoporosis later in life has not been fully studied. Osteoporosis is more common in women than men, and has therefore been studied more in women. We have decided to perform our study with exclusively male subjects so as to neutralize the hormonal effects such as age of menopause and use of estrogen supplementation that serve as important factors when determining bone density in women, in order to focus on the study group of hospital doctors and pensioners, a group at risk for low vitamin D levels in their younger years, and to explore the possible effects of this deficiency on bone density years later.

Methods and materials:

a. Study design: A cross-sectional study analyzing bone mineral density at present.

b. Subjects: Hospital doctors and pensioners over the age of 65 who agree to participate in the study.

Inclusion Criteria: Men over the age of 65, who give informed consent.

Exclusion Criteria: Doctors who did not consistently work in the hospital during their careers, current or previous chronic steroid treatment, thiazide diuretic use, hyperparathyroidism, malabsorption or gastrectomy, kidney disease, osteoarthritis, current or previous cancer diagnosis, known osteoporosis.

c. Variables:

Osteopenia and osteoporosis as defined by the WHO:

Osteopenia: Bone mineral density (BMD) in a dual-energy X-ray absorptiometry test (DXA) that is more than one standard deviation below the age-calibrated average used as a reference. In short, T score between -1 and -2.5

Osteoporosis: BMD in DXA that is 2.5 standard deviations or more below the reference.

In short, T score less than or equal to -2.5.

d. Statistical methods

We compared the T scores calculated by one DXA system at Shaare Zedek Medical Center, calibrated for each subject's gender, age, height and weight, with a T score of 0 as a reference value. We also used epidemiological data of BMD scores in the Israeli population, from a registry that was published in 2012.

Sample size estimation was based on the expected difference between the study group and a T score of 0 (calibrated for age), when expecting a medium effect. Assuming the significance is 5% (1-tailed), the power is 50%, and the difference between the average of the study group and a T score of 0 will be 0,5 standard deviations, a sample size of 27 was calculated.

The association between two quantitive variables was assessed by calculating the Pearson correlation coefficient. The association between categorical variables was assessed using the Chi squared test.

Results: 28 physicians participated in our study. 14 had osteopenia and 3 had osteoporosis. The incidence of osteopenia and osteoporosis was not significantly different from the expected in the population in this age.

Conclusion: In this group of hospital doctors and pensioners over the age of 65 the incidence of osteopenia and osteoporosis was not higher than the general population over the age of 65. Several explanations for this result are possible.

XX-Disorder of Sexual Development with Ovarian Dysgenesis Is Caused By a Mutation in the Nucleoporin-107 Gene

Ariella Weinberg-Shukron[1,2], Paul Renbaum[1], Rachel Kalifa[3], Sharon Zeligson[1], Ziva Ben-Neriah[4,5], Amatzia Dreifuss[3], Amal Abu-Rayyan[6], Noa Maatuk[7], Nilly Fardian[3], Dina Rekler[3], Moien Kanaan[6], Abraham O. Samson[7], Offer Gerlitz[3], David Zangen[8], Ephrat Levy-Lahad[1,2]

[1]Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel. [2]Hebrew University, Hadassah Medical School, Jerusalem, Israel. [3]Department of Developmental Biology and Cancer Research, IMRIC, Hebrew University, Hadassah Medical School, Jerusalem, Israel. [4]Genetic clinic, Hadassah Medical Center, POB 12000, Jerusalem 91120, Israel. [5]Present address: Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel. [6]Hereditary Research Laboratory, Bethlehem University, Bethlehem, Palestine. [7]Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel. [8]Division of Pediatric Endocrinology, Hadassah Hebrew University Medical Center, Jerusalem, Israel.

Background: Ovarian development and maintenance are poorly understood. XX-female gonadal dysgenesis (XX-GD) is a rare, genetically heterogeneous disorder that is characterized by underdeveloped, dysfunctional ovaries with subsequent lack of spontaneous pubertal development, primary amenorrhea, and hypergonadotropic hypogonadism. We report an extended consanguineous family of Palestinian origin in which four females exhibited XX-GD.

Methods & Results: Using homozygosity mapping and whole exome sequencing, we identified a recessive missense mutation in nucleoporin-107 (NUP107, c.1339G>A, p.D447N). This mutation segregated with the XX-GD phenotype and was not present in available databases or in 150 healthy, ethnically matched controls. NUP107 is a component of the nuclear pore complex, and the NUP107-associated protein Seh1 is required for oogenesis in Drosophila. We found that Nup107 RNAi knockdown in Drosophila somatic gonadal cells resulted in female sterility. Transgenic rescue Drosophila females bearing the Nup107D364N mutation, which corresponds to the human NUP107:p.D447N, resulted in almost complete sterility, with a marked reduction in progeny, morphologically aberrant eggshells, and disintegrating egg-chambers, indicating defective oogenesis and resembling the human phenotype. In order to characterize the defects observed in Nup107D364N mutant ovaries, we immunostained the dissected ovarioles for two proteins representing two major pathways involved in gonadogenesis and oogenesis. C(3)G, a protein that forms the transverse filaments of the synaptonemal complex (SC), which is important in meiosis and homologous recombination was mis-localized in Nup107D364N mutant ovaries. While ovarioles from WT rescue flies showed normal localization of C(3)G to the oocyte's nucleus, in mutant Nup107D364N ovarioles C(3)G was distributed throughout the oocyte's cytoplasm. In contrast, the EGF-R ligand Gurken (grk), which directs the establishment of the dorsal-ventral axis of the oocyte and the future embryo in Drosophila, was correctly localized to the dorsal corner in Nup107D364N mutant oocytes.

Conclusions: In summary, these results indicate NUP107 as a novel genetic etiology for ovarian mis-development and suggest that nucleoporin defects may play a role also in milder and more common conditions such as premature ovarian failure. Future research will elucidate the signaling pathways involved in NUP107 mediated ovarian development and will be a valuable insight into ovarian development and dysgenesis mechanisms.

Internal

Single cell TESTING versus amniocentesis and NIPT: Ultra-high resolution preimplantation screening for microduplication-microdeletion syndromes

David A. Zeevi*, Tal Dror, Efrat Burak, Sophie Kirshberg, Elinor Hakam-Spektor, Dina Kort, Elina Farhi, Merav Ben Shlomo, Sharon Zeligson, Rachel Beeri, Talia Eldar-Geva, Ephrat Levy-Lahad, Gheona Altarescu

Medical Genetics Institute, ZOHAR PGD Unit, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Invasive prenatal testing and recent advances in noninvasive prenatal testing (NIPT) have afforded pregnant couples the ability to test for some pathogenic microdeletions during pregnancy. These structural chromosomal abnormalities include 22q11.2 deletion (DiGeorge syndrome), 1p36 deletion, Cri-du-chat, Prader-Willi, and Angelman syndrome deletions which, altogether, appear in 1:1000 childbirths. Unlike Down syndrome, the risk for the aforementioned disorders is independent of maternal age such that prenatal testing of pregnant women of all ages is recommended. Nonetheless, due to the small size of the deletions (ranging from 1Mb-3Mb long), preimplantation screening for high-risk de-novo microdeletions remains too technically challenging for large-scale application.

Aim: To assess whether moderately low coverage next generation sequencing can be utilized to screen clinically relevant microdeletion/microduplication syndromes in preimplantation embryos.

Methods: Structural chromosomal aberrations, resulting from parental balanced translocations, were tested in 96 different blastomere/blastocyst biopsies by array comparative genomic hybridization (aCGH) on the Illumina/BlueGnome platform at the Shaare Zedek Medical Center (SZMC) in Jerusalem. Residual whole genome amplified DNA from the same aCGH workflow was also subjected to moderately low coverage whole genome shotgun sequencing on a NextSeq 500 (Illumina) instrument. All resultant reads were aligned to the human reference genome (hg19) and custom in-house software was established for the determination of ultra-high resolution chromosomal copy number across the entire human genome. This same software was applied for the detection of pathogenic microdeletions in 12 polar body samples from the Hou et al. ("Genome analyses of single human oocytes" Cell. 2013. 155(7):1492-506) deep sequencing data set.

Results: Deep sequencing identified all 84 unbalanced and 12 balanced/euploid embryo samples that were detected by aCGH (100% of the cases). Notably, even copy number variation (CNV) gains/losses (unbalanced translocations) as small as 4Mb-7Mb long were easily detected by deep sequencing in 16 of the 84 unbalanced embryo biopsies. Therefore, to further assess the sensitivity of our CNV detection, slightly higher coverage sequencing data from the Hou et al. study was scrutinized for smaller copy number gains and losses. Strikingly, this analysis identified multiple structural abnormalities with pathological implications. In addition to large structural abnormalities, CNVs as small as 0.3Mb and 0.5Mb were detected with high confidence. The 0.3Mb microdeletion included the PARK2 gene whose loss-of-function is associated with juvenile Parkinson disease; the 0.5Mb deletion included the NPC2 gene whose deletion is associated with Niemann-Pick Disease, Type C.

Conclusions: We have expanded the scope of preimplantation genetic screening (PGS) to include genetic disorders that are currently screened only by amniocentesis or NIPT. Indeed, our moderate low coverage deep sequencing workflow offers the requisite high resolution CNV detection which is crucial for preimplantation diagnosis of common microdeletion disorders such as DiGeorge, Cri-du-chat, Prader-Willi, and Angelman syndromes. This methodology is also applicable for any couple performing PGS or PGD for a familial balanced translocation. Moreover, our method is rapid (24 hours from biopsy to test result), robust (accommodating tens of samples per batch), and highly cost-effective with respect to aCGH.

Hemi-NeSTR: Turbo batch primer design for targeted STR genotyping of single cells for PGD

David A. Zeevi*, Merav Ben Shlomo, Shira Shaviv, Dina Kort, Elina Farhi, Gheona Altarescu, Rachel Beeri, Paul Renbaum, Talia Eldar-Geva, Ephrat Levy-Lahad, Maximilian Peters

Medical Genetics Institute, ZOHAR PGD Unit, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Standard molecular PGD involves short tandem repeat (STR) genotyping of single cells from preimplantation oocytes or embryos. Accordingly, PGD laboratories generally possess well established PCR primer panels for commonly tested molecular disorders such as cystic fibrosis. However, in this day and age of whole exome sequencing and chromosomal microarray, new pathogenic mutations for molecular PGD testing are identified in uncharted genomic regions at a dizzying pace. To keep up with this demand, PGD labs must expeditiously design new STR amplicon panels on a weekly basis even though this manual batch primer design is overly time-consuming and tedious.

Aim: To design and assess a batch hemi-nested PCR primer design program to streamline new assay development for molecular PGD applications.

Methods: The Hemi-NeSTR program was designed for batch combination of primer3-based primer design with in silico PCR (isPCR) primer specificity checking. In the first step, Hemi-NeSTR is programmed to scan multiple STR (with flanking DNA) sequences in a genomic region of interest (usually 4Mb in size) for the longest stretch of di- or tri-nucleotide repeats in each target. Subsequently, primer3 designs multiple primer pairs per input target which are then sent for primer specificity checking to an isPCR server which has already tested every possible primer pair combination for specificity (predicted amplification of single amplicon only) against the human reference genome (hg19). For STR targets in which Hemi-NeSTR successfully identifies one specific primer3 designed primer pair, Hemi-NeSTR continues to design a primer3- and isPCR-certified external forward primer for coupling with the initial designed reverse primer. This feature facilitates automatic hemi-nested primer design of multiple target STR sequences at once.

Results: Over the course of one year, Hemi-NeSTR was used to design an average of 16.6 hemi-nesting STR-flanking amplicons in each of 39 different 4Mb sized genomic regions. For each region, 78.4%+/-18.7% of the designed primer pairs successfully amplified their respective STR targets. After linkage analysis, an average of 46.8%+/-21.4% of the designed STR amplicons were identified as informative for single cell haplotype analysis. Thus far, 17 novel mutation-flanking STR panels were applied in live PGD cases. Generally, each panel consisted of 5-6 informative STR markers for haplotype analysis of single cell embryo biopsies. Using hemi-nested PCR amplification strategies, 97.2%+/-6.1% of the markers in each panel were successfully amplified with Hemi-NeSTR designed PCR primers. In all PGD cases, a diagnosis was achieved for each biopsy and currently there are 8 ongoing pregnancies from Hemi-NeSTR facilitated PGD.

Conclusions: Hemi-NeSTR completes hemi-nested PCR primer design of 30 different STR target sequences within 5 minutes. The equivalent manual operation requires a minimum of 2 full human work days. Thus, Hemi-NeSTR facilitates rapid new assay development without compromising on single cell amplification efficiency or endpoint embryo diagnostic effectiveness; a welcome addition to the PGD laboratory toolbox.

Proof-of-principle rapid noninvasive prenatal diagnosis of autosomal recessive founder mutations

David A. Zeevi[1]*, Gheona Altarescu[1,2], Ariella Weinberg-Shukron[1,2], Fouad Zahdeh[3,4], Tama Dinur[5], Gaya Chicco5, Yair Herskovitz1, Paul Renbaum1, Deborah Elstein5, Ephrat Levy-Lahad[1,2], Arndt Rolfs6, Ari Zimran[2,5]

[1]Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel

[2]Hebrew University Faculty of Medicine, Jerusalem, Israel

[3]Department of Genetics, The Alexander Silberman Institute of Life Sciences, Faculty of Science, The Hebrew University of Jerusalem, Edmond J. Safra Campus, Givat Ram, Jerusalem, Israel

[4]Hereditary Research Lab, Life Sciences Department, Bethlehem University, Palestinian authority

[5]Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel

[6]Albrecht Kossel Institute for Neuroregeneration, University of Rostock, Medical Faculty, Gehlsheimerstrasse 20, 18147 Rostock, Germany

Background: Noninvasive prenatal testing can be used to accurately detect chromosomal aneuploidies in circulating fetal DNA; however, the necessity of parental haplotype construction is a primary drawback to noninvasive prenatal diagnosis (NIPD) of monogenic disease. Family-specific haplotype assembly is essential for accurate diagnosis of minuscule amounts of circulating cell-free fetal DNA; however, current haplotyping techniques are too time-consuming and laborious to be carried out within the limited time constraints of prenatal testing, hampering practical application of NIPD in the clinic. Here, we have addressed this pitfall and devised a universal strategy for rapid NIPD of a prevalent mutation in the Ashkenazi Jewish (AJ) population.

Methods: Pregnant AJ couples, carrying mutation/s in GBA, which encodes acid-glucosidase, were recruited at the Shaare Zedek Medical Center (SZMC) Gaucher Clinic. Targeted next generation sequencing of GBA-flanking single nucleotide polymorphisms (SNPs) was performed on peripheral blood samples from each couple, relevant mutation carrier family members, and unrelated individuals that are homozygotes for an AJ founder mutation. Allele-specific haplotypes were constructed based on linkage, and a consensus Gaucher disease-associated founder mutation-flanking haplotype was fine-mapped. Together, these haplotypes were utilized for NIPD. All test results were validated by conventional pre- or post-natal diagnostic methods.

Results: Ten parental alleles in 8 unrelated fetuses were successfully diagnosed based on the noninvasive method developed in this study. The consensus mutation-flanking haplotype aided diagnosis for 6 of 9 founder mutation alleles.

Conclusions: The founder NIPD method developed and described here is rapid, economical, and readily adaptable for prenatal testing of prevalent autosomal recessive disease-causing mutations in an assortment of worldwide populations.

The Spinal Muscular Atrophy with Pontocerebellar Hypoplasia Gene VRK1 Regulates Neuronal Migration through an APP Dependent Mechanism

***Hadar Vinograd-Byk*[1,2], *Tamar Sapir*[3], *Lara Cantarero*[4,5], *Pedro A. Lazo*[4,5] *Sharon Zeligson*[1], *Dorit Lev*[6], *Tally Lerman-Sagie*[7], *Paul Renbaum*[1], *Orly Reiner*[3] *and Ephrat Levy-Lahad*[1,2]**

[1]Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem 91031, Israel,

[2] Hebrew University Medical School, Jerusalem 91120, Israel

[3]Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot 76100, Israel

[4]Instituto de Biología Molecular y Celular del Ca´ncer

Consejo Superior de Investigaciones Científicas, Universidad de Salamanca, 37007 Salamanca, Spain

[5]Instituto de Investigacio´n Biome´dica de Salamanca

Hospital Universitario de Salamanca, 37007 Salamanca, Spain, and

[6]Medical Genetics Institute

[7]Pediatric Neurology Unit, Wolfson Medical Center, Holon58100, Israel

Spinal muscular atrophy with pontocerebellar hypoplasia (SMA-PCH) is an infantile SMA variant with additional manifestations, particularly severe microcephaly. We previously identified a nonsense mutation in Vaccinia-related kinase 1 (VRK1), R358X, as a cause of SMA-PCH. VRK1-R358X is a rare founder mutation in Ashkenazi Jews, and additional mutations in patients of different origins have recently been identified.VRK1is a nuclear serine/threonine protein kinase known to play multiple roles in cellular proliferation, cell cycle regulation, and carcinogenesis. However, VRK1 was not known to have neuronal functions before its identification as a gene mutated in SMA-PCH. We show that VRK1-R358X homozygosity results in lack of VRK1 protein, and demonstrate a role for VRK1 in neuronal migration and neuronal stem cell proliferation. Using shRNA in utero electroporation in mice, we show that Vrk1 knockdown significantly impairs cortical neuronal migration, and affects the cell cycle of neuronal progenitors. Expression of wild-type human VRK1 rescues both proliferation and migration phenotypes. However, kinase-dead human VRK1 rescues only the migration impairment, suggesting the role of VRK1 in neuronal migration is partly noncatalytic. Furthermore, we found that VRK1 deficiency in human and mouse leads to downregulation of amyloid-β precursor protein (APP), a known neuronal migration gene. APP overexpression rescues the phenotype caused by Vrk1 knockdown, suggesting that VRK1 affects neuronal migration through an APP-dependent mechanism.

3300 BRCA1 and BRCA2 mutation carriers: The Israeli Consortium for hereditary breast and ovarian cancer

Michaelson-Cohen R, Medical Genetics Institute, Shaare Zedek Medical Center

Bella Kaufman, Oncology, Sheba Medical Center, Tel-Hashomer

Rafael Catane, Oncology, Shaare Zedek Medical Center

Eitan Friedman, Genetics, Sheba Medical Center, Tel-Hashomer

Ephrat Levy-Lahad, Medical Genetics Institute, Shaare Zedek Medical Center

Background: BRCA1/BRCA2 mutations are the most common cause of hereditary breast and ovarian cancer (HBOC). The HBOC-Consortium was created for unified data collection on Israeli BRCA carriers.

Methods: A uniform computerized database was used by 12 cancer-centers

Results: Data was collected on 2145 BRCA1, 1131 BRCA2, and 22 double-mutation carriers.

BRCA1 vs. BRCA2 carriers had more breast cancer (BC) (40.0% vs. 36.3%, p=0.06), more ovarian cancer (OC) (17.1% vs. 10.6%, p<0.001), were younger at cancer diagnosis (BC 45yrs. vs. 49 yrs., p<0.001, OC 53yrs. vs. 62yrs., p<0.001), had more familial BC (64.5% vs. 59.0%, p=), and familial OC (36.7% vs. 27.3% p=).

BRCA1 carriers of 185delAG vs. 5382insC (BRCA1) had less BC (38.6% vs. 46.4%, p=0.02), at older age (46yrs. vs. 40yrs., p=0.023), but more OC (17.6% vs. 12.9%, p<0.05).

RR-BSO rates were assessed in carriers aged 38-80yrs. BC patients had higher rates than unaffected carriers (92.6% vs. 78.1%, p<0.001), but underwent RR-BSO later (51yrs. vs. 48yrs. p= p<0.001). Carriers with familial OC were more likely to undergo RR-BSO than carriers without familial OC (83.0% vs. 74.7%, NS). Carriers with familial cancer had RR-BSO earlier than those without (48 yrs. vs. 50yrs., p=0.037), especially BRCA2 carriers with familial OC (47 yrs. vs. 51yrs., p=0.018).

18/497(3.6%) male carriers had BC. 1/3 of them were BRCA1 carriers, and had younger at cancer diagnosis compared to BRCA2 mutation carriers (50yrs. vs. 57yrs., p<0.05).

Conclusions: RR-BSO rates in Israeli carriers are very high, particularly in women affected with BC and in women with family history of OC. Consortium data are consistent with lower penetrance for BRCA2 mutations.

Non-invasive prenatal testing (NIPT) in unusual aneupoidy cases: partial trisomies and low-level mosaicism

Rachel Michaelson-Cohen Department of Obstetrics and Gynecology and the Medical Genetics Unit, Shaare Zedek Medical Center

Background: NIPT for aneuploidies is extremely efficient, particularly for trisomy 21(t21) and t18, with sensitivity and specificity >99%. Clinical utilization of NIPT has grown rapidly.

Patients and methods: In our referral center, women undergo NIPT for several indications. We describe performance in 3 cases.

Three rare aneuploidies were diagnosed combining NIPT (USA-based-laboratories), karyotyping.

First case: 42-year-old woman, integrated-first-second-trimester screening: high t18 risk. Ultrasound: atrioventricular septal defect and hydronephrosis. NIPT: high t18 probability.

Second case: 36-year-old primigravida, IVF-ICSI-pregnancy, mildly-increased nuchal-translucency. NIPT: normal male. Later sonogram demonstrated thickened nuchal-fold.

Third case: 28-year-old, normal first, second trimester screening. 15 week ultrasound: cardiac-echogenic-focus and choroid-plexus-cyst. NIPT: t21.

Results: First case: declined invasive testing, at delivery baby showed minor t18 signs, however lacked classic features. Neonate died of respiratory complications at 3 weeks.Cord-blood-karyotype: 46,XX,der(14)t(14;18)(p10;q10) (Partial t18).

Second case: Karyotype and CMA (amniocytes): atypical Klinefelter syndrome, with isochromosome-X.

Third case: QF-PCR from amniocytes: normal, however, full-karyotyping: low level t21 mosaicism (50%).

Conclusions: Many factors limit NIPT accuracy. One main limitation is genetic discrepancy between fetal and placental tissue. This is true in simple aneuploidies, moreover in incomplete/ mosaic trisomies.

In the first case, although chromosome 18 only partially-duplicated, it was correctly identified by NIPT. However, rare isochromosome Xq Klinefelter induced false-negative NIPT, consistent with lower performance of NIPT for detection of rare sex-aneuploidies. Xq-duplication probably causes even lower detection-rate than complete duplication.

For low-level mosaicism, NIPT detected a level of mosaicism of t21, below QF-PCR detection-threshold.

These unusual cases are examples that demonstrate NIPT strengths and weaknesses.

BRCA screening in un-affected Ashkenazi Jewish women. Randomized controlled trial of different pre-test strategies

Sari Leiberman Ph.D. student in the Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel. Genetic counselor, Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel

Sari Lieberman, Ariela Tomer, Avraham Ben-Chetrit, Oded Olsha, Shimon Levine, Rachel Beeri, Sivan Koka, Malka BenUziyahu, Aviad Raz, Amnon Lahad, Ephrat Levy-Lahad

Background: Approximately half of BRCA1/BRCA2 carriers lack significant family history, and would only be identified through general testing. The Ashkenazi Jewish (AJ) population is a model for such screening, given high prevalence (1/40) and testing sensitivity (>95%) of three common mutations. Towards implementation, we aim to examine the impact of excluding pre-test face-to-face genetic counseling (GC) in the population screening setting.

Methods: Healthy AJ women age > 25 years are randomized to two pre-test arms: written information only (WI) vs. GC. Post-testing, GC is provided to non-carriers indicating significant family history and to all carriers. Psychosocial outcomes (satisfaction with health decision, stress, anxiety, personal perceived control (PPC), knowledge) are assessed one week (Q1) and 6 months (Q2) post-testing.

Results: Among the first 680 participants (mean age 46 years), we identified 10 carriers (1.5%). Only 2/10 carriers had significant family history. Post-testing, 95% of GC and 94% of WI participants (NS) report being satisfied/very satisfied with testing. Overall >85% would recommend population screening. Stress (Impact of Events) scores were similar in both groups. At Q1, personal perceived control (PPC) scores and knowledge were higher in GC (p=.005; p=.0001), but absolute differences were small; PPC: 0.11 of 2 points, knowledge: 1.11 of 10 points. At Q2, only PPC scores remained higher in GC: 1.39 vs. 1.25 in WI (p=.02). Carriers had higher PPC and knowledge than non-carriers. At Q1, carriers' stress level was higher (14.9 vs. 5.3, p=.0006), as expected.

Conclusion: Screening using streamlined testing would identify substantially more carriers (regardless of family history) while addressing logistic and cost limitations. These ongoing results suggest that compared to WI, pre-test GC provides a mild, temporary, increase in knowledge, accompanied by a greater sense of control. Forgoing pre-test GC may therefore be a legitimate alternative in large scale screening, particularly if alternative methods for imparting knowledge are explored.

Population screening for BRCA1/BRCA2 mutations: A translational study of the common Ashkenazi mutations

Sari Leiberman Ph.D. student in the Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel. Genetic counselor, Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel

Sari Lieberman, MSc, Ariela Tomer, MSc, Avi Ben Chetrit, MD, Oded Olsha, MD, Rachel Beeri, PhD, Sivan Koka, MSc, Hila Fridman, MSc, Karen Djemal, MD, Shlomo Segev, MD, Amnon Lahad, MD, MPH, Aviad Raz, PhD, Ephrat Levy-Lahad, MD

Background: In Ashkenazi Jews (AJ), testing three common BRCA1/2 mutations fulfills WHO population screening criteria. We compared streamlined BRCA screening via self-referral to proactive recruitment in medical settings.

Methods: Unaffected AJs, age≥25 without known familial mutations, were either self-referred or recruiter-enrolled. Pre-testing, participants received written information and reported family history (FH). Post-testing, in-person genetic counseling was provided to non-carriers with significant FH and to carriers. Psycho-social questionnaires were self-administered one week and 6 months post-enrollment.

Results: Of 1771 participants, 58% were recruiter-enrolled and 42% were self-referred. Screening uptake was 67%. Recruiter-enrollees were older (mean age 54 vs. 48, p<0.001) and fewer had suggestive FH (23% vs. 33% p<0.001). Of 32 (1.8%) carriers identified, 40% had no significant FH. Post-test counseling compliance was 100% in carriers and 89% in non-carriers with FH. All groups expressed high satisfaction (>90%). At 6 months, carriers had significantly increased distress and anxiety, greater knowledge and similar satisfaction. 90% of participants would recommend general BRCA screening in AJ.

Conclusion: Streamlined BRCA screening results in high uptake, very high satisfaction and no excess psychosocial harm. Proactive recruitment captured women less selected for FH, but older. Further research is necessary to target younger women and assess other populations.

Deciphering the Mechanistic Relationship between CTG Expansion, Hypermethylation and SIX5 Reduction in Myotonic Dystrophy Type 1 Using Mutant Human Embryonic Stem Cells

Shira Yanovsky-Dagan*[1]*, Michal Avitzour*[1]*, Gheona Altarescu*[2]*, Paul Renbaum*[2]*, Talia Eldar-Geva*[3]*,Oshrat Schonberger*[3]*, Stella Mitrani-Rosenbaum*[4]*, Ephrat Levy-Lahad*[2]*, Ramon Y. Birnbaum*[5]*, Lior Gepstein*[6]*, Silvina Epsztejn-Litman*[1]*, and Rachel Eiges*[1]*

[1]Stem Cell Research Laboratory, Medical Genetics Institute, [2]Zohar PGD Lab, Medical Genetics Institute, [3]IVF Unit Shaare Zedek Medical Center affiliated with the Hebrew University School of Medicine, Jerusalem 91031, Israel. [4]Goldyne Savad Institute for Gene Therapy, Hadassah Hebrew University Medical Center, Jerusalem 91240, Israel. [5]Department of Life Sciences, Ben-Gurion University of the Negev, Beer Sheva 84105, Israel. [6]Sohnis Family Research Laboratory for Cardiac Electrophysiology and Regenerative Medicine, Bruce Rappaport Faculty of Medicine,Technion-Israel Institute of Technology, Haifa 31096, Israel.

Myotonic dystrophy type 1 (DM1) results from CTG repeat expansions in the 3`UTR of the myotonic dystrophy protein kinase (DMPK) gene. The CTG expansion commonly results in hypermethylation and reduced expression of the downstream neighbor gene, SIX5. The contribution of hypermethylation to the disease pathogenesis is poorly understood, nor are the mechanisms by which SIX5 expression is reduced. Here we characterized DNA methylation upstream of the CTG repeats in mutant human embryonic stem cells (HESCs), and explored its potential role in regulating local gene transcription. Using a wide range of DM1-affected HESCs (14 cell lines), as well as DM1-affected iPS cells, we identified a disease-associated differentially methylated region (DMR) upstream to the CTG repeats that abnormally gains methylation in a way that strongly correlates with expansion size and coincides with the reduction in SIX5 expression. This association, which is most pronounced in undifferentiated cells, is recapitulated in in vitro derived cardiac muscle cells; disease relevant cell types. Using in vitro and zebrafish enhancer assays, we provide evidence for the enhancer activity of the DMR, and demonstrate that this function is lost by the gain of abnormal methylation. Taken together, this study is the first to describe a disease associated DMR that functions as an exon coding sequence (DMPK) in addition to an epigenetically regulated enhancer (SIX5), whose activity is hampered by a heritable mutation (CTG expansion). In addition and more generally, this study emphasizes the power of mutant HESCs in advancing our understanding of the mechanisms underlying heritable epigenetically regulated conditions.

Establishment of Homozygote Mutant Human Embryonic Stem Cells by ParthenogenesiS

Silvina Epsztejn-Litman1, Yaara Cohen-Hadad[1], Shira Aharoni1, Gheona Altarescu[2], Paul Renbaum[2], Ephrat Levy-Lahad[2], Oshrat Schonberger[3], Talia Eldar-Geva3, Sharon Zeligson[2], Rachel Eiges[1*]

[1]Stem Cell Research Laboratory and [2]Zohar PGD Lab, Medical Genetics Institute, [3]IVF Unit, Shaare Zedek Medical Center affiliated with the Hebrew University School of Medicine, Jerusalem, Israel.

We derived of a diploid 46(XX) human embryonic stem cell (HESC) line that is homozygous for the common deletion associated with Spinal muscular atrophy type 1 (SMA) from a pathenogenetic embryo. By characterizing the methylation status of three different imprinted loci (MEST, SNRPN and H19), monitoring the expression of two parentally imprinted genes (SNRPN and H19) and carrying out genome-wide SNP analysis, we provide evidence that this cell line was established from the activation of a mutant oocyte by diploidization of the entire genome. Therefore, our SMA parthenogenetic HESC (pHESC) line provides a proof-of-principle for the establishment of diseased HESC lines without the need for gene manipulation. As mutant oocytes are easily obtained and readily available during preimplantation genetic diagnosis (PGD) cycles, this approach should provide a powerful tool for disease modelling and is especially advantageous since it can be used to induce large or complex mutations in HESCs, including gross DNA alterations and chromosomal rearrangements, which are otherwise hard to achieve

Marked Differences In Hypermethylation Between C9/Als-Ftd Hesc Lines And Patient-Derived Ips Cells

Yaara Cohen[1], Gheona Altarescu[2], Talia Eldar-Geva[3], Ephrat Levi-Lahad2, Ming Zhang[4], Ekaterina Rogaeva4, Gotkine, Marc[5], Silvina Epsztejn-Litman1 and Rachel Eiges[1*]

[1]Stem Cell Research Laboratory and [2]Zohar PGD Laboratory, Medical Genetics Institute and [3]IVF Unit, Shaare Zedek Medical Center affiliated with the Hebrew University School of Medicine, Jerusalem 91031, Israel. [4]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, ON MSS 3H2, Canada. [5]Department of Neurology, Hebrew University-Hadassah Medical Center, Jerusalem 91120, Israel.

The leading known cause of Amyotrophic lateral sclerosis (ALS) and/or frontotemporal degeneration (FTD) is a G4C2 repeat expansion in the first intron of C9orf72 (termed C9 mutation), between noncoding exons 1a and 1b This mutation can manifest as ALS, FTD or a combined phenotype (ALS-FTD) and accounts for 20%-80% of familial and 5%-15% of sporadic ALS and FTD cases. While in most people the number of G4C2 repeats is steady and varies between 2 to 19 units, in ALS-FTD it abnormally expands to over 30 copies and becomes increasingly unstable. The mechanism by which the C9 mutation leads to selective death of neurons is unknown.

We established two human embryonic stem cell lines (SZ-ALS1, SZ-ALS3) with the GGGGCC expansion with nearly 300 repeats (G9 mutation). The embryos, which were obtained through preimplantation genetic diagnosis (PGD), were donated by a couple in which the mother was an expansion carrier (30 yrs-old). Our newly established C9/ALS-FTD HESC lines display key features of pluripotent cells; namely unrestricted growth in culture, expression of undifferentiated cell specific markers and potential to differentiate into a wide range of cell types by forming teratomas. In addition, we have generated iPS cells (more than 15 different clones) from a skin biopsy of the yet asymptomatic mother, and compared methylation levels upstream to the GGGGCC repeats in the iPS clones with that of HESC, blood and fibroblast cell counterparts. Interestingly, we find that the iPS cells are unusual in their hypermethylation levels. While the HESC, blood and fibroblasts are completely unmethylated, methylation is at its maximum in the iPS cells (50% in all examined clones representing levels of 100% on the mutant allele), indicating that direct cell reprogramming incorrectly hypermethylates this region as a consequence of the mutation. To further substantiate these findings and examine whether methylation is elicited with age or disease symptoms, we also generated iPS cells from a 65 year old C9/ALS patient in whom disease commenced 2 years ago. Here again, we observed dramatic gain of aberrant methylation (50% in all clones) as a consequence of cell reprogramming. Hypermethylation was not associated with age or manifestation of the disease. Taken together, our findings suggest that hypermethylation in C9/ALS-FTD is normally gained later during development, and that direct cell reprogramming may inappropriately enhance abnormal methylation in C9orf72.

Operating a Monitoring Unit in the Geriatric Department: Impact on Outcome

Abram Abramovitch, MD,[1,2] Reuven Friedmann, MD,[1*] Shoshana Zevin, MD,[3] Amos M. Yinnon, MD[2] and David Raveh-Brawer, MD[4]

Department of Geriatrics,[1] Division of Internal Medicine,[2] Department of Medicine B[3] and Bioinformatics Unit,[4] Shaare Zedek Medical Center, affiliated with the Hebrew University-Hadassah Medical School, Jerusalem, Israel. *equal first contributor

Background: Due to increasing numbers of elderly and/or seriously ill patients, there is growing demand for limited intensive care unit beds. Consequently, many hospitals have established monitoring units (MU) in their medical departments. In 2014 a 5-bed MU was opened in our acute geriatric department. We are unaware of the presence of an MU in another acute geriatric department.

Purpose: To determine outcome of consecutively admitted patients in this geriatric MU compared with that of two control groups.

Methods: We enrolled all patients, hospitalized ≥24 hours in the geriatric MU during a 5-month period, compared with two control groups: (1) patients admitted to geriatric departments, matched at a ratio of 1:2, according to three criteria: gender, age ±5 years and need for mechanical ventilation; (2) all patients admitted to the medical MU during the same time interval. The primary endpoint was the admission survival rate.

Results: During the study period all 89 patients admitted to the Geriatric MU were enrolled, 178 control patients admitted to the geriatric department and all 95 patients in the Medical MU. There were no significant differences between the first two groups, except for a higher incidence of bi-level airway-positive non-invasive (BIPAP) ventilation [18 (20%) vs 8 (5%), p=0.009] and of acute renal failure [39 (44%) vs 26 (15%], p<0.001) in the geriatric MU patients. The Geriatric MU patients were significantly older (82.2±9.6 vs 68.2±14.4, p<0.001) than the Medical MU patients. The predicted death rate of the Geriatric MU group, Medical MU group and department control group was respectively, 49±26, 39.6±27 and 36.7±27 (respectively p=0.02 and <0.001). The observed in-hospital mortality rate of Geriatric MU patients was higher (40, 44.9%) than that of the department control group (48, 27%)(p=0.002). Correction with the Standard Mortality Ratio (SMR), which divides the observed by the predicted death rates, demonstrated the complete cancellation of the difference between these groups, indicating that the more severely ill geriatric MU patients did relatively better than the department control patients, in particular patients requiring hemodynamic pressure support and those with acute renal failure.

Conclusions: For elderly and/or severely ill patients for whom an intensive care unit bed is unavailable, care in a monitoring unit in the acute geriatric department leads to improved overall outcome for subsets of patients, including hemodynamic instability and acute renal failure.

Can procalcitonin contribute to the diagnosis of Clostridium difficile colitis?

D.S. Shapiro, MD,[1] R. Friedmann, MD,[1*] A. Husseini, MD,[1] H. Ivgi, PhD,[2] A.M. Yinnon, MD,[3,4] and M.V. Assous, MD, PhD[2]

Department of Geriatrics,[1] Clinical Microbiology and Immunology Laboratory[2] Infectious Disease Unit and Division of Internal Medicine,[3] Shaare Zedek Medical Center, affiliated with the Hebrew University Hadassah Medical School, Jerusalem, Israel. *Equal first contributor

Background: Procalcitonin (PCT) is normally not secreted into serum, but during bacterial infections high serum levels can be detected. We aimed to determine, among patients who develop nosocomial diarrhea, whether serum PCT can distinguish between Clostridium difficile toxin (CDT)-positive and -negative patients.

Methods: The study was prospective, comparative and non-interventional. Included were adults (≥18), who developed nosocomial diarrhea. The study group included patients with a positive fecal test for CDT, the control group patients with a negative CDT test. Included were 50 consecutive patients who developed diarrhea during hospitalization: 25 patients were CDT positive (study group) and 25 patients were CDT negative (controls).

Results: Baseline demographic and underlying illnesses were similar in both groups, and so were number of diarrheal stools/day and maximal fever. Duration of diarrhea was 6±4 days and 3±1 in the study and control groups, respectively (p=0.001); mean blood count was 20±15 and 9.9±4, respectively (p=0.04). CRP level was higher in the study than control group (10.9±7.4 and 6.6±4.8, p=0.028). PCT level was higher in the study group (4.4±4.9) compared with the controls (0.3±0.5) (p=0.102); a PCT level >2 ng/mL was found in 7/25 patients (28%) and 1/25 (4%) respectively (Odds Ratio 9.33, 95% CI 0.98 to 220, P=0.049). Multivariate analysis showed that only duration of diarrhea and left shift of peripheral leucocytes were significant indicators of CDT (p=0.014 and p=0.019, respectively). The mortality rate was 12/25 (48%) versus 5/25 (20%), respectively (p=0.04).

Conclusion: We found a non-significant tendency to higher PCT levels in patients with CDT-positive versus CDT-negative nosocomial diarrhea. However, a PCT level >2ng/mL may help distinguish between these patients.

Novel genetic changes in Autosomal dominant, ACTH independent macronodular adrenal hyperplasia associated with hypercortisolism and giant adrenals

Munter G[1], Beeri R[2], Altarescu G[2], Weiss R[2], Berthon A[3] and Stratakis C[3]

[1]Internal Medicine C and Endocrine Unit, Shaare Zedek Medical Center affiliated with Faculty of Medicine-Hebrew University, Jerusalem

[2]Genetics Department, Shaare Zedek Medical Center affiliated with Faculty of Medicine-Hebrew University, Jerusalem

[3]Section on Endocrinology and Genetics (SEGEN), Program on Developmental Endocrinology and Genetics (PDEGEN), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Bethesda, MD, USA.

ACTH independent macronodular adrenal hyperplasia (AIMAH) is a rare cause of Cushing's syndrome. Both Phosphodiesterase 11A4 (PDE11A4) mutations and inactivating mutations of armadillo repeat containing 5(ARMC5) have been associated with familial AIMAH. A family with autosomal dominant AIMAH was studied trying to elucidate the involved genetic basis.

Methods and results: Adrenal hypercortisolism with giant bilateral AH was diagnosed in three adult members of the family, a mother and two sons. Further evaluation excluded the presence of aberrant receptors. Bilateral adrenalectomy of the index case was performed showing huge adrenal glands (460 gr). DNA were extracted from peripheral blood lymphocytes. Sequencing of ARMC5 coding region in the proband revealed a novel heterozygote mutation, S767X. Interestingly, sequencing of PDE11A4 coding region revealed a heterozygote rare variant R867G, that has frequency of 2-3% in the general population. PDE11A4 gene defects have been associated with Carney complex and AIMAH, including R867G, probably acting as a phenotype modifier. Inmunohistochemical studies of the excised adrenal tissue showed a very low expression of PDE11A4 and ARMC5 compared to normal adrenals. The family was screened for hypercortisolism, adrenal hyperplasia (MRI) and genetic testing. All the patients with AIMAH carried both variants. Other siblings carrying either one mutation or none were healthy, with normal adrenal size. A 15 years old daughter of the index case harbored both variants, but her HPA axis evaluation was normal and the adrenals showed a normal size.

Conclusions: A family with ADAIMAH causing giant adrenal hyperplasia associated with a novel mutation in ARMC5 in conjunction with PDE11A4 mutation, causing low protein expression is reported. Coexistence of PDE11A4 variant in all three affected individuals may indicate a phenotype modifier role. Because clinical and biochemical abnormalities appear during adulthood, young phenotypically normal mutation carriers may be at risk of developing clinical disease in the future.

Hypernatremia And Copeptin Levels In The Elderly Hospitalized Patient

Michal Liber MD[1], Moshe Sonnenblick MD[1], Gabriel Munter MD[2]

Geriatric Department[1], Shaare Zedek Medical Center, affiliated with the Hebrew University-Hadassah Medical School Jerusalem, Israel.

Internal Medicine C and Endocrine Unit[2], Shaare Zedek Medical Center, affiliated with the Hebrew University-Hadassah Medical School, Jerusalem, Israel.

Introduction/Objective: Elderly patients have a higher prevalence of hypernatremia compared to the rest of the population. The aim of this study was to find demographic and clinical characteristics of the elderly hypernatremic patient hospitalized in the internal medicine/geriatric ward, and to further/better understand the role of ADH secretion in the pathogenesis of hypernatremia.

Design: Case-control study

Setting: Internal Medicine/Geriatric ward in a University affiliated hospital.

Participants: 33 elderly hypernatremic patients (admission sodium>150 meq/l, age>70) compared to 34 normonatremic patients.

Measurements: Demographic, functional (mental status and ADL) and clinical data (APACHE II score) were collected at admission. Serum Copeptin levels were obtained 48 hours from admission. Mortality and change in the functional status were followed up to 30 days from discharge.

Results: Patients with hypernatremia presented with significantly lower baseline functional and cognitive states and higher APACHEII score (21.3 ±8.6 vs. 15.4 ±6.7, P<, 0.01). Mortality within 30 days of discharge was higher in the hypernatremic group (58% vs. 32%, P<0.05). Higher Copeptin levels were found in the hypernatremic group compared to the normonatremic group (100.2±60.6 pmol/L vs. 66.5±57.2 pmol/l, P<0.05). High levels of Copeptin were associated with higher in hospital (P<0.05) and 30 days mortality (P<0.01). Sodium levels were found correlated to Copeptin levels; yet, an even stronger correlation was demonstrated between Copeptin levels and Apache II score(r= 0.52, p<0.001).

Conclusions: Hypernatremia in the elderly at admission is associated with a high rate of mortality. Copeptin level in the elderly seems to be a good single disease severity marker.

Does acute urinary tract obstruction cause transient proteinuria?

I. Alexandrovich[1], *D.S. Shapiro*[1], *M. Sonnenblick*[1], *R. Friedmann*[1] *L. Shavit*[2]

Department of Geriatrics[1] and Adult Nephrology Unit [2]Shaare Zedek Medical Center, Jerusalem, Israel

Background: Transient proteinuria has been described in 4% of men and 7% of women in association with febrile disease, vigorous exercise and symptomatic urinary tract infection (UTI). Although the mechanisms of this phenomenon remain incompletely understood, it is believed to be mediated by humoral-induced alterations in glomerular permeability and probably proximal tubular dysfunction. Current knowledge supports the possibility that urinary tract obstruction (UTO) can induce tubular injury and the hypothesis explored in this study is that relief of acute UTO can cause significant but transient proteinuria. The aims of this study were to determine (1) whether patients with UTO have higher incidence/severity of proteinuria compared with controls and (2) whether proteinuria resolves spontaneously at short term follow up.

Methods: This is a prospective, matched case-control study that included patients who were hospitalized in the internal medicine and geriatric departments of Shaare Zedek Medical Center from January 2012 to February 2016. A total of 100 patients were studied, of which 50 had acute UTO, and 50 had urinary indwelling catheter without urinary retention. Patients with UTI were excluded. Proteinuria was quantified using two to three consecutive 24 hour urinary collections and its prevalence, severity, and quantative changes during a week of in hospital stay were compared between the study groups.

Results: There were no statistically significant differences between the groups in age (83.12± 7.94 versus 84.48±9.39 (p=0.44)), major comorbidities, chronic medical treatment and causes of hospitalization. Pathological proteinuria (defined as 24 hour total protein excretion > 140 mg/day) was observed in 100% of patients with UTO and 94% of control group. No patients with nephrotic range proteinuria were detected. Average quantity of urinary protein was similar between groups (638.07±419.69 vs 620.99±639.57, 828.43±743.15 vs 648.69±741.48, and 728.30±944.76 vs 732.80±841.8 in first, second and third collections respectively, p=0.88, p=0.23, p=0.99). In addition, quantity of urinary protein did not change during a week of follow up in neither study groups (p =0.19 for trend).

Conclusion: This study demonstrates a very high prevalence of significant but not nephrotic range proteinuria in a cohort of elderly patients with acute illness and multiple comorbidities. Urinary retention does not increase the prevalence or severity of proteinuria, and proteinuria does not resolve after releif of UTO during a short term follow up. However, future study with longer follow up period is needed to determine the transient nature of proteinuria following urinary retention.

Prevalence and possible risk factors for prolonged admissions in medical departments

Friedmann R, Pavlov N, Raveh-Brawer D, Yinnon AM and Henshke-Bar-Meir R.

Department of Geriatrics and Internal Medicine, Shaare Zedek Medical Center.

Background: Prolonged hospitalization (PH) increases the rate of complications and is associated with significant additional expense.

Study objectives: to determine the causes and predictors for prolonged hospitalization.

Methods: We defined prolonged hospitalization (PH) as< 70th percentile of the average duration of stay. The study included patients from two medical departments and the acute geriatric ward. Demographic and clinical data were collected on admission, in order to determine predicting factors for PH. Actual causes for PH were tested for all patients by two methods: firstly, with an interview of the attending physician (using a structured questionnaire) on the fourth day of admission, and secondly, by reviewing the patients' medical records using a validated tool.

Results: During the 5-month study period, data were collected for 1092 patients hospitalized in the two medical wards and one geriatric department; 336 (30%) met the definition of prolonged hospitalization (PH). Multivariate indicators of PH included: (1) patients who are not married (Odds Ratio 1.3, 95% CI 0.17-.070, p<0.01); (2) admission to the geriatrics ward versus medical departments, even though the latter departments also admit mostly elderly patients (OR 2.7, 1.5-4.7, p<.001 ;((3) a diagnosis of malignancy (OR 0.5, 0.29-0.99, p<0.05), chronic renal failure (OR 1.5, 1.1-2.2, p<0.05) or infectious disease on admission (OR=1.5, CI 1.1-2, p<0.05) (4) hospitalization in the previous six months (OR=1.5, CI 1.1-2, p<0.01). Cardiopulmonary resuscitation prior to or in hospital was not an independent predictor of PH Being bedridden and dependent and having a high expected mortality rate (according to the Mortality Probability Models (MPM II), an extensively studied and validated score), were not found to be indicators of PH.

The attending physicians received a structured interview on the fourth day of the admission; their assessment of the patients on that particular day was compared with the actual outcome, i.e. regular or prolonged admission. The main reason for extended admission was incomplete recovery of the principal disease leading to the current hospitalization (286, 85%) as compared to 139 (93%) in the control group with non-extended duration of admission (p=0.014). Nosocomial complications were more frequent in the patients with prolonged admissions (46, 14%) than among patients with non-extended stay (16, 11%)(NS). Similarly, waiting for a consultation or investigation was more common among patients with extended stay (15, 4%) than among patients with non-extended stay (3, 2%) (NS). Overall, 23 (7%) of the prolonged admissions were ascribed to non-medical reasons (i.e. waiting for transfer to a chronic care facility) compared to only 2 (1%) for patients with non-extended care (p=0.018).

Conclusion: this study found independent demographic and clinical predictors for prolonged hospitalization already on admission. In addition, causes for prolonged admissions were described, both qualitatively and quantitatively and some of the non-medical causes should be targeted for remedial action.

Are There Evidences For Harm In Tube Feeding In Patients With Advanced Dementia?

Reuven Friedmann MD. Geriatrics Department, Shaare Zedek Medical Center.

The question whether to sustain life of a patient with advanced dementia by tube feeding is a serious ethical one, and as long as there are no real evidences that can clearly show harm versus benefit by the physical data obtained by controlled studies, the judgment should be only by ethical arguments.

The Wisely Workgroup of the American Geriatric Society suggested not recommending tube feeding for a patient with advanced dementia. They recommended engaging individuals and caregivers in discussions which examine the evidence base of the procedure. But their recommendation rely on non-controlled studies, which seems to target their results towards the desired end point; to withhold tube feeding in the patient with advanced dementia, which can be accepted when discussed on ethical basis only.

Most of the studies on which these recommendations rely on ignore some crucial points:

The methods of tube feeding defer when comparing nasogastric tube with percutaneous endoscopic gastrostomy (PEG) tube by many means (e.g. aspiration, restrain, metabolic improvement), but most of the studies cited did not make this distinction, and therefore their results show bad outcomes.

At least two controlled studies showed significant better outcome for patients in whom the PEG was inserted while otherwise stable medically, compared with those whose PEG insertion was done during a hospitalization due to acute illness. The PEG insertion for the patients in the study which showed worse result in pressure sores healing or prevention, were all hospitalized for an acute disease at that time. There are no details about this point in the control hand fed group.

Were the patients with tube or hand feeding in the deferent studies really comparable? Why the patients with PEG did had tube feeding, and why were the patients with hand feeding fed orally? Not because they defer in their feasibility in oral feeding? The survival rate of 79.9% in 180 days in the orally fed group obviously shows that in this group oral feeding is feasible!!!

It is suggested to leave the debate about tube feeding in the patient with advanced dementia to ethical debate only, till there will be real controlled studies.

Autologous transplant, and not ATO alone, remains the preferred therapy for relapsed APL: a report from the CIBMTR, Acute Leukemia working party of the EBMT and two specialized centers

Ganzel C[1], Mathews V[2], Alimoghaddam K[3], Ghavamzadeh A[3], Kuk D[4], Devlin S[4], Wang H[5], Zhang M-J[6],Weisdorf D7, Douer D[4], Rowe JM1, Estev J[8], Nagler A[9], Mohty M[10], Tallman MS[4]

[1]Shaare Zedek Medical Center, Jerusalem, Israel[2] Christian Medical College & Hospital, Vellore, India[3] Shariati Hospital, Tehran, Iran[4] Memorial Sloan Kettering Cancer Center, New York, New York [5]CIBMTR Statistical Center, Milwaukee, Wisconsin [6] Medical College of Wisconsin, Milwaukee, Wisconsin [7]University of Minnesota, Minneapolis, Minnesota [8] Hospital Clinic, Institut d'investigacions biomediques August Pi i Sunyer, Barcelona, Spain [9]Sheba Medical Center, Ramat Gan, Israel [10]Saint-Antoine Hospital and University Pierre & Marie Curie, Paris, France

Introduction: Despite its favorable prognosis, 10-20% of APL patients relapse with contemporary therapeutic strategies. At relapse, reinduction therapy is often followed by autologous hematopoietic cell transplantation (auto-HCT). In the last two decades, arsenic trioxide (ATO) has become part of the standard reinduction regimens. Such an approach is often followed successfully by auto-HCT. However, long-term survivors have also been reported after ATO treatment alone without HCT. We retrospectively compared the outcome of auto-HCT, with or without ATO, and ATO-based therapy given alone following relapse in patients with APL.

Patients and Methods: Data on APL patients in first relapse were collected from the two largest transplant registries (CIBMTR, EBMT) and two specialty referral centers (Hematology-Oncology & Stem Cell Transplantation Research Center, Shariati Hospital, Tehran and Christian Medical College & Hospital, Vellore, India). The outcome of patients who received ATO at relapse and did not undergo transplantation was compared to that of patients who received any reinduction therapy, including ATO and subsequent auto-HCT. Overall survival was calculated from two months post relapse with left truncation at date of CR2 for patients receiving ATO alone and date of transplant for those receiving auto-HCT. Cox proportional hazard regression was used to estimate the univariate and multivariate associations with overall survival. Potential prognostic factors included age, disease risk based on WBC >10,000/µl, the presence of extramedullary disease, and duration of CR1, in addition to the primary comparison of auto-HCT and ATO-based reinduction therapy.

Results: 242 patients were identified, of whom 34 were excluded due to missing relapse date (n = 25), death or lost to follow-up before 2 months after relapse (n = 7), or receiving auto-HCT within two months of relapse (n = 2). The median age was 31, 63% of the patients were males and median WBC count at diagnosis was 4,750/µl. The final cohort of 208 patients included 68 receiving ATO alone and 140 receiving auto-HCT. The groups were comparable in terms of age, gender, duration of CR1 and risk group. Fifty-six percent of the auto-HCT patients received ATO-based treatment as salvage therapy and the others received various combinations of chemotherapy and ATRA.

There is a statistically significant survival advantage for the HCT group (HR = 0.34 (0.27-0.42) , p<0.001) compared to the ATO only group. At 5 years, OS was 42% (95% CI: 31% - 58%) and 78% (95% CI: 71% - 86%) for the ATO-only and HCT groups, respectively. In addition, there was a significant OS association with longer duration of CR1 (p=0.002) and presence of extramedullary disease (p = 0.041); which remained significant in a multivariate model (p < 0.001). Disease risk at diagnosis was not associated with OS.

Conclusions: These data suggest that auto-HCT results in improved OS after APL relapse, better than ATO-based therapy alone. Further studies to identify improvements in auto-HCT and which patients treated with ATO alone may be cured are needed.

In Philadelphia-Chromosome-Negative Acute Lymphoblastic Leukemia, Late Relapses are Not Uncommon, Occur Mostly in Patients at Standard Risk and Have a Relatively Favorable Outcome. Results of the International ALL Trial: MRC UKALLXII/ECOG-ACRIN E2993

Chezi Ganzel1, Xin Victoria Wang2, Adel K Fielding5, Jacob M. Rowe1,3, Susan M. Richards6. Georgina Buck6, Rajesh Chopra, I. Jill Durrant, David I. Marks, Ian M. Franklin, Andrew K. McMillan, Mark R. Litzow7, Elisabeth M. Paietta8, Selina M Luger9, Peter H. Wiernik10, Dan Douer11, Hillard M. Lazarus12, Martin S. Tallman13, Anthony H. Goldstone4

Background: Late relapse in acute leukemia is considered a relatively rare event but information regarding adult acute lymphoblastic leukemia (ALL) patients is scarce. Data are presented from one of the largest prospective adult ALL studies, the MRC UKALLXII/ECOG E2993, to evaluate the rate and characteristics of late relapse in ALL. For this purpose, late relapse was defined, arbitrarily, as relapse 3 years post achievement of complete remission (CR).

Methods: The UKALLXII/ECOG E2993 was an international ALL trial. All patients received identical induction therapy. Patients with a sibling donor were assigned to receive an allogeneic hematopoietic stem cell transplant (HSCT); all others were randomized to undergo an autologous transplant or protracted standard consolidation/ maintenance therapy. For this report only patients registered before the tyrosine kinase inhibitors era are included in the analysis.

Results: 1518 study patients were eligible for this analysis, 1208 (79.6%) Philadelphia-chromosome negative (Ph-neg) and 267 (17.5%) Philadelphia-chromosome positive (Ph-pos). 1381 (91%) of the patients achieved CR; 93% of the Ph-neg and 82% of the Ph-pos. 572 patients (37.7%) underwent allogeneic HSCT. The median duration of follow-up of patients who achieved CR was 10 years. Among the 1381 patients who achieved CR, 626 (45.3%) had a documented relapse; 566 (90.4%) relapsed within 3 years of CR and 60 (9.6%) relapsed beyond 3 years ('late relapse'). Among these 60 patients, 18 (2.9%) relapsed after 5 years.

Patients	n	CR	All relapses	Relapses < 3 years	Relapses ≥ 3 years	Relapses ≥ 5 years
All patients	1518	1381 (91%)	626 (45.3%)	566 (90.4%)	60 (9.6%)	18 (2.9%)
Ph-neg	1208 (79.6%)	1123 (93%)	485 (40.1%)	429 (88.5%)	56 (11.5%)	17 (3.5%)
Ph-pos	268 (17.5%)	219 (82%)	124 (56.6%)	122 (98.4%)	2 (1.6%)	1 (0.8%)

Relapse beyond 3 years occurred in 4.3% of all who achieved CR, in 5% of Ph-neg and 0.01% of Ph-pos patients. Among the 60 late relapses, the median time to relapse was 46 months. 61.7% of the late-relapse patients were males, median age was 32 years, 88.3% were B-lineage ALL and the median white cell count at diagnosis was 6000/ul. 56.7% were in cytogenetic standard risk, 8.3% at high risk and the data of 35% are unknown. The median survival for the late relapse patients was longer than for those who relapsed within 3 years.

	Relapse > 3 years	Relapse > 3 years
Median survival from relapse (months)	5.4	11.2
3-year OS from relapse	6.5%	29%
5-year OS from relapse	5.6%	19%

Conclusions: Late relapses in adults with Ph-neg ALL are not uncommon. About 10% of relapses occur beyond 3 years and 4.3% of all ALL patients who achieved a CR can expect to have a late relapse. Most of the late relapse patients were at standard risk and appeared to have a relatively favorable outcome post relapse. Patients with ALL, particularly those who are Ph-neg, cannot be considered as cured at 3 years and need to be closely followed.

Is mother's height a risk factor for hip dysplasia (DDH)? 1 year risk study

Grossman, M R.N M.A, Amitai, Y MD Lebel E MD

Background: Developmental dysplasia of the hip (DDH) leads to instability or dislocation of the hip and occurs in 1-5 newborns of 1000 live-births. The natural course of the disease leads to degenerative changes of the hip joint resulting in shortening of the limb, limited movement, limping, pain and requiring corrective surgery and at times total hip replacement. Currently, early diagnosis is based on physical examination and ultrasound imaging of the hips. Early diagnosis and treatment is essential in order to avoid late complications. Delay in diagnosis might have an important impact on the cost of the health care because of the need for further complex interventions. The etiology of DDH is unknown but several risk factors are recognized: familial history, female gender, breech presentation, first vaginal delivery, oligohydramnios, skeletal malformations or deformations and overweight babies. Antropometric measures of the mother vs. baby are currently not considered a risk factor for DDH although it may influence the size of uterus and pelvis and thus mechanically affect the fetus.

Purpose: This study was designed to evaluate the correlation of mother's height, ratio between mother's height/ newborn's weight and the occurrence and severity of DDH.

Methods: the study was conducted at the pediatric-hip clinics in the Shaare Zedek Medical Center (Jerusalem). Diagnosis of DDH was based on physical examination and Graf-method hip sonography. Evaluation was performed by orthopedists qualified for this exam. The study was approved by the IRB (Helsinki committee) of Shaare Zedek Medical center. During a period of one year, all mothers (bringing their babies to the clinic) were invited to participate in the study and were asked to sign a written. After receiving consent, data were prospectively recorded regarding the pregnancy, delivery, and risk factors for DDH, mother height, and the newborn birth weight. Criteria for inclusion were: term-born babies (>36 weeks), birth-weight >2500 gr. and singleton delivery. All confidential medical data was handled as directed by medical-confidentiality rules.

Data collection and processing was done by Excel and SPSS 17.0 software. Analysis included multivariate analysis of all the risk factors (mother's height, newborn weight and the ratio of the mother's height/newborn's weight), Student-t test for independent samples, odds-ratio and Chi-square test for dichotomy variables. ANOVA and multivariate regression was used to evaluate prediction values of each risk factor for DDH. The effect of mother's height on DDH was evaluated by Spearman's test.

Results: During the study period, 203 babies were evaluated in the clinic. Forty two were excluded due to prematurity, low birth-weight or twins' delivery. The mothers of 161 babies were included. DDH was diagnosed in 63 (39%) and hips were found normal in 98 (61%) babies.

Significant correlation was found between mother's height and the occurrence of DDH ($P<0.05$). As a threshold height of <154 cm was set, a significant risk factor for the occurrence of DDH was also found ($p<0.05$). Degree of DDH was more severe and correlated with lower mother's height ($p<0.05$). Also, mothers of babies with bilateral DDH were found to be significantly shorter ($p<0.05$) than mothers of babies with unilateral disease. In evaluation of the classical risk factors, positive family history, female gender, and first vaginal delivery, were found significant, whereas breech presentation, oligohydramnios, click, and lower limbs deformation were not found significant risk factors for DDH.

Conclusions and recommendations: Short maternal height was demonstrated in the current study as a significant risk factor for DDH. Screening for DDH is based on detection of newborns that have specific risk factors. These factors may be divided into genetic and mechanical factors. The current study demonstrates increased risk for DDH in babies born to shorter mothers, and supports the inclusion of low mother's height (<154 cm) as a risk factor for DDH. Further studies should be performed on these findings.

North American Leukemia, Intergroup Phase III Randomized Trial of Single Agent Clofarabine As Induction and Post-Remission Therapy, and Decitabine As Maintenance Therapy in Newly-Diagnosed Acute Myeloid Leukemia in Older Adults (Age ≥60 Years): A Trial of the ECOG-ACRIN Cancer Research Group (E2906)

Prof. Jacob M. Rowe, Dr. Tami Granot, Hematology Department, SZMC

Background: Induction therapy with daunorubicin (Dauno) & cytarabine (Ara-C) (DA) has been the standard of care for eligible older adults (age ≥ 60 years) with newly diagnosed acute myeloid leukemia (AML) for over 2 decades. Single agent Clofarabine (CLO) induction & consolidation therapy has demonstrated important clinical activity in this age group in large phase II studies. Lower induction mortality (IM) & similar reported complete remission rate (CR) & overall survival (OS), as well as notable activity in those with higher risk disease features [including unfavorable cytogenetics, therapy-related AML (t-AML) & prior antecedent hematologic disorder (AHD)] raises the possibility that a non-Ara-C-based regimen could achieve similar or superior OS with lower toxicity.

Methods: We participated in a randomized United States Intergroup Phase III trial of single agent CLO [30mg/m2 x 5 days induction; 20 mg/m2 re-induction (if indicated) & 2 cycles Consol.] vs. standard DA therapy [Dauno 60mg/m2 D1-3 & Ara-C 100mg/m2 D1-7 induction x 1-2 cycles; 2 cycles Consol. with Ara-C (1.5g/m2 Q12hrs D1-6 age 60-69; once daily if age 70+)] in patients (pts) age ≥ 60 yrs with newly diagnosed AML. Patients with serum creatinine >1.0 (or GFR <60 mL/min) and those with AML-M3 and ECOG performance status >3 (PS>2 if age 70+ yrs) were excluded. Randomization was stratified by age (60-69 vs. 70+), t-AML, & AHD. Pts with HLA-matched donor were eligible for allogeneic transplantation (AlloHCT) after induction, and those completing Consol. were eligible for randomization #2 (R#2) to maintenance decitabine [20mg/m2 x 3D, monthly x 1 year] versus observation. With a target accrual of 747, E2906 was powered to determine non-inferiority [and possible superiority] of CLO vs. standard DA, and primary endpoint was OS. A weighted statistical analysis was performed to account for confounding impact of R#2. AlloHCT patients were censored at transplant in this analysis. Responses & cytogenetics were confirmed centrally and OS & CR rates were monitored by an independent Data Safety Monitoring Committee (DSMC) at pre-specified time points.

Results: As of Feb 23, 2015, 727 pts were randomized. Median age was 68 years (range 60-86); 57% were male, and 38% were age ≥70 yrs. Treatment arms are well balanced for all baselineclinical & AML characteristics, & 30% had unfavorable cytogenetics. Of 659 with complete treatment information reported, 30.4% on DA vs. 40.1% on CLO received 2 cycles of induction (p=0.006).

Median follow-up of surviving patients is 7.6 months.

374 pts have died (174, DA; 200, CLO) & significantly inferior OS was observed for CLO vs. DA [Hazard Ratio (HR) 1.41 (95% CI 1.12-1.78)] . Planned subgroup analyses were performed, demonstrating significant differences in OS after CLO for patients age 60-69 yrs, without AHD, & with intermediate risk cytogenetics; but not for those with Unfav. Cytogen. or t-AML. Based on the primary weighted analysis, DSMC recommended suspension of new accrual to E2906 on Feb 23, 2015 & all active patients on CLO were transitioned to DA Arm.

In SZMC, 22 pts enrolled to the study. 8 are alive and being followed for survival since 2012. 6 out of 8 had AlloHCT. 2 were randomized to the Decitabine arm.

Conclusions: Despite similar CR & IM, OS after single agent CLO is inferior to standard DA therapy for pts age ≥60 years with newly diagnosed AML who are fit for intensive therapy, and DA remains the standard of care. However no difference in OS was observed after CLO in some pre-specified high risk AML subgroups. R#2 & AlloHCT arms continue in E2906 for pts already enrolled. Embedded prospective minimal residual disease study at CR is being performed to identify pts at higher risk after CLO & DA.

Clinical manifestations, risk factors, and prognosis of patients with Morganella morganii sepsis.

***David Erlanger*[1], *Yonit Wiener-Well*[2], *Amos M. Yinnon*[3], *Marc V. Assous*[4], *Eli Ben-Chetrit*[2]**

[1]MD Thesis student, Technion - Israel Institute of Technology, Israel

[2]Infectious Disease Unit, Shaare Zedek Medical Center, affiliated with The Hebrew University, Israel

[3]Division of Internal Medicine, Director, Shaare Zedek Medical Center affiliated with the Hebrew University Hadassah Medical School, Jerusalem, Israel

[4]Microbiology and Immunology Laboratory, Head, Shaare Zedek Medical Center, Jerusalem, Israel

Background: There are only few studies of Morganella bacteremia, with small sample size and significant heterogeneity. The aim of this study was to evaluate risk factors, clinical and outcome data of patients with M. morganii bacteremia.

Methods: One hundred and thirty six patients diagnosed with M. morganii bacteremia were identified via the Shaare Zedek Medical Center database between 1998 and 2014. Control group patients with E. coli sepsis, were matched by year of diagnosis and acquisition site of infection. Clinical and outcome data was evaluated.

Results: Mean age and gender of both groups was similar. Complicated soft tissue infection was a more prevalent source of infection in the study group (30% versus 3.2%, p<0.001). Only 20% of the patients in the study group suffered from urinary tract infection (UTI), as compared with 40% in the control group (p=0.001). The mean (±SD) Charlson Comorbidity Index (CCI) was higher in the study group (4.3 ±2.5 versus 3.4±2.8, p=0.01). Appropriate empirical antibiotic treatment was given to 60% versus 82% of the study group and control group patients, respectively (p=0.001). Polymicrobial bacteremia was diagnosed in 44% of the study patients and in only 13% of the controls (p<0.001). The length of stay of patients in the study group was longer (25±22 versus 13.6±16 days, p<0.001). Of the M. morganii patients 57 (42%) died, compared with 31 (25%) of the control group (p=0.004). Multivariate analysis indicated no association between pathogen type and increased in-hospital mortality. However, a debilitative state, a CCI>4, septic shock and a clinical syndrome other than UTI were all significant risk factors for mortality (p<0.01).

Conclusions: Patients with M. morganii sepsis often suffer from more severe comorbidities and a worse degree of sepsis. In addition, there is an increased risk of inappropriate empirical treatment, longer hospitalization and higher death rate. Clinicians should suspect infection due to M. morganii in debilitative, septic patients with soft tissue infections and treatment with broad-spectrum antibiotics should be considered.

Streptococcus bovis new taxonomy - does subspecies distinction matter?

***Eli Ben-Chetrit*[1*], *Yonit Wiener-Well*[1*], *Livnat Kashat*[2,3], *Amos M. Yinnon*[3], *Marc V. Assous*[2]**

[1]Infectious Diseases Unit,

[2]Clinical Microbiology and Immunology Laboratory,

[3]Division of Internal Medicine, Shaare Zedek Medical Center affiliated with the Hebrew University Hadassah Medical School, Jerusalem, Israel. *Both authors contributed equally.

Background: Bacteremia with strains belonging to the former Streptococcus bovis/equinus complex is associated with hepatobiliary disease, colorectal lesions, and infective endocarditis (IE). This study addressed the clinical significance of subspecies distinction of previously designated S. bovis blood culture isolates according to the updated nomenclature.

Methods: During 2002-2013, blood culture isolates previously designated as S. bovis (biotypes I/II), were re-cultured. Isolates were identified using 16S rRNA gene sequencing and MALDI-TOF MS (Vitek MS, BioMerieux). Clinical data of patients aged ≥18 were reviewed retrospectively. A review of four recent series was performed as well.

Results: Forty blood isolates were identified using 16S rRNA sequencing: 26 bacteremic patients had S. gallolyticus ssp. pasteurianus (SGSP), 6 had S. gallolyticus ssp. gallolyticus (SGSG), 2 had S. gallolyticus ssp macedonicus (SGSM), and 6 had S. infantarius (SI) bacteremia. Speciation was done using Vitek MS and Biotyper (BioMerieux) MALDI-TOF technology in 37 and 36 samples, respectively, and was successful in all samples (100%). Subspecies identification was confirmed in 30 (83%) samples. The mean age of study patients was 74±17 with male predominance (65%). All subspecies were associated with colonic adenoma or polyps (eight patients, 20%). Definite or probable IE was diagnosed in 22 (59%) patients and was associated with all subspecies. Combining our results with those of four other series resulted in overall 320 bacteremic cases with either SGSM, SGSP, SI or SGSM. Eighty eight (28%) had colon pathology, and 66 (21%) had IE. SGSG was significantly more prevalent in cases of IE ($p<0.001$). Colon pathology was detected with all subspecies ($p=0.22$).

Conclusion: All 'bovis/equinus' complex subspecies were associated with colon pathology or IE. We therefore question the necessity of timely and expensive diagnostics such as 16S rRNA sequencing to attain definite subspecies distinction, since recovery of any subspecies in blood cultures mandates transesophageal-echocardiography and colonoscopy. Identification of pathogens, using MALDI-TOF technology, at the complex and subspecies level, was rapid and complete.

Prediction of Resistance to Intravenous Immunoglobulin in Children with Kawasaki Disease

***Maskit Bar-Meir, MD,MSc*[1,2], *Itai Kalisky,MD*[1], *Andrei Schwartz, ,MD*[3], *Eli Somekh, MD*[3,4], *Diana Tasher, MD*[3,4] ; Israeli Kawasaki Group

Background: Approximately 10-20% of patients are refractory to initial IVIg therapy, and these 'non-responders' are at higher risk of coronary artery abnormalities. Early identification of these patients, who may benefit from additional therapy is challenging. The aim of the present study is to identify predictors for IVIg resistance.

Methods: We reviewed clinical records of 312 consecutive KD patients from 9 medical centers in Israel (development dataset) and 186 patients from additional 5 centers (validation dataset). Using multivariate analysis we identified predictors of IVIg resistance. A third small prospective cohort of consecutive KD patients from a single medical center was used to test the accuracy of the predictors.

Results: Coronary artery abnormalities in the initial echocardiogram and presenting before day 5 of fever were independent predictors of IVIG nonresponse. Using either of these variables generated an area under the receiver-operating-characteristics curve of 0.7 (95%CI:0.6,0.77) . Sensitivity to predict non-response was 81% (95%CI:67,90) and specificity was 50% (95%CI:44,56) . Similar results were found in the validation dataset and in the small prospective cohort.

Conclusions: Two clinical predictors show high sensitivity in identifying IVIg nonresponders among our KD patients.

Methicillin-Resistant Staphylococcus aureus outbreak in the Neonatal intensive care unit- an epidemiological, clinical and molecular investigation

Rivka Birenbaum , Marc V. Assous and ***Maskit Bar-Meir***

Background: MRSA is an important nosocomial pathogen causing significant morbidity and mortality. An outbreak caused by this bacteria occurred between October 2009 and August 2010, in the Shaare Zedek Medical center neonatal intensive-care unit.

Methods: In this work we performed phenotypic and molecular characterization of the strains that caused the outbreak using spa typing and Multiple loci VNTR analysis. Additionally, we characterized the risk factors for MRSA infection in the NICU setting.

Results: Two MRSA strains were identified: the major strain, found in 93% of infected newborns, was identified as t008. The minor strain was identified as t002. The outbreak came to an end after diagnosing and treating a staff member that was a carrier of MRSA t008.

These two MRSA strains are the common strains prevalent in the community in Israel.

The main risk factors for infection were length of stay and antibiotic treatment prior to infection.

Conclusion: Routine surveillance cultures obtained from newborns and staff in the NICU and control measures including cohorting and isolation of carriers are important means to control outbreaks and even prevent them. Antibiotic stewardship may also reduce the risk of infection.

Morbidity among the Israeli Defense Force Response Team during Nepal, Post-earthquake mission, 2015.

Lachish T*[1]*, Bar A*[2]*, Alalouf H*[3]*, Schwartz E*[4]*.

[1]The Infectious Diseases Unit, Shaare-Zedek Medical Center, Jerusalem, Israel.

[2]Surgeon General Headquarters, Israeli Air Force, I.D.F.

[3] Military Public Health Department, I.D.F.

[4] The Center for Geographic Medicine, The Chaim Sheba Medical Center, Tel-Hashomer, Israel, And Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Background: On the 25th of April 2015, a 7.8 magnitude earthquake struck Nepal. Soon-after, the Israel Defense Force (IDF) dispatched a rapid-response team and within 96 hours from the onset of disaster already opened a full equipped tertiary field hospital in Kathmandu. Shaare-Zedek Medical Center Contributed a significant number of the medical personnel to this mission, including the Medical Director of the field hospital. There is limited data regarding the spectrum of diseases among rescue teams to disease stroked areas. The aim of this study was to assess the prevalence and spectrum of diseases during the mission of the IDF field hospital to Nepal, post-earthquake 2015.

Methods: The mission team included 260 soldiers and reserves, medical and non-medical staff (rescue and support teams). Pre-travel vaccinations were given to the entire team prior to departure. The field hospital was self-equipped including food and water supply with a self-serving kitchen, yet had a shortage of running water. A Public Healthcare team and Infectious Diseases physicians were present and active during the entire mission. A questionnaire based survey assessed the morbidities and risk-factors throughout the mission, among all staff members of the field hospital.

Results: 137 team members completed the questionnaire. Medical complaints or symptoms were recorded in 87of them (64%). The most common symptoms were gastrointestinal (53% of all responders, 84% of the 87 with symptoms). Respiratory symptoms were recorded in 16% and fever occurred in only 8% of all participants. Most symptoms were self-limiting and lasted between several hours to 3 days. There was no significant difference in the rate or spectrum of morbidity between the medical and the non-medical staff.

Conclusions: The Israeli field hospital was a stand-alone facility, with an active public health and Infectious Diseases team, yet 53% of its' staff suffered from gastrointestinal complaints. Prevention of morbidity and specifically of GI complaints upon arrival to a disaster stroked area in a developing country is difficult, especially when the living conditions are basic and there is a shortage of running water.

The Risk for Clostridium difficile Colitis during Hospitalization in Asymptomatic Carriers

Shelly Kagan*, MD,[1] ***Yonit Wiener-Well*, MD,***[2] ***Eli Ben-Chetrit MD2, Livnat Keshet, MA,***[3,] ***Jessica Aouzerate, BA***[3]***, Amos M. Yinnon, MD2,***[4] ***and Marc V.Assous, MD, PhD***[3]

Hebrew University-Hadassah Medical School[1], Jerusalem, Israel, Infectious Disease Unit[2], Microbiology laboratory[3] and Division of Internal Medicine[4], Shaare-Zedek Medical Center, affiliated with the Hebrew University-Hadassah Medical School, Jerusalem, Israel, *equal first contribution

Background: The incidence of Clostridium difficile (CD) Infection is rising. It is associated with advanced age, antibiotics, proton-pump inhibitors and histamine antagonists, hospital and nursing-home stay. Reports suggest that up to one third of carriers will develop a symptomatic infection, and the significance of carriage is not clear. To-date, CD screening is not recommended for asymptomatic patients.

The study aimed to assess the risk of CD carriers to develop diarrhea and its severity during hospitalization and answer the question of CD carriage screening justification.

Methods: Rectal swabs were obtained from newly admitted patients and processed by the glutamate dehydrogenase and Clostridium toxin immunoassay to determine the prevalence of asymptomatic carriage. Carriers were paired with non-carrier controls at a 1:2 ratio and followed throughout their hospitalization.

Results: There were no significant differences between the groups in baseline characteristics, aside from recent antibiotic use. Of the 394 specimen tested, n= 34 (8.6%) were of asymptomatic carriers. 30 carriers and 60 non-carriers were included. The results showed that carriers of CD were significantly more likely to develop diarrhea during their hospitalization (23.3% vs. 6.7%, p=0.038), and developed diarrhea earlier than non-carriers (2.9 vs. 5.7 days from admission, p=0.024). High morbidity and mortality were associated with CD carriage at admission - 48.1% of CD carriers died during hospitalization compared with 13.3% of non-carriers (p<0.001).

Conclusions: These data suggest that CD screening of groups at risk may have clinical and epidemiological benefits. Further studies regarding prevention of diarrhea in carriers and control of transmission of spores are needed.

A novel clinical index reflecting mucosal inflammation in pediatric Crohn's Disease

A Ben Shoham[a e]***, MA Cozijnsen***[a e]***, JC Escher***[b]***, L de Ridder***[b e]***, JM Hulst***[b]***, D Turner***[a u]

[a] Shaare Zedek Medical Center; [u]The Juliet Keidan Institute of Pediatric Gastroenterology and The Hebrew University of Jerusalem; [b]Erasmus MC/Sophia Children's Hospital, Rotterdam, The Netherlands;[e] Equal contribution

Background: Mucosal healing (MH), defined as lack of evidence of inflammation by endoscopy, is increasingly becoming an important therapeutic goal in Crohn's Disease (CD). Repeated assessments by colonoscopy are less feasible in children since they are associated with risks and discomfort. The Pediatric Crohn's Disease Activity Index (PCDAI) is the primary tool for assessing disease activity in pediatric CD patients but it does not correlate with mucosal inflammation as well as biomarkers as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fecal calprotectin (FC).

Aims: To develop a multi-item clinical index, based on clinical and laboratory measures, to reflect mucosal inflammation and MH, as defined by the validated Simple Endoscopic Score for Crohn's Disease (SES-CD). Such a tool would serve as an outcome measure in clinical trials as well as in assessing response to treatment in clinical practice.

Method: Data from the ImageKids study were utilized to construct and validate the proposed index. We excluded patients with isolated upper GI disease and further restricted the analysis to patients who have had their clinical and lab workup no longer than 4 weeks prior to and no longer than 2 week following colonoscopy. The association of the SES-CD with clinical data, PCDAI items, laboratory tests and fecal markers, were analyzed in multivariate analyses.

Results: The construction and validation of the index utilized data of 73 children and 70 children respectively (age 13.7±2.5 years; disease duration 1.95 years [IQR 0.2-3.3]; PCDAI 21±16, 31% with remission and 27% with moderate-to-severe disease; SES-CD 11±9, 19% with MH [score ≤3] and 41% with moderate-to-severe mucosal inflammation). In the final model, abdominal pain, stool pattern and laboratory items, including ESR, CRP and FC, were strongly associated with SES-CD and thus retained in the proposed index. The correlation between the SES-CD and the proposed index was 0.659 (P<0.001), higher than its correlation with PCDAI (0.514), FC (0.517), ESR (0.344) and CRP (0.249). The sensitivity and specificity of the index to diagnose MH were 71% and 75%, respectively.

Conclusions: In children with ileocolonic CD, an index based on select PCDAI items together with fecal and serum inflammatory markers were used for constructing a non-invasive clinical index that may help to assess MH.

Vascular calcifications and bone mineral density in recurrent kidney stone formers (KSF)

Linda Shavit1[1,2], Daniela Girfoglio[1] ,Vivek Vijay[1], Pietro Manuel Ferraro[3], Shabbir Moochhala[1], Robert Unwin[1]

[1]Centre for Nephrology, Royal Free Campus, University College London Medical School, London, UK; [2]Adult Nephrology Unit, Shaare Zedek Medical Center, Jerusalem, Israel; [3]Division of Nephrology, Catholic University of the Sacred Heart, Rome, Italy

Introduction and aims: Recent large-scale epidemiological studies have provided evidence for an association between nephrolithiasis and cardiovascular disease (CVD), though the underlying mechanism is unclear. Vascular calcification (VC) is a strong predictor of cardiovascular morbidity and mortality; the hypothesis that it is more prominent in KSF has been investigated in the current study. The aims of this study were to: 1) determine whether recurrent KSF have more VC and osteoporosis compared with control; 2) evaluate an association between hypercalciuria and VC/osteoporosis.

Methods: We investigated 111 subjects, of whom 57 KSF and 54 age- and sex-matched controls (drawn from a list of potential living kidney donors). Abdominal aortic calcification (AAC) and vertebral body trabecular bone mineral density (CT BMD) were assessed using existing abdominal CT imaging. Using these CT scans, manual calcium scoring was undertaken to calculate total aortic calcium load (AAC severity score). The prevalence, severity and associations of AAC and CT BMD between KSF and controls were then compared.

Results: There were no statistically significant differences in age and gender between groups. Mean age was 46.7 ± 6.4 years in KSF and 46.9 ± 5.6 in controls, 57 % of the patients in both groups were male. The prevalence of diabetes, HTN and dyslipidemia was higher in KSF, and smoking history was more prevalent in controls.

AAC was found in both groups, the incidence was only slightly higher in KSF (39% vs 35%). However, the severity of AAC was significantly higher in KSF by both univariate and multivariate models adjusted for age, sex, HTN, diabetes and smoking status (p-value < 0.001). Similarly, KSF had significantly lower CT BMD by both crude and adjusted analyses (p-value < 0.001). Among stone formers, the association between AAC score and hypercalciuria was not statistically significant (p-value 0.86).

Conclusions: VC might be an underlying pathogenic mechanism explaining previously reported associations between nephrolithiasis and CVD. Moreover, bone demineralization is much more prominent in KSF, providing preliminary evidence of possible common underlying pathways leading to increased extraosseous calcium deposition and osteoporosis.

Vitamin D levels, Vitamin D supplementation and prognosis in patients with chronic kidney disease.

Yossef Namir*[1], ***Matan J Cohen****[2], ***Yosef S Haviv***[3], ***Itzchak Slotki***[1], ***Linda Shavit***[1]

*Equal contribution

[1]Adult Nephrology Unit, Shaare Zedek Medical Center, Jerusalem, Israel

[2]Department of Medicine, Shaare Zedek Medical Center, Faculty of Medicine, Hebrew University, Jerusalem, Israel

[3]Soroka medical center and Ben Gurion University of the Negev, Beer Sheva, Israel

Background: Vitamin D (Vit D) deficiency plays a central role in the pathogenesis of chronic kidney disease (CKD) complications, both skeletal and non-skeletal. The purpose of this study was to examine whether 25(OH) D levels and supplementation with oral cholecaciferol (Vitamin D3, Vit D3) are associated with morbidity and mortality among patients with significant CKD.

Methods: CKD patients attending the nephrology clinic at Shaare Zedek Medical Center between 1.7.2008 and 31.1.2012, tested at least twice for 25(OH) D levels were enrolled. Primary endpoints included death, end stage renal disease (ESRD) requiring start of dialysis, a rise of at least 50% in serum creatinine, or composite endpoints of the above.

Results: A total of 516 patients were studied, of whom 178, 257 and 81patients had baseline vitamin D levels < 15ng/ml, 15 to 30ng/mL and > 30ng/mL, respectively. We found an association between baseline 25(OH)D level below 15 ng/mL and renal outcomes (start of dialysis or a rise of at least 50% in serum creatinine) in both crude and multivariate analyses (HR 3.17, 95% CI 1.12 to 8.94). Vit D3 supplementation demonstrated beneficial effects on combined renal outcomes and death in univariate analyses (p=0.02). Moreover, an increment of 10 ng/mL in 25(OH)D levels was associated with a 25% reduction in mortality (HR 0.755 (95% CI 0.54-1.00) in crude but not adjusted analyses.

Conclusions: Significant Vit D deficiency in CKD can serve as a biological marker indicating patients in whom adverse renal outcomes can be anticipated. Moreover, Vit D3 supplementation and rise of serum 25(OH) D levels may have beneficial influence on hard renal outcomes.

Neutrophil/Lymphocyte ratio for early detection of Acute Kidney Injury (AKI) in patients admitted to the Emergency Room.

Mohsan Abu el Filat MD, Itzchak Slotki MD, Linda Shavit MD

Division of Adult Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel

Introduction: Neutrophil to lymphocyte ratio (NLR) is a readily available biomarker of systemic inflammation. Several studies have provided evidence for an association between elevated NLR and adverse outcomes in a variety of medical and surgical conditions, including CKD. In this study, we evaluated the predictive capacity of single Emergency Room (ER) measurement of NLR for early diagnosis of acute kidney injury (AKI).

Methods: We prospectively studied 294 patients aged 71.6 17 β. NLR was measured at presentation to the ER. AKI was defined as a new-onset 1.5-fold or more increase in serum creatinine or a 25% decrease in estimated GFR sustained for at least 3 days despite volume resuscitation. The primary outcome was AKI. Secondary outcomes were in-hospital mortality and duration of hospital stay.

Results: 36 patients (12.2%) developed AKI and 26 (9%) died. Mean NLR was significantly higher in AKI compare to non AKI patients (11.7 15.2 β vs 6.457.19 β, p=0.048). A multivariate model adjusted for age, gender, blood pressure, hemoglobin and plasma albumin confirmed that NLR was higher in AKI patients (p=0.031). Receiver operating characteristics curve revealed AUC 0.72 (95% CI 0.63-0.80) sensitivity 0.78, specificity 0.65, OR 6.4 (CI, 2.7 to 16.0) for a cutoff value of NLR 5.5. The associations between NLR and in hospital mortality and NLR and duration of hospital stay were not statistically significant.

Conclusion: Single ER measurement of NLR can be a useful tool for early diagnosis of AKI. This finding is particularly important in light of the widespread availability and low cost of NLR, especially compared with other biomarkers currently under study in the context of AKI.

A Personal Journey Through The End Of Life - A Literary And Pictorial Description

Romem Anat, R.N, DNP, Jorunn Opstad-Carmel, R.N, B.A

Shaare Zedek Cancer Pain and Palliative Medicine

AIM: To present the unique story of a patient's struggle with terminal illness as described through the written words of the patient, alongside a figurative description of the struggle as perceived by the patient's core palliative care team.

Background: The realization of end of life (EOL) is a stressful and emotionally straining experience. Coping with the circumstances is extremely challenging both to the patient and to the caregiver. The ability to express one's thoughts and emotions is paramount to a successful and meaningful closure. Oftentimes this goal eludes both patient and his caregivers. Alternative modes of communication need to be explored.

Design: A qualitative biographical exploration of the EOL experience using diarizing by the patient and a pictorial interpretation of the above as perceived by the palliative-care team.

Finding: The analysis of one participant's diary yielded a wealth of information about her journey through the disease process, including coping, communication, and symptom management strategies as well as life and death priorities. The diary exposes the duality of hopefulness of a fantastic miraculous cure on the one hand and the bitter realization of the impending end on the other. The pictorial interpretation provided by the caregivers exposed deep and strong emotions from their perspective.

Conclusion: Verbal and pictorial diarizing could potentially provide both patient and caregiver with a powerful tool to process and express meaningful ideas and deep buried emotions.

Dexrazoxane added to adjuvant doxorubicin-based chemo-therapy in breast cancer: a retrospective cohort study with comparative analysis of toxicity and survival

***E. Tahover*[1], *A. Segal*[1], *R. Isacson*[1], *O. Rosengarten*[1], *T. Grenader1*, *M. Gips*[1], *N. Cherny*[1], *N. Heching*[1], *T. Tichler*[1], *L. Mesika*[1], *R. Catane*[1], *A. Gabizon*[1].**

[1]Shaare Zedek Medical Center, Oncology, Jerusalem, Israel.

Background: Dexrazoxane is a cardioprotective agent for patients receiving doxorubicin who are at risk for cardiotoxicity. Concerns have been raised regarding the use of dexrazoxane, particularly in adjuvant therapy, because of the risk of interference with the antitumor effect of doxorubicin. We analyzed retrospectively a cohort of our institute database to assess the effect of dexrazoxane on myelosuppression in breast cancer patients receiving doxorubicin-based adjuvant therapy. Secondary objectives were febrile neutropenia, dose-schedule modifications, cardiac events, and overall survival.

Patients and methods: 822 female patients receiving adjuvant doxorubicin and cyclophosphamide for breast cancer were included. 104 of them also received dexrazoxane. Blood counts were analyzed up to 30 days after last doxorubicin dose. Cardiac events (cardiac-related hospitalization, abnormal ECHO or MUGA scan) were collected from first doxorubicin dose to data cut-off date. Survival was defined as the time from first course of adjuvant chemotherapy to date of death from any cause.

Results: Median follow-up was 5.3 years for patients with dexrazoxane and 6.2 years for patients without dexrazoxane. Patients who received dexrazoxane were older (median, 59 vs 52 years), and more likely to receive dose-dense therapy (73% vs 59%) and adjuvant trastuzumab (29% vs 15%).

Dexrazoxane caused a significantly higher rate of hematological side effects: more patients developed neutropenia (45% vs. 31%, p=0.003), anemia (86% vs. 73%, p=0.005) and thrombocytopenia (37% vs. 22%, p=0.001). Dexrazoxane also caused more febrile neutropenia hospitalizations (20% vs. 10% p=0.001) and dose reductions (22% vs. 8% p<0.001), but the frequency of dose delays was not different. The rates of neutropenia were significantly higher in the dose-dense therapy subgroup of patients treated with dexrazoxane (30% vs 16%, p<0.001, for grades 3-4), but not in patients receiving treatment every 21 days.

The incidence of cardiac events was the same with and without dexrazoxane, and with or without trastuzumab.

There was a non-significant difference in survival in favor of the dexrazoxane group (6.5% vs 11.8%) and an older median age of death in the dexrazoxane group (65 vs 60 years). Most of the deaths (84%) occurred in patients who developed metastatic disease.

Conclusion: Adding dexrazoxane to doxorubicin causes higher rates of bone marrow suppression, with more febrile neutropenia and more dose reductions. There was no difference in the incidence of cardiac events, yet a cardioprotective effect cannot be ruled out given the design and limited power of our study. Dexrazoxane had no detrimental effect on survival, despite higher hematological toxicity, older median age, and a higher fraction of HER2-positive disease in the dexrazoxane group.

Co-encapsulation of Alendronate and Doxorubicin in Pegylated Liposomes: A novel formulation for chemo-immunotherapy of cancer

***Hilary Shmeeda*[1], *Yasmine Amitay*[1,2], *Stephan T. Stern*[3], *Yechezkel Barenholz*[2,] and *Alberto Gabizon*[1,2]**

Oncology Institute, Shaare Zedek Medical Center, Jerusalem, ISRAEL

Hebrew University-School of Medicine, Jerusalem, Israel.

NCL NCI/NIH, Frederick, MD, USA

We developed a pegylated liposome formulation of a dissociable salt of a nitrogen-containing bisphosphonate, alendronate (ALD), co-encapsulated with the anthracycline, doxorubicin (DOX), a commonly used chemotherapeutic agent. Liposome-encapsulated ammonium ALD generates a gradient driving DOX into liposomes, forming a salt that holds both drugs in the liposome water phase. The resulting formulation (PLAD), allows for a high loading efficiency of DOX, comparable to that of clinically approved pegylated liposomal doxorubicin sulfate (PLD), and is very stable in plasma stability assays. Cytotoxicity tests indicate greater potency for PLAD compared to PLD. This appears to be related to a synergistic effect of the co-encapsulated ALD and DOX. PLAD and PLD differed in in vitro monocyte-induced IL-1 release (greater for PLAD) and complement activation (greater for PLD). A molar ratio ALD:DOX of ~1:1 seems to provide an optimal compromise between loading efficiency of Dox, circulation time, and in vivo toxicity of PLAD. In mice, the circulation half-life and tumor uptake of PLAD were comparable to PLD. In the M109R and 4T1 mouse tumor models, PLAD was superior to PLD in growth inhibition of subcutaneous tumor implants. This new formulation is a promising tool to exploit the antitumor effects of aminobisphosphonates in synergy with chemotherapy.

A phase I study of pegylated liposomal mitomycin C prodrug in advanced solid tumor patients.

[1]*Grenader T,* [2]*Golan T,* [3]*Ohana P, 3Amitay Y,* [2]*Shmeeda H,* [4]*La-Beck NM, 1Tahover E,* [2]*Berger R,* [1,3,5]*Gabizon AA.*

[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]Sheba Medical Center, Tel HaShomer, Israel; [3]Lipomedix Pharmaceuticals Ltd., Jerusalem, Israel;[4]Texas Tech University Health Sciences Center-School of Pharmacy, Abilene, Texas; [5]Hebrew University-School of Medicine, Jerusalem, Israel.

Background: Promitil® is a pegylated liposome formulation of a lipid-based prodrug of mitomycin C (MLP). MLP is activated to mitomycin C (MMC) by thiolytic cleavage. Pre-clinical studies of Promitil have shown long circulation time, reduced toxicity, and improved therapeutic index over MMC. The primary objectives of this study were to determine the maximal tolerated dose (MTD), identify dose-limiting toxicities (DLT), and characterize the pharmacokinetic (PK) profile of Promitil. Secondary objectives were to evaluate the safety profile of Promitil and anti-tumor responses.

Methods Enrolled patients were diagnosed with advanced solid tumors. Promitil was administered intravenously at 4-week intervals starting with an MLP dose of 0.5mg/kg and escalating at 0.5mg/kg stepwise increments. Each dose level cohort consisted of 3-6 patients. Dose escalation proceeded if no DLT observed after the 1st cycle. Each patient was scheduled to receive 3 cycles with PK analysis in 1st and 3rd cycles, and undergo re-evaluation in the 12th week, unless early discontinuation was clinically indicated. Treatment continuation beyond 3 cycles was at the discretion of the investigators.

Results: Twenty-seven patients received 100 Promitil infusions (median = 3 cycles/patient; range = 1-12). Per protocol maximum tolerated dose was not reached at 3.5 mg/kg (=1.03mg/kg MMC-equivalents) in a cohort of 6 patients. However, prolonged thrombocytopenia developed after repeated doses of 3 mg/kg or cumulative doses of 10-12 mg/kg. Dose-related grade 3 or higher adverse events included fatigue, anemia, and thrombocytopenia. Delayed thrombocytopenia grade 2-3 after 3 or more cycles of Promitil in patients treated at lower dose levels (2-3mg/kg) led us to terminate dose escalation. The 1st cycle MTD of Promitil is 3mg/kg and the recommended dose for additional cycles is 2mg/kg at intervals of 28 days. PK analysis indicates MLP has a slow, nearly mono-exponential clearance, with a half-life of 20-24 hours and a small volume of distribution similar to blood volume. One patient had a partial response. Stable disease was observed in 10 patients across all dose levels.

Conclusion Promitil may be active in a variety of tumor types and is better tolerated than free MMC. The single dose MTD and the 12-week maximal cumulative dose of Promitil in MMC-equivalents are 3-fold greater than for MMC. Thrombocytopenia is dose limiting toxicity.

Prognostic value of neutrophil to lymphocyte ratio in advanced oesophagogastric cancer: exploratory analysis of the REAl-2 trial

T Grenader1,2, T Waddell[3], C Peckitt[3], J Oates[3], N Starling3, J Bridgewater2 and D Cunningham[3]

[1]Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel; [2]UCL Cancer Institute, London; [3]The Royal Marsden Hospital, London.

Background: The REAL-2 trial demonstrated that capecitabine and oxaliplatin were effective alternatives to fluorouracil and cisplatin respectively when used in triplet chemotherapy regimens for previously untreated oesophagogastric cancer. Recently, high neutrophil to lymphocyte ratio (NLR) has been reported to be negatively prognostic in a number of solid tumors. The aim of the current analysis was to evaluate the prognostic value of NLR in the REAL-2 cohort.

Material and methods: A post-hoc exploratory analysis was performed on REAL-2 patients with available absolute neutrophil count and absolute lymphocyte count. A high NLR was defined using a cut-off value of >3.0. NLR was then correlated with clinical outcomes including overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). Survival curves were generated using the Kaplan-Meier method and comparison between groups was performed using cox regression. Long-term survivors were defined as those surviving beyond 24 months.

Results: Data were available in 908 of the 1002 REAL-2 participants. Of these, 516 (51.5%) were deemed to have a high NLR. NLR was highly significant for OS ($p<0.001$) in a multi-variate model including PS, age, disease extent, presence of liver metastases, and presence of peritoneal metastases. For PFS, high NLR was associated with a hazard ratio of 1.63 (1.41 - 1.87), $p<0.001$, compared to low NLR in univariate analysis. Corresponding median PFS in the 2 groups was 8.1 months (95% CI 7.0 to 9.2) in low NLR and 6.0 months (95% CI 5.4 to 6.4) in high NLR. There was no significant difference in response rates between the 2 groups (ORR 47.3% low NLR compared to 42.5% high NLR, odds ratio 0.82 (95% CI 0.63 - 1.08), $p=0.15$). No interaction was found between NLR status and treatment arm.

There were a total of 82 long-term survivors in this analysis population. Of these, 51 (62%) had low NLR compared to 31 (38%) with high NLR. This equates to 13% of all patients with low NLR achieving survival beyond 24 months compared to only 6% of patients with high NLR, $p<0.001$.

Conclusion: Our results confirm that high NLR status had a significant negative prognostic effect in the REAL-2 trial population. Based on the multi-variate analysis, this effect was independent of other known prognostic factors. NLR level could provide additional prognostic information for patients and clinicians in daily practice, and may be a relevant stratification factor in future clinical trials.

Diethylstilbestrol for the treatment of patients with castration-resistant prostate cancer: Shaare Zedek Medical Center experience.

Grenader T, [1] Plotkin Y, Gips M, Cherny N, Gabizon A.

Department of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel.

Background: The aim of the present retrospective study was to evaluate the efficacy and safety of diethylstilbestrol (DES) as treatment for patients with castration-resistant prostate cancer (CRPC) and to identify predicting factors of response to DES.

Methods: Patients treated with DES during the castration-resistant phase following the failure of prior treatment with LH-RH analogs during the castration-sensitive phase were retrieved from a prostate cancer database of our institution. Patients were treated with a daily dose of DES of 1-4 mg (mean, 2.6 mg) and anticoagulants for thromboembolic prophylaxis until disease progression. We analyzed their medical records, biochemical prostate-specific antigen (PSA) response and time to disease progression (TDP). Disease response and progression were identified according to the PCWG2 criteria. Patient data were examined using Kaplan-Meier survival analysis and statistical correlation tests with intra-patient comparison of the LH-RH and DES treatment phases.

Results: Forty-three DES-treated CRPC patients were found in our database through July 2011. The median age was 66 years. Sixty-three percent of the patients achieved a ≥50% decline in their serum PSA levels during DES therapy. Median TDP was 20.4 months for LH-RH analog treatment in the castration-sensitive phase, and 7.1 months for DES treatment in the castration-resistant phase. Durable responses (>1 year) were observed in 31% of the patients. Median overall survival was 57 months from the start of the DES therapy. There was no significant correlation between the TDP under LH-RH analogs and under DES therapy among the 38 patients eligible for correlation analysis. However, the magnitudes of serum PSA responses under DES and LH-RH analogs were significantly correlated with each other, and with the TDP under DES therapy. There were no treatment-related deaths. Four patients (9%) developed thromboembolic complications while under treatment, some of which appeared to be related to a discontinuation of thromboprophylaxis.

Conclusion: DES confers substantial clinical benefit in the treatment of CRPC, with a relatively good safety profile when administered with thromboprophylaxis. The use of DES may be effective in CRPC, irrespective of the length of the hormone-sensitive period with LH-RH treatment. The magnitude of PSA response to previous treatment with LH-RH analogs, as well as to DES, was predictive of the duration of response to DES.

Next-Generation Sequencing (Foundation Medicine) in patients with advanced cancer: Are We Ready for Widespread Clinical Use? Shaare Zedek Medical Center experience.

Tal Grenader

Department of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel.

Background: The next-generation sequencing (NGS) assay targeting cancer-relevant genes has been widely adopted for use in patients with advanced cancer. Cancer genomic sequencing assays allow detection of new genetic alterations that have assisted in identifying new targets for therapy and develop new therapies. The primary aim of this study was to assess clinical utility of commercially available NGS.

Methods: We retrospectively collected demographic, clinicopathologic data, recommended therapy and clinical outcomes of 30 patients with a variety of advanced solid tumors referred to Foundation Medicine NGS. Initial pathologic examination was conducted at the pathology department of our hospital. The comprehensive clinical NSG assay was performed on paraffin-embedded tumor samples using the Clinical Laboratory Improvement Amendments (CLIA)-certified FoundationOne® platform (Foundation Medicine, Cambridge, Mass., USA).

Results: The mean number of genomic alterations was three (range 0-19). The mean number of therapies with potential benefit was 1.5 (range 0-8). In 12 cases a comprehensive clinical NSG assay did not reveal any therapy with potential benefit according the genomic profile. 10 of the 30 patients received treatments recommended by a genomic profile results. In six of the ten cases disease progressed within two months and four patients died within three months of treatment initiation. Three of the 30 patients benefited from the comprehensive clinical NSG assay with subsequent recommended therapy. Median progression-free survival was 12 weeks (95% CI 10-57) in patients treated with molecularly targeted agents chosen on the basis of tumour genomic profiling versus 48 weeks (95% CI 8-38) in the control group treated with physician choice therapy(p=0.12).

Conclusions: Our study suggests that NGS can detect additional treatment targets in individual patients but prospective medical research and appropriate clinical guidelines for proper clinical use are vital.

Pharmacologic studies of a prodrug of mitomycin C in pegylated liposomes (Promitil®): High stability in plasma and rapid thiolytic prodrug activation in tissues

Yasmine Amitay[1], Hilary Shmeeda[2], Yogita Patil[3], Jenny Gorin[1,2], Dina Tzemach[2], Lidia Mak[2], Patricia Ohana[1], Alberto Gabizon[2,3]

[1] Lipomedix Pharmaceuticals Ltd., Giv'at Ram, Jerusalem, Israel; [2] Shaare Zedek Medical Center, Jerusalem, Israel; [3]Hebrew University-School of Medicine, Jerusalem, Israel.

Purpose: Pegylated liposomal (PL) mitomycin C lipid-based prodrug (MLP) has recently entered clinical testing. We studied the preclinical and clinical pharmacology of PL-MLP.

Methods: The stability, pharmacokinetics, biodistribution, and other pharmacologic parameters of PL-MLP were examined. Thiolytic cleavage of MLP and release of active mitomycin C (MMC) were studied using dithiotreitol (DTT), and by incubation with tissue homogenates.

Results: MLP was incorporated in the bilayer at 10% molar ratio with nearly 100% entrapment efficiency, resulting in a formulation with high plasma stability. In vitro, DTT induced cleavage of MLP with predictable kinetics, generating MMC and enhancing pharmacological activity. A long circulating half-life of MLP (10-15 hours) was observed in rodents and minipigs. PL-MLP was less toxic in vivo than equivalent doses of MMC. Studies in mice with H3-cholesterol radiolabeled PL-MLP demonstrated relatively greater tissue levels of H3-cholesterol than MLP. MLP levels were highest in tumor and spleen, and very low or undetectable in liver and lung. Rapid cleavage of MLP in various tissues, particularly in liver, was shown in ex-vivo experiments of PL-MLP with tissue homogenates. Free MMC was either extremely low or undetectable in plasma. Urine from PL-MLP injected rats revealed delayed but significant excretion of MMC indicating in vivo activation of MLP. Therapeutic studies in C26 mouse tumor models demonstrated improved dose-dependent efficacy of PL-MLP over MMC.

The pharmacokinetics of PL-MLP in a first-in-man study showed a median t1/2 of 23 hours among dose cohorts, with no trend by dose or cycle, while Cmax and AUC0-∞ increased linearly over the dose range 0.5-2.0 mg/kg, and greater than linearly from 2.5-3.5 mg/kg.

Conclusions: Thiolytic activation of PL-MLP occurs in tissues but not in plasma. Liposomal delivery of MLP confers a favorable pharmacological profile and greater therapeutic index than MMC.

Targeting Of Liposomal Mytomycin-C Prodrug To Folate Receptors In Vitro

Yogita Patil, Yasmine Amitay, Patricia Ohana, Hilary Shmeeda, Alberto Gabizon

Shaare Zedek Medical Center, Jerusalem, Israel; Hebrew University-School of Medicine, Jerusalem, Israel; Lipomedix Pharmaceuticals Ltd., Jerusalem, Israel

Summary: Folate-targeted liposomes carrying a reducible prodrug conjugate of mytomycin C demonstrate increased cell uptake and cytotoxic activity in vitro in tumor cells over-expressing the folate receptor. Intracellular delivery of the liposomal prodrug via folate receptor enables activation of the prodrug by intracellular reducing agents.

Introduction: Mitomycin C (MMC) is a powerful anti-bacterial, antifungal and anti-tumor antibiotic often active against multidrug resistant cells. Despite a broad spectrum of antitumor activity, MMC clinical use is relatively limited due to its fast clearance and dose-limiting toxicity [1]. To exploit the potential antitumor activity of MMC and reduce its toxicity we have developed a lipophilic prodrug of MMC. A reducible prodrug conjugate of mitomycin-C (MLP) formulated as previously described in pegylated liposomes (PL-MLP), has displayed significant antitumor activity and reduced toxicity in mouse tumor models [2]. PL-MLP has minimal in vitro cytotoxic activity unless reducing agents are added to the cell culture to activate the prodrug. In the present study, we hypothesized that targeting these liposomes via folate receptors facilitates an intracellular activation of prodrug without added reducing agents. We formulated folate targeted PL-MLP liposomes and examined the cytotoxic activity in three different folate receptor-expressing cell lines.

Experimental Methods: PL-MLP liposomes were prepared as described [2, 3]. MLP was incorporated with almost 100% efficiency into pegylated liposomes composed of hydrogenated phosphatidylcholine/cholesterol/PEG/MLP at a molar ratio 55:30:5:10, respectively. For the cell uptake study, 3H-cholesterol radiolabeled liposomes were prepared by the addition of 3H-cholesterol-hexadecyl ether (3H-CHE) during liposome preparation. The folate-conjugated PEG (5000)-DSPE ligand was post-inserted into preformed liposomes (PL-MLP and 3H-CHE labeled PL-MLP) by incubation at 55°C for 30 min, at a molar ratio of 0.5% of total phospholipid. Liposomes were then centrifuged at 3,000 rpm for 10 min to remove non-incorporated folate ligand. This formulation was tested in vitro for cell uptake and cytotoxic activity in three cell lines that over-express the folate receptor: human KB-FR and IGROV-FR carcinoma cells, and mouse J6456-FR lymphoma cells.

Results And Discussion: Micellar insertion of folate ligand to PL-MLP liposomes was achieved efficiently upon incubation at high temperature (55°C). The presence of folate ligand did not interfere with prodrug activation in vitro by reducing agents. In cell uptake studies, 3H-CHE-labeled PL-MLP liposomes with and without folate ligand were incubated for 3 hrs at 37°C with KB-FR cells. Folate targeted liposomal prodrug showed a 4-fold increase in liposome cell uptake and MLP concentration increased by 9-fold in KB-FR cells compared to non-targeted liposomes. The cytotoxic activity of folate targeted PL-MLP liposomes was significantly increased up to 5-fold compared with PL-MLP liposomes in all tested folate receptor-expressing cell lines. Thus, folate targeting allows uptake and subsequently intracellular activation of prodrug without added reducing agents and thereby increased cytoxicity in vitro.

Conclusion: Folate targeted PL-MLP provides an additional therapeutic strategy in cancers that over-express the folate receptor. Folate targeting of liposomal prodrug MLP enhances cell uptake and cytotoxicity of liposomal prodrug in folate receptor-expressing tumor cells. Increased in vitro cytotoxicity implies intracellular activation of the prodrug. In vivo studies with folate targeted PL-MLP liposomes are ongoing.

Tackling under-diagnosis of COPD using Spirometry and questionnaire: A targeted, case-finding study

Ariel Rokach MD MHA, Abraham B. Bohadana MD, Ofir Kotek BMSc, Nissim Arish MD, Ayal Romem MD MHA, Chen Chen Shuali MD, Hava Azulai MD, Gabriel Izbicki MD.

Pulmonary Institute, Shaare Zedek Medical Center, Jerusalem, Israel

Background: COPD is a leading cause of mortality and disability worldwide. Early case identification might be important in order to implement early interventions. This can help preventing COPD exacerbations, preserve lung function and quality of life, and decrease mortality.

Aims: To identify smokers with pre-bronchodilator airflow obstruction, who are considered to be at high-risk for the development of COPD.

Methods: Smokers aged 35 years or older were screened. All of them performed pre-bronchodilator pulmonary function test (PFT).

A standardized, 5-question questionnaire on smoking status and pulmonary symptoms was administered. (a simple score between 1-5 was given to each participant according to symptoms: cough, sputum, shortness of breath). Those with evidence of abnormal PFT were advised to seek further medical assistance. Correlation between the questionnaire and PFT was done. The impact of the intervention was assessed by phone interview three months later. The subjects were asked about their smoking habits.

Results: Seven hundred and nineteen smokers were screened. 520 were males (72.3%) and 199 were women (27.7%). Suspected airflow obstruction defined as FEV1/FVC<0.7 was detected in 134 smokers (18.6%). Thirty four (4.7%) had mild obstruction (FEV1>80%), 74(10.3%) had moderate obstruction (50%<FEV1<80%) and 26 (3.6%) had severe obstruction (FEV1<50%). The majority of them did not know about respiratory diagnosis. Spearman test was done in order to find correlation between airflow obstruction and pack year smoking, age and symptoms (questionnaire). A strong correlation was found between airflow obstruction and the parameters measured. Following our short intervention, the amount of cigarettes smoked per day was significantly reduced from 21 to 17.7 (P<0.0001)

Conclusions: Obstruction in PFT was common present in 18.6% of the smokers. A simple questionnaire was strongly correlated to airflow obstruction. This questionnaire might become a good screening tool to detect COPD among smokers. The screening showed potential benefit by reducing the amount of cigarettes that were smoked three months after the PFT was done.

Do We Really Need The 4Th Value Of The 100-G 3-Hour Oral Glucose Tolerance Test (Ogtt)?

Dr Sapir Alon, Dr Lior Drukker, Dr Tamar Halevy-Shalem, Prof Arnon Samueloff.

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, The Hebrew University Medical School, Jerusalem, Israel

Objective: To test the use of a 100-g 2-hour OGTT for the diagnosis of GDM compared to "the gold standard" 100-g 3-hour OGTT

Materials & Methods: 8589 Results of 100-g 3-hour OGTT's between the years 2006-2011 were obtained from the computerized data base of the obstetrics department in the Shaare Zedek Medical Center.

By ignoring the 4th value of the test, we retrospectively created a 100-g 2-hour OGTT. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the 100-g 2-hour OGTT and compared to 100-g 3-hour OGTT.

Results: Of the 8589 results 1779 (20.7%) met the criteria for the diagnosis of GDM (The test was considered positive if two threshold values of Carpenter & Coustan were met, or if one threshold value of the National Diabetes Data Group was met). When excluding the 4th value, 1665 (19.4%) cases met the same criteria for the diagnosis of GDM. The sensitivity, specificity, PPV and NPV of the 100-g 2-hour OGTT in compared to 100-g 3-hour OGTT were 93.6%, 100%, 100%, 98.4% respectively.

Conclusion: The use of the 100-g 2-hour OGTT for the diagnosis of GDM as compared to the 100-g 3-hour OGTT will reduce the test sensitivity to 93.6% but will save 33% of the time and up to 25% of the cost, while maintaining a high NPV of 98.4%. It still remains to be seen whether women whose diagnosis of GDM depends on the 4th value have different pregnancy outcomes compared to all other women diagnosed with GDM.

Replacement of the 3-hour by 2-hour 100-g OGTT has the potential to improve system throughput if pregnancy outcomes are not compromised.

Ultrasound Prediction Of Shoulder Dystocia

Sapir A, Drukker L, Shen O, Samueloff A, Rabinowitz R And Sela H.y

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Shaare Zedek Medical Center, Jerusalem, Israel.

Introduction: In clinical practice suspected macrosomia is used as a risk-factor for shoulder dystocia (SD). We aimed to evaluate the performance of various sonographic (US) parameters in the prediction of SD in term singleton deliveries.

Materials and methods: Retrospective study, 2011-2014, all patients with viable singleton pregnancy who underwent US estimations of fetal weight within 7 days of vaginal delivery at term (37-42 weeks) were included. US parameters assessed were abdominal diameter - biparietal diameter (AD-BPD) ≥ 26mm, and estimated fetal weight (EFW) using the Hadlock formula (1985) ≥4000gr. AD was calculated as abdominal circumference (AC) divided by π. Statistics: β2 ($p<0.05$ significant) and multivariate logistic regression (LR) (OR, 95%CI, p value).

Results: Out of 5372 who met inclusion criteria, 31(0.58%) were complicated by SD.

Median time from US to delivery was 1.33 [0.61-2.73] days. US parameters that were associated with SD included: AD-BPD>26 mm ($P<0.001$), Mean AC ($p<0.001$), Mean Head circumference ($p=0.02$) and EFW ≥ 4000gr ($p<0.001$).

A multivariate model including only US parameters revealed OR of 9.97 for AD-BPD>26mm and 2.28 for EFW>4000gr. Furthermore once interaction between these 2 parameters was integrated into the model the OR for SD was 12.37 for AD-BPD≥26mm and 3.58 for EFW≥4000gr. Sensitivity and specificity of EFW, AD-BPD and using both were 32% / 45% / 22% and 92% / 94% / 97% respectively.

Conclusion: Ultrasound AD-BPD≥26mm has high OR and is more sensitive for prediction of SD than either EFW alone or combination of both. We recommend this measurement should be used in conjunction with other clinical and sonographic parameters in counseling patient regarding risk of SD.

A new clinical tool - The probabilities of macrosmia based on sonographic measurements of AC and EFW

A. Sapir, L. Drukker, R. Rabinowitz, A. Samueloff, H. Y. Sela

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center

Objective: To clarify the probabilities of macrosomia (birth weight ≥ 4000gr) based on sonographic measurements of abdominal circumference (AC) and estimated fetal weight (EFW) using the Hadlock (1985) formula in term (37-42 weeks) singleton pregnancies.

Study Design: Patients who underwent sonographic estimations of fetal biometric measurements (incorporating head, abdomen, and femur measurements) within 7 days of term singleton delivery at a tertiary care institution between the years 2010-2015 were included in this retrospective cohort.

Fetal weight estimation was calculated using the formula of Hadlock (1985)(Log10 EFW = 1.3596 + 0.0064(HC) + 0.0424(AC) + 0.174(FL) + 0.00061(BPD)(AC) - 0.00386(AC)(FL))

All newborns weight was noted. The probabilities of macrosomia were calculated and stratified based of EFW in gaps of 100 grams, and AC measurement as well.

Results: Of 80394 deliveries, 9073 met our inclusion criteria. 1058 newborns were macrosomic (11.6%). The probabilities of macrosomia depending on EFW and AC summarized in table 1.

Conclusion: Our large databases clarify the probabilities of macrosomia based on sonographic measurements of AC and EFW. The new table is a helpful tool to be used in decision making counseling Patients with suspected macrosomia and avoiding major error in clinical estimation of fetal weight.

Intramuscular versus vaginal progesterone administration in medicated IVF frozen embryo transfer (FET) cycles: a randomized clinical trial

Amir Weintraub, M.D, Anat Hershko Klement, M.D, Nivin Samara, M.D, Frederic Mitri, M.D., Yaakov Bentov M.D., M.Sc , Paul Chang M.D., Dan Nayot M.D, M.Sc., and Robert F. Casper M.D

TRIO Fertility and Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Toronto IVF Unit, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center

Background: Progesterone supplementation is used for all assisted reproductive technology cycles in order to support the luteal phase. Recent meta-analyses have shown that pregnancy outcomes are similar with vaginal and intramuscular progesterone administration for luteal support in fresh IVF cycles. There is less information about the route of progesterone administration for hormonal preparation of the endometrium in donor egg cycles or in frozen embryo transfer cycles.

The focus of this study was on frozen embryo transfer (FET) or donor oocyte embryo transfer where hormonal therapy is used for endometrial preparation and no functional corpus luteum is present. Since there is literature supporting an association of contraction frequency and pregnancy outcome, The objective of this study was to determine if there was a difference in the number of subendometrial waves per minute, measured by vaginal ultrasound, in response to vaginal versus intramuscular administration of progesterone.

Methods: This was a randomized non-blinded clinical trial. Patients were assigned by their treating physician to a frozen blastocyst transfer (FET) cycle, either using autologous eggs or fertilized donor eggs. Patients were randomly allocated into one of two treatment groups: "vaginal progesterone" and "intramuscular (IM) progesterone. All study patients received the standard medicated FET protocol in our center, which included oral micronized 17b-estradiol starting on day 3 of the cycle. Once completing 10 days of treatment, patients had intravaginal ultrasound determinations of endometrial thickness and pattern; Once sufficient endometrial proliferation was observed (>7 mm with a triple-line pattern), the patients received progesterone treatment with embryo warming and transfer on day 6 of progesterone. Patients randomized to the vaginal progesterone arm were treated with 200mg vaginal suppositories three times daily (Prometrium). Patients randomized into the IM progesterone arm were treated with a single daily injection of 50mg progesterone in oil. On the fifth day of progesterone exposure all patients had a blood sample for progesterone levels and a trans-vaginal ultrasound in which sub-endometrial wave contractions were counted.

Results: Thirty four patients completed the study, seventeen patients in each of the study groups. Clinical pregnancy rates were comparable between study groups. When comparing cycles that ended in a pregnancy to cycles without conception, the number of waves was significantly lower among pregnant patients (P value 0.02). For each additional contraction observed the chance for a pregnancy is reduced by 0.39 (95% confidence interval 0.17-0.9).

Conclusions: The mode of progesterone administration does not affect clinical pregnancy rate. Subendometrial wave frequency could be used as a surrogate marker of the chance for successful implantation.

Rates, proportions and mortality trends among very low birthweight singleton infants of 24 to 32 weeks gestation

Ella Kitroser MD[1], Valentina Boyko MSc[3], Liat Lerner-Geva, MD PhD[3,4], Cathy Hammerman, MD[2], Arnon Samueloff, MD[1], Michael S. Schimmel MD[2], Brian Reichman, MB ChB[3,4], Sorina Grisaru-Granovsky MD PhD[1] in Collaboration with the Israel Neonatal Network

[1]Departments of Obstetrics and Gynecology, and [2]Neonatology, Shaare Zedek Medical Center, Jerusalem, affiliated with the Hebrew University Medical School of Jerusalem; [3]Women & Children's Health Research Unit, Gertner Institute, Tel Hashomer and [4]Sackler School of Medicine, Tel Aviv University, Tel Aviv; Israel.

Background: The very low birthweight (VLBW, ≤1500g) infants mortality represents a significant determinant of infant mortality around the world. VLBW mortality rates decreased markedly, however the traditional epidemiological models are limited in the dissection of the specific contribution of parallel social and medical factors. We aimed to quantify the contribution of changes in either specific mortality rates and/or in the distribution of population characteristics, risk factors and therapies on the mortality rate of VLBW infants

Methods: Population based observational study comprising 10,704 singleton VLBW infants born in Israel, 1995-2010. Comparison was performed between the earliest (1995-2000) and the latest (2006-2010) epochs. The Kitagawa decomposition was applied to separate and quantify changes in the contributions of specific mortality rate and population and therapy characteristics

Results: The study population composed 3,728 (1995-2000) and 3,246 infants (2006-2010) with mortality rates of 19.7 % and 13.8%, respectively. Of the 5.9% decrease in mortality, 60.6% was attributed to the decrease in specific mortality rates and 39.4% to changes in the proportions of population characteristics and therapies, predominantly early initiation of prenatal care, antenatal steroids and cesarean delivery.

Conclusions: Provision of early antenatal care and administration of antenatal steroids are primary targets for intervention of health care services to promote additional decreases in VLBW infant mortality.

The association between ABO blood group and obstetric hemorrhage

Lior Drukker, Naama Srebnik, Deborah Elstein, Lorinne Levitt, Arnon Samueloff, Rivka Farkash, Sorina Grisaru-Granovsky, Hen Y. Sela

Department of Obstetrics and Gynecology, Sharee Zedek Medical Center

Background: Maternal post-partum hemorrhage is a major cause of morbidity. Therefore, recognizing the women at risk for hemorrhage has continued to be a priority in the hope that early identification may lead to appropriate prevention strategies and elicit prompt response upon post-partum hemorrhage. There are contradicting studies in the literature regarding the correlation between ABO blood groups and bleeding tendency in the non-pregnant state, with the O blood group being a risk factor for bleeding. The hypothesized mechanism for the link between blood group and hemorrhage is alleged to be related to the von Willebrand factor (VWF), since individuals with O blood type compared with other blood groups have 25%-35% lower plasma levels of VWF.

Methods: Our study aim was to compare women with O to non-O blood groups with regard to maternal post-partum hemorrhage and transfusion need. We performed a retrospective cohort study in a single tertiary center between 2005 and 2014. For the purpose of the study, parturients were categorized as O and non-O blood groups. Data included all deliveries but excluded patients with missing blood grouping or hemoglobin values, and/or stillbirth. Drop in hemoglobin was defined as hemoglobin concentration at admission for delivery minus the lowest hemoglobin concentration post-delivery. Study outcomes were postpartum hemorrhage, hemoglobin drop >2-7gr/dL, and packed red blood cells transfusion. Statistics: descriptive, β2 ($p<0.05$ significant) and multivariable regression models (odds ratio [OR], 95% confidence interval [CI], p value).

Results: A total of 125,768 deliveries were included in the analysis. After multivariable analysis, women with O blood type in comparison to women with non-O blood type had significantly higher odds of postpartum hemorrhage (OR= 1.14; 95%CI 1.05-1.23, $p<0.001$), higher odds of statistically significant hemoglobin decrease of >2, 3, or 4gr/dL (OR = 1.07; 95%CI 1.04-1.11, $p<0.001$, OR = 1.08 ;95%CI 1.03-1.14, $p=0.002$ OR = 1.14; 95%CI 1.05-1.23, $p=0.001$; respectively), and higher odds, albeit not statistically significant of 5, 6, or 7gr/dL decrease in hemoglobin (OR= 1.13; 95%CI 1.00-1.29, $p=0.055$, OR= 1.05; 95%CI 0.84-1.32, $p=0.66$, OR= 1.15; 95%CI 0.79-1.68, $p=0.46$; respectively), but no difference in blood products transfusion (OR = 1.03; 95%CI 0.92 - 1.16, $p=0.58$).

Conclusion: Women with blood type O may be at greater risk of obstetrical hemorrhage.

Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for cesarean section, and adverse maternal and neonatal outcomes

Lior Drukker, Yael Hants, Rivka Farkash, Rosa Ruchlemer, Arnon Samueloff, Sorina Grisaru-Granovsky

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center

Background: Maternal iron deficiency anemia (IDA) impacts placenta and fetus. We evaluated effects of IDA at admission for delivery on cesarean rates, and adverse maternal and neonatal outcomes.

Methods: a single tertiary center between 2006 and 2012 identified women with a live-birth singleton fetus in cephalic presentation of any gestational age and excluded planned cesarean, chronic/gestational diseases identified with anemia. Study population was divided into anemic and non-anemic women using WHO criteria, and further classified according to the severity of anemia: mild (11 gr/dl > Hemoglobin ≥10 gr/dl) moderate (10 gr/dl > Hemoglobin ≥7 gr/dl) and severe (Hemoglobin <7 gr/dl). Main outcome measures: cesarean rate, and adverse outcomes (maternal: packed cells transfusion, early post-partum hemorrhage, preterm delivery; and neonatal: 5' Apgar <7, Neonatal Intensive Care Unit [NICU] admission, extreme birthweights). Continuous variable analysis and multivariate backward step-wise logistic regression models were prepared with Odds Ratios (OR) and 95% confidence intervals (CI).

Results: In all, 96,066 deliveries were registered, of which 75,660 (78.8%) were included. IDA was present in 7,977 women (10.5%): mild 77%, moderate 22.9%, and severe 0.1%. Anemia at birth was significantly associated with cesarean section (OR 1.30; 95%CI - 1.13-1.49, $P<0.001$), packed cells transfusion (OR 5.48; 95%CI - 4.57-6.58, $P<0.001$), preterm delivery (OR 1.54; 95%CI - 1.36-1.76, $P<0.001$), macrosomia (OR 1.23; 95%CI - 1.12-1.35, $P<0.001$), Large for Gestational Age (OR 1.29; 95%CI - 1.20-1.39, $P<0.001$), Apgar 5' < 7 (OR 2.21; 95%CI - 1.84-2.64, $P<0.001$), and NICU admission (OR 1.28; 95%CI - 1.04-1.57, $P=0.018$). Compared with non-anemia, women with moderate to severe anemia were at higher risk for cesarean section (OR 1.49; 95%CI - 1.14-1.93, $P=0.003$), packed cells transfusion (OR 14.49; 95%CI - 11.47-18.31, $P<0.001$), preterm delivery (OR 1.73; 95%CI - 1.37-2.19, $P<0.001$), and Apgar 5' < 7 (OR 2.94; 95%CI - 2.17-3.99, $P<0.001$).

Conclusion: Iron deficiency anemia at delivery is associated with an increased risk for cesarean section and adverse maternal and neonatal outcomes in otherwise healthy women. Monitoring/correction of hemoglobin concentrations even in late pregnancy may prevent these adverse events.

Impact of surgeon annual volume on short-term maternal outcome in Cesarean Delivery

Lior Drukker, Yael Hants, Rivka Farkash, Sorina Grisaru-Granovsky, Ori Shen, Arnon Samueloff, Hen Y. Sela

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center

Background: The annual procedure volume is an accepted marker for quality of care and has been documented in various medical fields. Surgeon volume has been shown to correlate with morbidity and mortality in surgical and high risk medical procedures. Though cesarean delivery is one of the most common surgical procedures in the USA, the link between surgeon's annual cesarean delivery volume and maternal outcome has never been tested.

Methods: Our study aim was to evaluate the impact of obstetricians' annual volume on short term maternal outcome in cesarean deliveries. We conducted a retrospective cohort study in a single tertiary center between 2006 and 2013. Cesarean deliveries were categorized into two groups based on the annual volume of cesarean delivery of the attending obstetrician. LOW group included low annual volume obstetricians, whose annual volume of cesarean delivery was lower than median. HIGH group comprised high annual volume obstetricians whose annual volume was median and above. Further analyses were done for quartiles and for four clinical relevant groups according to the annual number of cesarean delivery performed/supervised by the attending (20 or less, 21-60, 61-120 and more than 120) The primary outcome was a composite adverse maternal outcome including one or more of the following: urinary or gastrointestinal tract injuries, hemoglobin drop > three gm/dL, blood transfusion, re-laparotomy, puerperal fever, prolonged maternal hospitalization and readmission. Secondary outcomes were operative times (skin incision to delivery and overall).

Results: A total of 11,954 cesarean deliveries were included, the median annual number of cesarean delivery performed/supervised by one obstetrician was 48. Unadjusted analysis suggested that HIGH group patients, had fewer urinary and gastrointestinal injuries 18/9278 (0.2%) vs. 16/2676 (0.6%), P<0.001, less blood loss as measured by hemoglobin drop > three gm/dL 1053/9278 (11.5%) vs. 366/2676 (13.8%), P<0.001 and fewer cases of prolonged maternal hospitalization: 80/9278 (0.9%) vs. 39/2676 (1.5%), P=0.006. The rate of blood transfusion, re-laparotomy, puerperal febrile morbidity and readmission to hospital did not differ between groups. Multivariable regression analysis showed that cesarean delivery performed/supervised by HIGH group resulted in a significantly lower composite adverse maternal outcome (15.8% vs. 18.9%, OR 0.86; 95%CI 0.78-0.95, p=0.004). This was primarily related to a decreased frequency of urinary and gastrointestinal injuries, lower likelihood of hemoglobin drop > three gm/dL and lower incidence of prolonged maternal hospitalization. Operative times were significantly shorter for HIGH group. Composite adverse maternal outcome ranged from 21.8% in the lowest quartile, to 17.9% in Q2, to 17.4% in Q3, and 15.6% in Q4. With Q4 defined as the reference, Q3 had an OR of 1.14 95%CI [1.01-1.29], p=0.029, Q2 had an OR 1.18 95%CI [1.02-1.36], p=0.021 and Q1 had an - OR 1.51 95%CI [1.14-1.99], p=0.004 for composite adverse maternal outcome. Composite adverse maternal outcome ranged from 21.5% in clinical group 1, to 17.5% in clinical group 2 to 17.9% in clinical group 3, and 15.2% in clinical group 4, p value=0.001). Cesarean delivery performed/supervised by clinical groups 2, 3 and 4 in compare to clinical group 1 were associated with a statistically significant risk reduction, (23%, 25% and 34% respectively).

Conclusion: Maternal composite morbidity is decreased as the volume of cesarean deliveries performed or supervised by an obstetrician increases.

Early postpartum hemorrhage (ePPH): a sentinel event for puerperal readmission risk and surgical intervention

Zmora Itay, Maayan Bas-Lando MD[1], Rivka Farkash MS , Arnon Samueloff MD[1], Sorina Grisaru-Granovsky MD PhD[1]

Department of Obstetrics & Gynecology[1], Shaare Zedek Medical Center, affiliated with the Hebrew University Hadassah School of Medicine, Jerusalem, Israel

Aim: The 3rd stage of labor is a major source of maternal morbidity and mortality. We aimed to determine risk factors for hospital readmission post-vaginal birth.

Methods: Retrospective cohort study performed in a tertiary center with strict protocols for management of 3rd stage abnormalities, 2006-2014. Data were collected from the validated computerized maternity database. Women who required readmission [for any diagnosis] within 6 weeks of vaginal delivery were compared to women not readmitted. Routine discharge after vaginal birth occurs between 36-48 hours; women are instructed to return for readmission according to regional and health insurance policies. Comparisons adjusted multivariate model; Odds Ratio (OR 95%CI), p <0.05.

Results: 101,185 women were identified with vaginal birth; 335 (0.33%) women were readmitted. Demographics are in Table. Readmission diagnosis: excessive vaginal bleeding 78 (23.3%), endometritis 154 (46%), residual conception tissue 33 (9.9%), and epidural or background disease complications 70 (20.9%). Of all vaginal births, 3297 (3.3%) had revision of the uterine cavity due to 3rd stage abnormality and suspected retained placenta fragments; 27 (8.1%) of them were readmitted. Women who were readmitted had significantly higher rates of postpartum hemorrhage (PPH): 26 (7.8%) versus 2219 (2.2%) p<0.0001; hemoglobin drop >3gr\dl 60 (17.9%) versus 5138 (5.1%) p<0.0001; blood transfusion 15(4.5%) versus 790 (0.8%) p<0.0001; and postpartum febrile morbidity 2627 (2.6%) versus 17 (5.1%) p=0.005. Women with abnormal 3rd stage bleeding and subsequent uterine cavity revision had an increased risk of surgical intervention at readmission: curettage 13 (48.1%) versus 56 (18.2%) p<0.0001; and operative hysteroscopy 4 (14.8%) versus 11 (3.6%) p=0.007. Multivariate analysis indicated early PPH and significant drop in hemoglobin as the most significant risks factors for readmission: OR 1.71 (1.05-2.78) and OR 2.72(1.93-3.85), respectively p<0.0001, regardless of manual uterine revision.

Conclusion: Puerperal hospital readmission risk with surgical intervention for excessive vaginal bleeding is increased for women with significant PPH, even after immediate postpartum manual uterine revision. Early postpartum follow-up visits, sonographic evaluation of uterine cavity, and medical ambulatory management may be indicated to prevent readmission and late procedures.

Epidural analgesia at Trial of Labor after Cesarean (TOLAC): a significant adjunct to successful vaginal birth after cesarean (VBAC)

Sorina Grisaru-Granovsky MD PhD[1], Maayan Bas-Lando MD1, Fred Haouzi MD[2], Rivka Farkash MS, [1] Arnon Samueloff MD[1], Alexander Ioscovich MD[2]

Departments of Obstetrics & Gynecology[1] and Obstetric Anesthesia[2], Shaare Zedek Medical Center, affiliated with the Hebrew University Hadassah School of Medicine, Jerusalem, Israel

Introduction: Epidural analgesia has been considered a risk factor for failed Trial Of Labor After Cesarean (TOLAC) and uterine rupture. This study aims to assess the exposure to epidural during TOLAC with respect to the mode of delivery and maternal - neonatal outcomes.

Materials and methods: A cohort study of women that consented to have a TOLAC after a single low-segment cesarean section with singleton fetus in vertex presentation between 2006 -2013, based on a validated computerized database at a center with strict TOLAC protocols. Epidural users were compared to non-users. Primary outcome was the mode of delivery at TOLAC: cesarean or successful vaginal delivery (VBAC). Secondary outcomes were maternal/neonatal morbidities. Univariate/multivariate analyses for associations between epidural and mode of delivery were adjusted for significant covariates/mediators.

Results: Of 105,471 births registered, 9464 (9.0%) had a previous cesarean and were eligible for TOLAC; 7149 (75.5%) of eligible partutients consented to TOLAC, among which 4081 (57.1%) received epidural analgesia. The VBAC rate was 90.0%. The repeat cesarean in labor rate was significantly lower in women using epidural (356; 8.7%) than non-users (361; 11.8%) ($p<0.0001$). Uterine rupture rates were comparable: 0.4% in users and 0.29% in non-users ($p=0.31$). Adjusted multivariate analysis of effect of epidural on TOLAC showed an increased rate of VBAC (OR 4.58 [3.67; 5.70]; $p<0.0001$) for epidural users while the risk for uterine rupture and adverse neonatal outcome were similar (Table)

Conclusion: Epidural analgesia at TOLAC is safe for mother and neonate, possibly emerging as a significant adjunct to reach VBAC and lower the repeat section rate.

Nulliparous, term, singleton, vertex (NTSV) risk assessment for cesarean delivery (CD): a new concept in the effort to lower CD rates

Meirav Nezer, Adiel Cahana, Rivka Farkash, Karen Kochan, Arnon Samueloff, Sorina Grisaru-Granovsky

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center

Background: Maternity care providers recognize the need to address the rising rates of CD. CD for NTSV is a sentinel for future CD and determinant of the overall CD rate. We aim to examine CD risk factors for NTSV in labor.

Methods: Retrospective cohort study designed to compare all NTSV births by the mode of delivery: vaginal delivery (VD) vs CD. Planned CD excluded. Data origin: validated computerized medical records in a single tertiary center 2006-2014, for a population under National Health Program. Statistics: descriptive, multivariate analysis (OR, 95% CI).

Results: During the study 121,483 deliveries where registered: NTSV 26,301(21.6%); 1,944 (7.4%) delivered by CD while in labor. Multivariate model revealed the following significant risks for CD for NTSV in labor: advanced maternal age (OR 3.6; 2.2,4.3), chronic diseases (OR 1.4; 1.1,1.7), previous >3 miscarriages (OR 1.94;1.04,3.6), low Bishop score at admission (<6) (OR 2.4; 2.1,2.8),induction of labor (OR 1.8; 1.5, 2.1), oxytocin during labor (OR 8.4; 6.8,10.2) , LBW (OR 1.4; 1.0,2.0), macrosomia (OR 2.4; 1.78,3.2) . Interestingly, epidural analgesia was protective of CD (OR 0.23; 0.19, 0.27).

Conclusions: A measure based on the NSTV population may provide a profile to assess overall CD risk. Hospital quality improvement teams will be able to use this in the future and focus on NTSV as a primary target to control CD rate.

Frozen Embryo Transfer: Adjacent or Non-adjacent to Failed Fresh Ovum Pick-up Embryo Transfer Cycle

[1]***Alexander Volodarsky-Perel, M.D.,*** [1,2]***,#Talia Eldar-Geva M.D., Ph.D.,*** [1]***Hananel E. G. Holzer M.D., 1Oshrat Schonberger Ph.D.,*** [1,2]***Michael Gal M.D., Ph.D.***
[1]IVF Unit, Division of Obstetrics and Gynecology, Shaare Zedek Medical Center. [2]The Hebrew University of Jerusalem Medical school.
#Equal contribution to the first author.

The optimal timing to perform frozen embryo transfer (FET) after a failed ovum pick-up embryo transfer (OPU-ET) cycle is unknown. This retrospective cohort study analyzed outcomes of FET cycles performed adjacently (<50 days, n=165) or non-adjacently (≥50 to 120 days, n=105) to the last OPU-day. Significantly higher rates of clinical pregnancy (CPR, 34.3% vs. 22.4%) and live birth (LBR, 28.6% vs. 16.4%) were found in the non-adjacent group. In the adjacent group, the types of GnRH-analogue for OPU-ET and the FET-endometrium preparation protocol differently associated with cycle outcomes: The GnRH-agonist protocol, the artificial FET, and a combination of both significantly reduced CPR (adjacent: 13.4%, 17.7%, 10.5% vs. non-adjacent: 39.0%, 35.5%, 41.7%, respectively) and LBR (adjacent: 9.0%, 10.5%, 7.0% vs. non-adjacent: 32.2%, 27.4%, 30.6%, respectively). In contrary, the GnRH-antagonist protocol, the natural FET, and a combination of both revealed similar outcomes between groups: CPR (adjacent: 28.6%, 36.6%, 32.1% vs. non-adjacent: 28.3%, 32.6%, 28.6%, respectively) and LBR (adjacent: 21.4%, 34.1%, 32.1% vs. nonadjacent: 26.1%, 32.6%, 28.6%, respectively). These results support the postponement of FET after a failed OPU-ET for at least one menstruation cycle if a preceding GnRH-agonist protocol was used and/or if artificial preparation for FET is indicated.

Selective inhibition of steroidogenic enzymes by ketoconazole in rat ovary cells

Michael Gal, M.D., Ph.D.[a] ***and Joseph Orly, Ph.D.***[b]
[a]IVF Unit, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, The Hebrew University School of Medicine, The Hebrew University of Jerusalem.
[b]Department of Biological Chemistry, The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem.

Objective: Ketoconazole (KCZ), an anti-fungal agent, is extensively used for clinical applications related to its inhibitory effects on adrenal and testicular steroidogenesis. With regard to KCZ effect in the ovary, the present data are less coherent. Therefore, the aim of present study was to characterize the effect of KCZ on steroidogenic enzymes in primary rat ovary cells.

Study design: Freshly prepared rat ovarian cells were cultured in suspension for up to 4 h while incubated with radiolabeled steroid substrates and at different time points the profile of the steroid products was analyzed by thin layer chromatography (TLC) comparing control cells with KCZ-treated cells.

Results: Ketoconazole selectively inhibits dose dependently and reversibly rat ovarian P450 dependent enzymes, including cholesterol side-chain cleavage cytochrome P450 (CYP11A1/ P450scc), the 17a-hydroxylase activity of CYP17A1/P450c17, and CYP19A1/ P450arom, with IC50 values of 0.3, 1.8, and 0.3ag/ml (0.56, 3.36, and 0.56aM), respectively. Unaffected by KCZ, at 10ag/ml, were the 17,20 lyase activity of CYP17A1, as well as five non-cytochrome steroidogenic enzymes including 3a-hydroxysteroid dehydrogenase-Δ5-4 isomerase type 1 (3aHSD1), 5a-reductase, 20a-hydroxysteroid dehydrogenase (20a-HSD), 3a-hydroxysteroid dehydrogenase (3a-HSD), and 17a-hydroxysteroid dehydrogenase type 1 (17HSD1).

Conclusion: These findings map the selective inhibitory effect of KCZ on ovarian cytochrome P450 enzymes controlling the de novo synthesis of steroids from cholesterol throughout progestins, androgens, and estrogens.

Ketoconazole inhibits ovulation due to arrest of follicular steroidogenesis in the rat ovary

***Michael Gal, M.D., Ph.D.*[1] *and Joseph Orly, Ph.D.*[2]**

[1]IVF Unit, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, The Hebrew University School of Medicine, The Hebrew University of Jerusalem. [2]Department of Biological Chemistry, The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem.

Objective: Ketoconazole (KCZ) is a known inhibitor of steroidogenic P450 enzymes in the adrenal cortex and the gonads. Previous studies examined the potential clinical use of KCZ for attenuation of ovarian response to gonadotropin treatments. This study aimed to use the superovuating rat model to explore the effect of KCZ on ovarian steroidogenesis, follicular function and development towards ovulation.

Methods: Prepubertal rats were treated with eCG/hCG resulting in multiple follicular development and ovulation. The effect of KCZ on this model was examined by administration of KCZ-gel formula and subsequent analyses of ovarian steroidogenesis, rate of ovulation, morphometric assessments of follicular parameters and cell-specific steroidogenic maturation of the treated ovaries.

Results: When applied shortly before gonadotropin stimulation, KCZ markedly reduced ovarian progesterone androstenedione, and estradiol levels down to 18.7%, 36.5% and 19.0%, respectively (P<.001). A single KCZ-gel administration of 6, 12, and 24 mg/rat inhibited the ovulation rates to 8.6±4.9, 5.1±4.3, and 2.4±3.2, respectively as compared to 13.6±4.4 in the gel-control group (P<.001). Consecutive KCZ doses administration (5 mg each every 8 h), started before onset of eCG treatment, for up to 16-32 h inhibited the ovulation rates to 10.3±6.3, 6.6±6.6, and 3.0±3.9, respectively (as compared to 16.5±4.1 in the gel-control group, P<.01). By contrast, KCZ failed to inhibit ovulation if onset of the drug administration commenced 24 h after eCG treatment. Anovulation by KCZ resulted from arrest of follicular development at Graafian stage of 800-840 µm (as compared to 920 µm in the gel-control group, P=0.029); absence of CYP11A1 expression in the granulosa cells; and, lack of cumulus cells mucification.

Conclusion: These results suggest that KCZ interferes with early vital steroidogenic functions that determine the normal program of follicular maturation towards ovulation. Hence, attenuation of folliculogenesis by KCZ may be harnessed to modulate gonadotropin-ovarian stimulation in fertility treatments.

Neonatal outcome following preimplantation genetic diagnosis (PGD)

Naama Srebnik*[1]*, Ehud Margalioth*[2]*, Gheona Altarescu*[3]*, Ruben Bromiker*[4]*, Hananel Holzer*[2]*, Michael Schimmel4, Talia Eldar-Geva*[2]*.

[1]Department of Obstetrics and Gynecology, Shaare Zedek Medical Center.

[2]IVF unit, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center.

[3]Department of Genetics, Shaare Zedek Medical Center.

[4]Department of Neonatology, Shaare Zedek Medical Center.

Background: Pregnancies achieved following In vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) treatments are at high risk for preterm birth and low birth weight. PGD is performed by an analysis of one or two cells obtained through oocyte, zygote, or embryo biopsy, adding a further invasive manipulation.

Aim: To examine whether embryo biopsy for PGD influences neonatal outcome.

Methods: This was a retrospective cohort study, analyzing 291 children born following PGD (198 singleton, 49 twin pairs, 1 triplte), 244 children born following ICSI (158 singletons and 43 twins pairs) and 663 children born following a spontaneous pregnancy (SC) (429 singletons, 117 twins pairs), matched for maternal age, parity and BMI. The following parameters were compared: gestational age, birth weight, prematurity (<37 and <34weeks), low birth weight (LBW, <2500gr, very LBW, <1500gr) and intra-uterine growth restriction (IUGR, <10'th percentile for gestational age).

Results: For singletons, mean birth weight was higher following PGD compared to ICSI, but not compared to SC. Mean gestational ages following PGD were lower compared to SC but higher compared to ICSI. LBW and IUGR rates were higher in ICSI pregnancies compared to PGD and SC. In twin pregnancies, birth weight was higher in PGD compared to ICSI and LBV rates were lower in PGD compared to ICSI and similar to SC. Polar-body and blastomere biopsies provided similar outcomes.

Conclusions: Embryo biopsy, per-se, did not cause IUGR or LBW compared to SC, despite lower gestational age with PGD. The worse outcome in ICSI compared to PGD pregnancies may be due to the infertility itself.

Preconception Screening for Cytomegalovirus: An Effective Preventive Approach

***Orna Reichman*[1], *Ian Miskin*[2,3], *Limor Sharoni*[4], *Talia Eldar Geva*[1], *Doron Goldberg*[1], *Avi Tsafrir*[1] *and Michael Gal*[1]**

[1]Department of Obstetrics & Gybecology, Shaare Zedek Medical Center, Hebrew University Medical School, Jerusalem, Isarel.

[2]Clalit Health Services, Jerusalem, Israel

[3]Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University Medical Center, Ein Karem, Jerusalem, Isarel.

[4]Department of Anethesiology and Critical Care, Haddasah-Hebrew University Medical Center, Ein Karem, Jerusalem, Israel

Background: Congenital cytomegalovirus (CMV) is the leading infectious cause of sensorineural hearing loss and delayed psychomotor development. Viral transmission to the fetus is far more likely to occur following a primary than a secondary maternal infection. Primary prevention seems to be the best means to reduce the burden of congenital CMV due to the lack of treatment options during pregnancy.

Method: We evaluated the approach of primary prevention on a cohort of 500 women planning pregnancy who attended the fertility clinic at Shaare Zedek Medical Center.

Results: Of the 444 who underwent CMV screening, 18 (4.1%) had positive IgM serology for CMV; of these, IgG avidity was high in 12 (remote infection) and low in 6 (recent infection). The latter were advised to delay pregnancy. All women who were sero-immune for CMV (366/444, 82.4%), including the 12 with remote infection, continued fertility treatment. The remaining patients (72/444, 16.2%), who were not immune to CMV at the initial screen, were advised to minimize CMV exposure by improving personal hygiene and to continue fertility treatment. None of the 69/72 (95.8%) women who were followed for one year were infected with CMV.

Conclusion: Cytomegalovirus testing and counselling at preconception seemed effective in reducing CMV exposure in pregnancy.

Intrauterine growth restriction fetuses at term ≤ 3 percentile - is induction of labor safe?

***Orna Reichman, MD, MSCE*[1], *Yael Yekel, MD*[1], *Tamar Shalem MD*[1], *Sarit Helman MD, Arnon Samueloff, MD*[1]**

[1]Shaare Zedek Medical Center, Hebrew University Medical School, Jerusalem, Israel

Objective: Intrauterine growth restriction (IUGR), defined as fetal weight ≤ 3 percentile, is an alarming finding. When diagnosed at term, delivery is usually recommended. Limited information is available regarding the outcome of induction of labor for IUGR≤ 3 percentile. We present our experience and determine the success rate for induction.

Methods: A prospective historical cohort study, conducted in a tertiary university affiliated hospital with 13,000 annual deliveries, between the years 2005-2012. All women with a singleton pregnancy, at term, that were induced for various reasons, and delivered a neonate ≤ 3percentile were included. Demographic characteristics, medical and obstetric history, obstetric management and outcome were recorded. Logistic regression models were constructed to evaluate the factors associated with successful induction including multivariable analyses to control for potential confounders.

Results: During the study period, 7436/ 96,066 (8.2%) women, underwent induction of labor at term, of whom 183/7436 (2.5%) delivered an infant with a birth weight ≤ 3percentile. Approximately half, 95/183 (52%) were nulliparous, 98/183 (53%) were induced by prostaglandin and 75/183 (41%) necessitated induction for reason other than IUGR such as preeclampsia and oligohydramnious. Most women, 139/183 (76%), delivered vaginally and only 44/183 (24%) underwent unplanned CS. Univariate analysis revealed a high risk for CS among nulliparous (OR = 5.12, (CI: 2.29-11.46, p<0.000)), induction with prostaglandins (OR=3.19 (CI=1.29-7.85, p=0.012)) and fetus with oligohydramnious (OR=2.78 (CI=1.17-6.60, p=0.020)). Of the 18 women presenting with combined risk factors (nulliparous, induction with prostaglandin and oligohydramnios) only 7/18 (39%) proceeded to deliver vaginally. The majority of neonates had a good outcome regardless mode of delivery. Only 1/183 infant (0.5%) had an Apgar score at 5 minutes less than 5'.

Conclusions: It seems to be safe to induce labor for fetus with IUGR ≤ 3percentile.

Delivery during time of shift change is not a risk factor for obstetric complication: a historical cohort study

Reichman O, Samueloff A, Gdansky E, Yekel Y, Calderon-Margalit R.

Department of Obstetrics & Gynecology, Shaare Zedek Medical Center

Background: The time of shift change is a unique time because the continuity of routine care is interrupted. The association between delivery during time of shift change and obstetric complications has not been evaluated.

Objective: We hypothesized that delivery during time of shift change is at risk for obstetric complications.

Methods: A historical cohort study was performed of all women with a singleton pregnancy undergoing a trial of labor at term during 2006-2010. Data was extracted from a computerized database that is continuously updated during Labor. The hour of delivery was divided into two categories: "morning shift" (09:30-15:00) and "time of shift change" which was defined 30 minutes prior to and 90 minutes past the official time of shift change, which occurs twice daily at 07:30 and 15:30. Multivariate logistic regression models were implemented to estimate the association between deliveries during "time of shift change" compared to "morning weekdays", with instrumental delivery (primary outcome) and prolonged second stage, unplanned cesarean section, postpartum hemorrhage, 5 minutes Apgar score < 7, admission to neonatal intensive care unit (NICU) and prolonged maternal hospitalization (secondary outcome). RESULTS: A total of 16,341 deliveries were included in the cohort. No statistical difference in instrumental vaginal delivery was documented for women delivering during "time of shift change compared to morning shift weekdays (OR = 0.96, 95% CI: 0.83- 1.11, p = 0.605). None of the secondary outcomes were found at risk for women delivering during "time of shift change".

Conclusions: Delivery during "time of shift change" does not pose additional risk for obstetric complications.

Grouping parturients by parity, previous cesarean and mode of delivery identifies parturients at risk for postpartum-hemorrhage

Orna Reichman, MD, MSc, Micahel Gal, PhD, Izzat Khayyat MD., Michael Emanuel BA, Arnon Samueloff, MD.

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Hebrew University Medical School, Jerusalem, Israel

Background: The prevalence of postpartum-hemorrhage varies between studies depending on the definition of postpartum-hemorrhage and the population studied. Significant differences are reported among sub-groups stratified by single risk factors including parity, mode of delivery and management of labor.

Aim: Our primary goal was to form a clinical classification aimed to identify sub-groups of parturients at risk for postpartum-hemorrhage by combining clinical universal risk factors.

Method: Retrospective cohort including all women who delivered at Shaare Zedek Medical Center, an affiliated university medical center, managing 10% of national deliveries, between January 2006 and December 2014. Parturients were grouped according to three characteristics, all known as universal risk factors for PPH: parity (primiparous, multiparous), previous cesarean and mode of delivery (spontaneous vaginal delivery, instrumental delivery, non-planned and elective cesarean): P-C-MoD classification. All together the classification included 12 sub-groups. Postpartum-hemorrhage was defined as a decrease of ≤ 3gram% hemoglobin or transfusion of blood products and was calculated for each of the sub-groups independently. A univariate analysis followed by a multivariate analysis was performed to study the risk for postpartum-hemorrhage among the sub-groups studied, controlling for confounding factors including age, onset of delivery, number of fetus and fetal birth weight

Results: The crude rate of postpartum-hemorrhage, for all 126,693 parturients was 7%. The prevalence for PPH differed significantly between independent risk factors compared to the combined risk factors of the P-C-MoD classification. Among primiparous, the prevalence was 14%, this changed significantly when combining primiparous with mode of delivery, ranging from 11% for spontaneous vaginal delivery to 27% among those with instrumental delivery. The prevalence of PPH among multiparous varied between 3% (spontaneous vaginal delivery) and 20% (emergency CD). There was significant difference in the prevalence of PPH between the sub-groups of the P-C-MoD classification. Primiparous who underwent ID were at increased risk for PPH, approximately one of four women in this group (27%) experienced PPH. Applying a univariate analysis revealed that the risk for PPH was significantly increased for primiparous undergoing ID compared to all other sub-groups reaching an OR of 12.8 (95% CI:11.9;13.8) compared to multiparous undergoing SVD. Applying a multivariate analysis minimally altered the results.

Conclusions: Grouping parturients by parity, previous cesarean and mode of delivery (P-C-MoD classification) is a useful tool to identify parturients at risk for postpartum-hemorrhage and is superior compared to single independent risk factors. Future studies are needed to confirm the external validity of this classification.

Delivering elsewhere between the first and second delivery is a risk marker for obstetric complications in the second delivery

***Orna Reichman*[1], *Meirav Nezer*[1], *Michael Gal*[1], *Ori Shen*[1], *Ronit Calderon-Margalit*[2], *Rivka Farkash*[1], *Arnon Samueloff*[1]**

[1]Shaare Zedek Medical Center, Hebrew University Medical School, Jerusalem, Israel

[2]Hadassah-Hebrew University School of Public Health, Jerusalem, Israel

Aim: We speculate that parturients who deliver elsewhere between the first and second delivery compose a unique clinical group, characterized by higher rates of cesarean section (CS) both in in first and second delivery, compared to parturients who deliver both deliveries at the same hospital.

Methods: A retrospective study in a tertiary university-affiliated-hospital. The cohort included all women in second delivery, aged ≤24 years with a singleton pregnancy who delivered their second child in our medical center during 2010-2012. Parturients who delivered both first and second children in our medical center ("stayers") were compared to parturients who delivered their first child in a different hospital ("switchers"). Groups were compared in regard to history of CS in first delivery and obstetric complications in second delivery including CS, instrumental vaginal delivery (IVD), preterm delivery (PTD), and postpartum-hemorrhage (PPH). Logistic regressions were constructed to study if delivering elsewhere between first and second delivery was a risk for adverse pregnancy outcome, followed by multivariate analysis controlling for confounders.

Results: The cohort included 4166 parturients, 3163 "stayers" and 1003 "switchers". History of CS in first delivery was approximately twice more prevalent in "switchers" compared to "stayers", 12% versus 6.3%, p<0.000. "Switchers" were at added risk for adverse pregnancy outcome in second delivery compared to "stayers" including higher rates of CS, OR=1.8 (95% CI: 1.20-2.11), higher rates of preterm delivery (≤37 weeks), OR=1.4 (95%CI: 1.0-1.9) and a non-statistical significant increase in IVD, OR=1.3 (95%CI: 0.8-2.1) and PPH OR=1.3 (95%CI 0.9-1.9). Furthermore, excluding women with previous CS from the cohort minimally altered the results (Table 1). Constructing a multivariate logistic regression model, controlling for factors that were statistically significant in the univariate analysis including: onset of delivery (induction, spontaneous, CS), analgesia and IUFD strengthened the risk for CS among "switchers" OR=2.1 (95% CI: 1.1 - 4.0, p=0.02).

Conclusions: We found that "switchers" underwent CS at first delivery twice as often compared to "stayers". This finding strengthens our hypothesis that "switchers" represent an inherently different group compared to "stayers" in relate to mode of delivery. Regarding the secondary outcome of our study, we found that "switchers" were at added risk for obstetric complication in second delivery compared to "stayers" including CS and PTD. Parturients who deliver elsewhere between first and second childbirth are at increased risk for CS and PTD in second delivery, hence the decision to deliver elsewhere after first delivery should be considered as a risk marker for obstetric complication.

Elastography assessment of the endometrial changes during the menstrual cycle of fertility treatment

Boldes.R, Barlev.M, Kafka.I, Hovav.Y, Shen.O, Gdansky.E,

Department of Obstetrics and Gynecology, Shaare Zedek Medical Centre, Bikur Holim campus, Jerusalem, Israel.

Objective: To explore the feasibility of using sonoelastography in evaluating the endometrium throughout the menstrual cycle during fertility treatments .

Methods: Women treated in our fertility clinic underwent three elastographic examinations throughout the cycle: early follicular phase, midcycle, and midlutheal phase. Elastographic results were correlated to hormonal profile, fertility treatment and positive pregnancy test. All of the elastographic examinations were carried out by three ultrasound training technicians, who described the dominant color obtained in the endometrium during examination. We translated the dominant color to a numerical value, based on the degree of stiffness of the tissue from solid to soft, on a scale from 1-4 in the following way: purple - blue = 1; dark and light blue = 2; green - yellow= 3; yellow - red=4. Statistical analysis was done by the Mann-Whitney and Friedman test, as appropriate.

Results: A total of 54 women participated in the study. Eighty five cycles were analyzed. We found significant changes in elastographic results throughout the menstrual cycle. Early follicular phase demonstrated a solid and firm endometrium (which was colored purple or dark blue). In the midcycle and midlutheal, there was a variety of results, with tendency towards a softer and more liquid type endometrium. As the cycle progressed we got elastographic results that were more red and yellow, which meant softer elastic tissue, and with a greater liquid component (P<0.001).

We analyzed the midcycle examination and compared between two subgroups: the first subgroup consisted of cycles where the midcycle examination was carried out preovulation. The second subgroup consists of cycles where the midcycle examination was done on the twelfth day, but actually the cycle was still in the follicular phase. The elastographic result was significantly different between the two subgroups: in the preovulatory cycles the results reflected a softer endometrium, whereas in the midfollicular phase subgroup the endometrium was still firm and solid, a picture very similar to the early follicular phase (P=0.003).

In analysis of the midlutheal examination, we compared cycles which ended in a positive pregnancy test with cycles which ended in a negative pregnancy test. We found that cycles with positive pregnancy demonstrated a softer and liquid rich endometrium (P=0.042).

No correlation between elstography and levels of estradiol and progesterone was found.

Conclusions: The elastograhic examination reflects the biochemical processes that take place in the endometrium throughout the menstrual cycle. The examination demonstrates the preovulatory changes in the endometrium. The examination may help in predicting fertility treatment outcome. More research is needed in order to understand better how to interpret the elastographic results, and how we can use sonoelastography in evaluating and treating fertility patients.

Prolonged second stage (P2S) in primipara, is it a line in the sand?

Shira Fridman Lev, Maayan Bas Lando, Rivka Farkash, Sorina Grisaru Granovsky, Arnon Samueloff

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center

Background: Duration and optimal management of P2S in the primipara partogram is still controversial and represents a source for primary cesarean deliveries. We assessed maternal and neonatal outcome of P2S in primiparas in labor at term.

Methods: Retrospective cohort study at a tertiary medical center between 2005 and 2014. All primiparous births with live singleton vertex fetus that reached full dilation were included. P2S was defined as >2 hours (group 1) without epidural or ≥3 hours (group 2) with epidural, compared with women with normal 2nd stage duration defined as <2 hours (group 3) without epidural and <3 hours (group 4) with epidural.

Statistics: comparisons adjusted multivariate model; Odds Ratio (OR 95%CI), p <0.05.

Results: During the study period 31,253 primiparous deliveries were recorded. 25,741 met study criteria: 22,542 (87.5%) had normal 2nd stage duration: group 3=6530 without epidural, group 4=16,012 with epidural; 3199 (12.5%) had P2S: group 1=502 without epidural, group 2=2697 with epidural. Demographics and outcomes are presented in the Table. P2S was associated with higher maternal morbidity: higher rates of cesarean delivery (CD) 0.2% & 16.1% in group 3 & 1, and 0.8% & 7.4% in group 4 & 2 (p<0.0001); instrumental deliveries 5.4% & 26.7% in groups 3 & 1, and 15.3% & 46.8% in groups 4 & 2 (p<0.0001) and composite adverse neonatal outcome, 5.9% & 11.2% in groups 3 & 1 and 9% & 13.1% in groups 4 & 2 (p<0.0001). Arrest of descent was the leading indication for CD. Multivariate analyses revealed independent association (OR [95%CI])) both in non-epidural and epidural users between P2S and higher rates of (1) CS (59.7 [33.3-107.1] and 8.1[6.4-10.1]), (2) composite maternal adverse outcome (2.37 [1.89-2.96] and 2.05 [1.86-2.25]) and (3) composite neonatal adverse outcome(1.92 [1.34-2.61] and 1.52 [1.34-1.73]), p<0.0001 for all.

Conclusion: P2S for primiparous women at term, according to the traditional definition and independent of use of epidural, is still associated with adverse maternal and neonatal outcomes. Implementation of new relaxed guidelines for 2nd stage might lead to further increases in CD and health costs.

Long Term Effect of Intensive Physical Exercise during Puberty on Bone Marrow Density - In Sport who Require Leanness Versus those Who Don't

Shiri Weinberg-Hendel, Ari Zimran, Naama Constantini

Department of obstructs and gynecology, Gaucher unit, Shaare Zedek Medical Center

Background: With the ageing of world population, osteoporosis is becoming a major problem. The disease, characterized by low bone marrow density (BMD), leads to fractures and an increase in both morbidity and mortality. Puberty is a crucial period for acquiring BMD. Factors which influence BMD are low energy availability, low calcium intake, disturbances in the menstrual cycle, types of physical activity and mechanical stress on the bones. Synchronized swimming is a unique sport characterized by many hours of non-weight - bearing exercise, and a requirement for leanness. Athletes who compete in sports, and who require leanness, such as in synchronized swimming. Intensive exercise combined with the requirement for leanness, may lead to a negative energy balance, as well as eating disorders along with the negative effect on BMD.

Aim: To determine the long term-effect of non-weight bearing competitive sports during puberty on BMD, in sports which require leanness versus those which don't, (represented in this study by synchronized swimming versus swimming), with respect to other factors known to effect BMD. We hypothesize that synchronized swimmers, are at higher risk for decreased BMD levels compared to swimmers.

Methods: 14 women in ages 20-40 with a history of at least 5 years of intensive training in synchronized swimming during puberty were compared to 14 women of the same age group, with a history of training in swimming to the same extent as the study group. Participants filled out questioners about their medical, sports, gynecological and dietary history, and were tested for BMD (lumbar spine, hip and total body) in a DEXA machine (DXA Hologic, Bedford MA usa) in Shaare Zedek Medical Center). Records were made for BMD, T-score (for healthy women ages 25-30), and Z-score (compared to same aged healthy women) and for other criteria addressed by the questioners.

Results: In both study groups the prevalence of osteopenia was higher than the general population. Synchronized swimmers were found to have higher left hip BMD BMD (SW 0.7485 [0.709 - 0.811], SS 0.8525 [0.7735 - 0.927], p=0.012), The only significant differences were found between the characteristics of the swimmers (SW) and synchronized swimmers (SS) groups were past BMI (SW 21.5±2.1, SS 18.7 ±1.3 p=0.000), BMI today (SW 22.7±2, SS 20.4 ±1.4 p=0.002), and time of weight bearing exercise (SW 5±2.5, SS 8±3.5 p=0.024). Osteopenia was diagnosed in 13 participants (7 SW vs 6 SS, p=0.705).

Conclusions: In refutation of our primary hypothesis, it appears that synchronized swimmers in Israel do have a tendency to osteopenia but not more than regular swimmers. This might be attributed to the longer out of water practice time (weight bearing exercise) required in synchronized swimming that might cancel out the negative effect of the leanness requirement. In addition to this we see that both sports, in which most of the exercise is not weight bearing, accompanied by the low energy availability to the pubescent athletes, may result in decreased BMD at old age.

Maternal and neonatal complications in a population of women diagnosed with inflammatory bowel disease; comparison between community clinics versus single center multidisciplinary clinic (IBD-MOM)

***Yael Cohen*[1], *Ori Hassin, Shitrit Ariella*[2], *Grisaru-Granovsky Sorina*[1]**

[1]Department of Obstetrics and Gynecology; [2]Digestive Diseases Institute, Shaare Zedek Medical Center

Background: IBD, Crohn's disease (CD) and ulcerative colitis (UC) affect women at reproductive age and thus potentially their pregnancy outcome. A multidisciplinary clinic was established in Shaare Zedek MC (SZMC) aimed to benefit the women with IBD and their neonates (IBD MOM).

Aim: 1. To evaluate the maternal and neonatal outcome for women with IBD as compared to a population of healthy pregnant women at a single center, SZMC. 2. To evaluate the maternal and neonatal outcome of women with IBD that are followed at the IBD - MOM clinic as compared to women with IBD who were treated by standard separate community clinics, i.e. for antenatal care and gastroenterological care.

Methods: A retrospective cohort study in a single tertiary center (SZMC) between the years 2015-2016. The data was collected from the patients' medical records, validated by telephone interviews, cross-linked with hospital computerized data. Disease severity used the 'IBD-MOM' score since the literature and clinical practice have yet no score for IBD in pregnancy (a non-validated score of IBD in pregnancy used only in the MOM clinic): perianal disease, active disease at conception, single/multiple drug use before or/and during pregnancy and exacerbations during pregnancy [0-1 for each]. Maternal and neonatal outcomes are reported. IBD was identified as ICD [9] codes 569.89. The comparison group consisted of healthy women who gave birth in SZMC between the years 2005-2015.

Results: During the study period we identified 296 women with IBD that delivered at SZMC; 90 (30.4%) were patients of the IBD - MOM clinic; these were compared with 61,705 healthy women as defined. Women with IBD had a significant higher rate of preterm birth (12.5% vs 5.4% p<0.0001) and neonates with lower birth weight (mean of 3061.152g vs 3233.913g P<0.0001). The study revealed that women who were attended at the IBD-MOM clinic during the pregnancy had a significant higher disease score at admission as compared to women attended in the community clinics (median score 2[1-3] vs. 0[0-1], p<0.0001): more disease exacerbations (37.8% vs 18.9%, p=0.001), and more hospitalization events (13.3% vs 2.9%, p=0.001) during pregnancy. Overall, the preterm delivery rate (<37 weeks gestation) was significantly higher in IBD-MOM as compared to IBD community attended women (18.9% versus 9.7%, p=0.028); however the early preterm rate (<34 weeks gestation) was similar in both groups (6.7% vs. 2.9%, p=0.084).

Conclusion: Women with IBD are at increased risk for preterm birth and the antenatal care should be directed towards adequate follow up and prevention. Women with severe and uncontrolled IBD are utmost benefited from a multi-disciplinary approach for pregnancy planning and follow-up.

Elective repeat cesarean section (ERCD) at term for all: is fear of Trial Of Labor After Cesarean (TOLAC) justified?

Yael Cohen, Tamar Stevei, Rivka Farkash, Arnon Samueloff, Sorina Grisaru-Granovsky

Department of Obstetrics and Gynecology, Shaare Zedek Medical Center

Background and Aim: TOLAC attempts are constantly declining due to doctors' and patients' concern of failure complications. We aim to compare characteristics of women choosing ERCD rather than TOLAC for delivery at term, to ascertain maternal and neonatal risks associated with failure of TOLAC (f-TOLAC)

Methods: A retrospective cohort study in a single center, during 2006-2014, with strict TOLAC protocol (single fetus, vertex, EFW <4200gm, no prostaglandin use, oxytocin induction/augmentation allowed if parity <5, continuous FHR monitoring, epidural recommended). ERCDs planned at 39-40 weeks gestation. Excluded: multiple gestation, non-vertex presentation, women in labor refusing TOLAC ad hoc. Maternal and neonatal outcomes are reported. Data from a validated computerized database. Multivariate regression adjusted for significant covariates/mediators.

Results: During the study 126,693 deliveries occurred; 11,440 (9.0%) women had one previous cesarean. Women who elected ERCD were significantly older, had more previous vaginal deliveries, infertility and pregnancy complications. Nevertheless, ERCD was associated with significantly fewer maternal/neonatal complications while f-TOLAC had significantly higher rates of: uterine rupture (1.95% vs 0.12%, p<0.0001), scar dehiscence (4.6% vs 1.4%, p<0.0001), postpartum hemorrhage (18.8% vs 6.5%, p<0.0001), blood products transfusion (5.5% vs 2%, p<0.0001), prolonged maternal hospitalization (50.1% vs 34.8%, p<0.0001), 5' Apgar <7 (2.9% vs0.5%, p<0.0001), NICU admission (5% vs3.3%, p=0.040) (Table) .

Conclusions: Women who elected ERCD seem to do better despite extant background complications. A validated prediction model for a customized approach to aid clinicians in identifying women likely to suffer f-TOLAC should be a priority for inter/national experts. This has long-term implications both clinically and financially.

Clinical and genetic characteristics of young women with breast cancer in Jerusalem, Israel

***T. Hadar*[1,2], *N. Ozer*[1], *O. Olsha*[1], *S. Lolas*[2,3], *A. Tomer*[2,3], *R. Abu-Dalo*[1], *M. Carmon*[1] *and E. Levy-Lahad*[2,3]**

[1]Unit for Breast Health, General Surgery Department, Shaare Zedek Medical Center, Jerusalem, Israel. [2]Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel. [3]Faculty of Medicine, Hebrew University of Jerusalem, Israel

Background: Our breast center treats a diverse patient population of Ashkenazi Jewish (AJ), non-AJ and Arab origin. There is little knowledge of founder mutations in the non-AJ and Arab populations.

Methods: Retrospective chart review of 25-40 year old AJ, non-AJ and Arab women who had surgery for primary stage 0 to 3 BC from January 2000 to May 2014.

Results: Clinical and genetic characteristics of young breast cancer patients origin:

Family origin in the non-AJ population was diverse. Common countries of origin were Morocco -23.3%, Iraq -17.2%, Kurdistan -8.3% and Iran -7.5%.

One non-AJ patient was found to have BRCA1-185delAG mutation and 3 others - non founder BRCA1 or 2 mutations. 2 Arab patient had mutations in BRCA1 and one in the ATM gene. Patients of AJ origin had 6 BRCA1-185delAG, 3 BRCA1-5382insC, and two non-founder mutations.

Conclusions: Young breast cancer patients treated in our institution have diverse geographic family origins. Almost all young AJs with BC referred to genetic counseling are tested. Most non-AJ and Arab women referred, were also tested, although little is known regarding founder mutations in these populations. Rate of mutations was in the expected range. No difference between the ethnic groups was found in terms of tumor characteristics. There was a low rate of contralateral prophylactic mastectomy -8.9%, none in the Arab group. We expect changes in genetic counseling and testing in the near future, with sophistication of testing methods and introduction of more extensive gene panel tests.

Concept changes in management of the axilla in breast cancer after the Z0011 trial, as reflected by a dramatic drop in frozen section utilization.

Moshe Carmon, Sofia Zilber J , Oded Olsha, Tal Hadar, Ribhi Abu Dalo, James Tankel, Eliahu Golomb

Introduction: Traditionally, axillary nodal status is a major factor in determining early breast cancer stage and prognosis (TNM; Tumor, nodes, metastasis). In the last decades biologic markers such as hormone receptors are taking the center stage, In 2002 the American B04 study showed that treatment mode of axillary nodes and their removal do not affect survival, with a 25 year follow-up. In 2011 the Z0011 study by A. Giuliano proved axillary clearance sentinel node positive breast cancer patients having a lumpectomy affects neither survival nor local recurrence rate. This brought a dramatic world-wide drop in the rate of axillary clearance, with reduced risk of arm lymphedema.

Aim: To assess the impact of the Z0011 study on surgical routines in the management of breast cancer patients, as reflected by the utilization of frozen section examinations of axillary nodes.

Patients and methods: We reviewed our prospective database of patients operated in our service before and after the publication of the Z0011 study in February 2011. The rate of frozen section examination of axillary sentinel lymph nodes performed in patients having lumpectomies were recorded and compared.

Results: 390 patients were included from the era before 2011 and 644 patients from the time following the publication. In the first group, 217 patients had a lumpectomy with a sentinel lymph node biopsy. The rest had either a mastectomy or an axillary lymph node dissection. Frozen section examination was performed in 199 of the 217 relevant patients (91.7%). In the group operated after 2011, 367 patients had a lumpectomy with a sentinel lymph node biopsy. Of these, 16.3% had a frozen section. The frozem section rate was 40% during 2012, and gradually dropped to 9% during 2016.

Conclusions: The main and dramatic Significance of the results of the Z0011 study is the world-wide reduction of the risk for arm lymphedema in breast cancer patients. . As a result of omitting axillary dissection in sentinel lymph node positive patients having lumpectomies, frozen section of the nodes during surgery lost its significance and is being abandoned quickly in these patients. This was dramatic in our breast service with a reduction from over 90% frozen section rate before the Z0011 publication to 40% in the year immediately after its publication. The rate continued to drop and reached 9% in 2016.The changes in the utilization of frozen section examinations for evaluation of axillary lymph nodes in breast cancer patients are significant. They reflect the changes in the significance attributed to the nodes in respect to prognosis and local recurrence as adjuvant treatment improves continuously. Many experts already imply the Z0011 study conclusions on patients having mastectomies. Many decisions regarding adjuvant chemotherapy are no longer depended on nodal status. We may be witnessing the end of the era of the central importance attributed to axillary lymph node status in breast cancer.

Contralateral prophylactic mastectomy: not an uncommon choice by normal risk breast cancer patients having breast reconstruction. Experience of one year, 86 consecutive patients and 127 mastectomies with immediate reconstruction.

Benyamin Kaminer, Tal Hadar, Izhak Tuchman, Oded Olsha, Ribhi Abu Dalo, Rami Binenboym, Yoav Gronowitz, Gili Halftec, Eliahu Golomb, Moshe Carmon

The Breast Unit Shaare Zedek Medical Center

Introduction: Modern surgical techniques, improved implants and increasing experience seem to increase the rate of immediate breast reconstruction when mastectomy is performed. The introduction and availability of a-cellular dermal matrix also helps when radiotherapy is an option or even planned since aesthetic results and safety have improved in this setting. Some subsets of patients choose to add a contralateral prophylactic mastectomy (CPM).

Aim: to check the rates of bilateral mastectomies, the rates and causes of having CPM, and the characteristics of patients choosing this option

Patients and methods: We reviewed our prospective database of patients operated in our service who had mastectomy with immediate reconstruction during 2015. Patient's characteristics and pathology were recorded and analysed

Results: 86 patients had a skin sparing or subcutaneous mastectomy with immediate implant reconstruction. Two had unilateral surgery for benign disease. Two additional patients had bilateral prophylactic surgery for mutations (one BRCA patient and one palb2 carrier patient).

41 patients (47%) had a bilateral mastectomy. Only 4 (4.8%) had a bilateral tumor. The rest chose to have a contralateral mastectomy without proven cancer. In 2 there were abnormal MRI findings without tissue diagnosis. Excluding these and pure prophylactic surgery, of the 37 remaining patients 11 had a BRCA mutation, 14 had a family or personal history of breast cancer and 12 (32%) had no known increased risk factors for future additional breast cancer.

Conclusions: Bilateral mastectomy with reconstruction is a major undertaking with significant physical and emotional consequences. The patients most likely to benefit from CPM are probably those with a significantly increased risk of additional future tumors. Indeed, all our BRCA patients preferred CPM. Yet, improved symmetry, reduced risk of a need to cope with future suspicious findings, and perhaps improved surgical outcomes are probably reflected by the high proportion of normal risk patients choosing CPM in our study.

The Abstract is based on data collected for the MD thesis of the first author, in progress.

Criteria for clinical use of Marginprobe in breast conserving surgery

Oded Olsha, Mahmoud Salman, Tal Hadar, Ribhi Abu Dalo, Moshe Carmon

Unit for Breast Health, General Surgery Department, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Reoperation is recommended when margins are involved after breast conserving surgery (BCS). Marginprobe (Dune Medical Devices Ltd, Caesarea, Israel) reduces involved margin and relumpectomy rates in nonpalpable intraductal and invasive breast cancers. It generates local radiofrequency fields a few mm deep and captures the reflected signal to detect bioelectric differences between normal tissue and cancer cells. This study investigated the indications for use and clinical outcome in patients having BCS since introduction of Marginprobe into routine clinical practice.

Methods: Files of patients having BCS using Marginprobe were examined retrospectively. The instrument was used at the discretion of the surgeon. Involved margins were tumor <1 mm from or involving the inked margin. Malignant final pathology was invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) and ductal carcinoma in situ (DCIS).

Results: Twenty-five patients of mean age 58 (median 60, range 32-82) had BCS using Marginprobe from September 2014 to September 2015. Fifteen (60%) had breast magnetic resonance imaging preoperatively. Preoperative and final pathology are shown in the table. Marginprobe indicated 1 involved margin requiring re-excision in 4 specimens, 2 margins in 7 specimens, 3 margins in 5 specimens and 4 margins in 9 specimens. 3 of 22 patients with malignancy at final pathology had involved margins, 2 (9%) of whom had more surgery to obtain clear margins. The third patient had a single duct with DCIS at the margin and had no further surgery.

Conclusions: After introduction into clinical use, Marginprobe was used exclusively in patients with lesions that confer a risk of margin involvement or whose margins are difficult to detect clinically (lobular or ductal in situ components). The reoperation rate was acceptably low for these lesions.

Table. Pathologic diagnosis in 25 operations using Marginprobe

Preoperative diagnosis	Number	Final diagnosis	Number
IDC	5 (3 with DCIS, 1 with microcalcifications, 1 with lobular features)	IDC	6 (3 upstaged from DCIS)
ILC	4	ILC	7
DCIS	15	DCIS	9
LCIS	1	BENIGN	3 (2 ADH, 1 ALH)

IDC -invasive ductal carcinoma; ILC -invasive lobular carcinoma; DCIS -ductal carcinoma in situ; LCIS -lobular carcinoma in situ; ADH -atypical ductal hyperplasia; ALH -atypical lobular hyperplasia.

Fibrin Sealant To Reduce Lymphatic Drainage After Axillary Dissection -A Single Cohort Study

Oded Olsha, Tal Hadar, Naomi Verocherinsky, Itamar Ashkenazi

Background: After axillary dissection drains are left in place for 5 to 10 days until 24 hour drainage decreases to a predetermined amount, almost always less than 50ml per day. The harmonic scalpel (Harmonic Focus, Ethicon Endo-Surgery, Cincinnati, OH) and electrothermal bipolar vessel sealing (Ligasure, Covidien, Dublin, Ireland]) have shown promise in reducing axillary drainage when compared with unipolar diathermy, but are expensive. TachoSil (Nycomed, Linz, Austria) is a fibrin sealant that has proven efficacy in the control of surgical hemorrhage in a variety of tissues. There is evidence suggesting that it may also reduce axillary drainage and it is less expensive by 30-40% than instruments used for vessel sealing. When we started using Tachosil as standard in axillary dissection, we recorded its use in each patient to determine the number of days of axillary drainage and if there were any adverse effects.

Methods: The use of Tachosil in patients undergoing axillary dissection was prospectively documented. A Tachosil patch 9.5 cm x 4.8 cm in size was placed over the axillary vein to cover the vein and the space between pectoralis minor and the chest wall medially, and the area over the exit of the intercostobrachial nerve and axillary vein laterally. Axillary drains were removed when drainage was less than 50 ml/24 hours or if there was leakage around the drain sufficient to stain the patient's clothing.

Results: Twenty-three consecutive patients undergoing axillary dissection who had fibrin sealant placed at the end of the procedure were included in this study. Seven had neoadjuvant chemotherapy. One of the patients had sentinel node biopsy before axillary dissection, and the rest had axillary dissection on the basis of known lymph node metastases. One additional patient had axillary dissection without breast surgery for axillary recurrence a year after mastectomy and negative sentinel node biopsy. 12 patients had a simultaneous mastectomy. All 12 patients with concurrent mastectomy had an additional drain under the skin flaps and 7 other patients had breast drains as part of their oncoplastic resections. The average number of lymph nodes removed was 25 (median 23, range 10 to 59). The average number of metastatic lymph nodes was 6 (median 3, range 0 to 59). Axillary drains were removed at a median of 4 days (mean 5.0, range 1 to 14). 15 (65%) of the axillary drains were removed on or before the fourth day. Complications were axillary seroma that did not require drainage (1), axillary cellulitis that resolved with oral antibiotics (2) and fever without an identifiable source (1), breast flap seroma (1), infection under breast flaps requiring open drainage (2).

Table-axillary drain removal in 23 patients treated with Tachosil

Postoperative day	No. of patients	Cumulative (% of total)
1-2	2	9
3-4	13	65
5-6	3	78
7-8	4	96
9-14	1	100

Conclusion: The use of Tachosil in axillary dissection limited the duration of axillary drainage compared with that quoted in the literature and may be a useful and less expensive method to achieve this end than vessel sealing instruments.

Hygroscopic Ultrasound Detectable Clips - Six Months Detectability, Uses In Breast Cancer Surgery

Moshe Carmon[1], Oded Olsha[1], David Gekhtman[1], Irena Nikitin[1], Yemin Cohen[2], Michael Messing[2], Natalia Lubashevski[2], Ribhi AbuDalo[1], Tal Hadar[1], Eliahu Golomb[1]

[1]The Breast Health Unit, Shaare Zedek Medical Center[1], The Hebrew University, Jerusalem

[2]The Rachel Nash Jerusalem Comprehensive Breast Clinic

Purpose: Radiologically detectable metal clips have been used for diagnosis and treatment of breast disease since the 1990's. These clips indicate lesions location and enable correlation across different imaging modes. Sonographically detectable clips (SDCs) have been introduced in the last decade. We assessed SDC use in breast cancer management, its safety, and rate and duration of their detectability.

Methods: We retrospectively studied patients who had deployment of SDCs from 2011-2013, using Hydromark clips (Biopsy Sciences, Clearwater, FL).

Results: 26 patients had SDC deployment, 19 by radiologists and 7 by surgeons during anesthesia for sentinel lymph node biopsy before neoadjuvant treatment. Nine of the 26 patients had neoadjuvant chemotherapy, with all clips remaining detectable 140 to 187 days after insertion. Of these, 3 had mastectomy and 6 had intraoperative ultrasound localization by the surgeon with one patient requiring re-excision (17%). 11 additional patients with non-palpable tumors and SDCs had intra-operative ultrasound localization by the surgeon, one of whom required re-excision (9%). One patient had a clip placed in a suspicious lymph node that was detectable by both intra-operative ultrasound and radioactive probe at surgery. The surgeon did not use the USDC in 4 other patients. There were no complications or clip migration.

Conclusions: SDCs are easily seen by the surgeon. They can be helpful in primary surgery in non-palpable breast cancers as well as after neoadjuvant chemotherapy. They remain visible by ultrasound over many months. Preoperative wire guide insertion and scheduling difficulties can often be avoided.

Surgical management of the axilla in breast cancer patients 75 years and over after the implementation of ACOSOG Z0011 study

Hadar T[1], Olsha O[1], Tahover E[2], Abu-Dalo R1, Carmon M[1]

[1]Breast Surgery Unit, Department of General Surgery, Shaare Zedek Medical Center, Jerusalem, Israel

[2]Oncology Department, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Elderly breast cancer patients are often under-treated. This has greater significance in terms of axillary management in the era of the implementation of ACOSOG Z0011 study which caused a shift towards less extensive axillary surgery, and with the tendency towards less radiation therapy for this patient population.

Methods: Retrospective review of women 75 years and older, who had surgery for primary invasive breast cancer from 2013-2014.

Results: 73 breast cancer surgical procedures were done. Median patient age was 79.

There was no significant difference in the American Society Association (ASA) score between patients having mastectomy and those undergoing breast conserving surgery.

59 (81%) of tumors were invasive ductal carcinoma (IDC). 65 (89%) were ER positive, 7 (9.6%) were HER2 positive. Median tumor size was 16mm for breast conservation procedures and 32.5mm for mastectomies.

There were 51 lumpectomy procedures. 4 had no axillary surgery. 38 had sentinel lymph node biopsy (SLNB), with frozen section (FS) in 10. In one case nodes were positive and the patient had intraoperative completion axillary lymph node dissection (ALND) and adjuvant radiotherapy (RT). 4 of 28 lumpectomies without FS had positive nodes, one of them having completion ALND during a second surgery for inadequate margins, and subsequent RT. Two others had adjuvant RT without completion ALND. Seven of 9 lumpectomy patients who had ALND without SLNB had adjuvant RT. 54.9% of the elderly patients who were treated with lumpectomy had adjuvant RT.

Of 22 mastectomies, one did not have an axillary staging procedure. One of five patients who had mastectomy and positive SLNB had completion ALND and adjuvant RT. One of 5 patients who had tumors larger than 50mm and 6 out of 14 (42.9%) patients who had axillary lymph node macrometastases received post-mastectomy radiation therapy.

Conclusions: In many cases, treatment of elderly (>75 years) breast cancer patients does not follow routine guidelines in terms of completion ALND and adjuvant RT, with many cases where Z0011 study is not implemented. There is no common treatment decision algorithm in this population.

The dynamic world of Breast Cancer: Is manual breast examination for early detection of breast cancer Obsolete?

Moshe Carmon, Oded Olsha, Ribhi Abu Dalo, Tal Hadar, Mahmoud Salman and Eliahu Golomb

The Breast Unit, Shaare Zedek Medical Center

Background: National mammographic screening programs for breast cancer have been expanding since the 1990's. Screening is continuously improving with the introduction of higher resolution mammography, the addition of screening ultrasound when appropriate and the introduction of MRI in high risk populations. Increased public education has improved compliance to screening. In regularly screened women smaller and smaller tumors are diagnosed.

In 1996 Israel launched a national mammographic screening program with compliance reaching as high as 80% in major cities.

Aim: To evaluate the contribution of routine manual breast examination for early detection of breast cancer in the era of technologically advanced screening by imaging with good public compliance.

Methods: We reviewed our cohort database of 413 breast cancer patients treated by a single surgeon during 2013 to 2015 and charted the mode of cancer diagnosis.

Results: Information regarding 413 patients was reviewed. Screening mammography was the mode of diagnosis in 169 patients (40%). In this group, patients age was 42-89 years, mean of 62. Manual self-examination and symptoms bringing the patient to consultation brought to diagnosis in 185 patients (45%). Patient's age ranged from 23 years to 90, with an average of 56 years. Ultrasound was responsible for the diagnosis in 22 patients (6%, age 34-72, mean 55), and MRI in 16 patients (4%, age 34-68 mean 52 years). Detection by routine manual examination was the mode of diagnosis in only 10 of the 413 patients (2.4%, aged 30-87, mean 51years)

Conclusions: When a screening mammography program is in effect and the public is well informed and educated, the weight of screening for early detection of breast cancer by manual examination is minimal. We believe that this should still be taken with caution, since clinician-patient encounter may be an important contributing factor to compliance to mammographic screening.

Trends in Breast Cancer Diagnosis Since the Initiation of the Israeli National Mammographic Screening Program: Effects on Arab as Compared with Jewish patients

Alexandra Rabotin, Tal Hadar, Oded Olsha, Eliahu Golomb, Ribhi Abu-Dalo, Michael Freund and Moshe Carmon

The Breast Unit, Shaare Zedek Medical Cente

Background: National mammographic screening programs for breast cancer have been expanding since the 1990's. Different ethnic and socioeconomic groups worldwide and within countries have different clinical breast cancer characteristics as well as degree of accessibility to health care. Cultural differences in attitude to diseases and treatment may also play a role.

Aim: To evaluate the differences in the effects of the Israeli National Mammographic Screening Program that was initiated in 1996 on Jewish and Arab patients treated in our hospital.

Methods: We compared clinical and epidemiological data from our cohort database of Arab and Jewish breast cancer patients treated in our hospital during 1997-1999 Group (A) and 2011 through 2013 (group B).

Results: Of 150 patients in group A 13 were Arab and 129 were Jewish. In group B 60 patients were Arab and 307 Jewish. In group A, 17% only of the Arab patients were diagnosed by screening mammography Vs 27% of Jewish patients. This doubled to 54% in Jewish patients in group B but increased only by 6% to 23% in the Arab patient group. In group A no Arab patients had T1a/b tumors Vs 3.6% of Jewish patients, with 28% T1 Tumors in Arab compared to 45% in Jewish patients. This increased to 7.7% T1a+b tumors in Arab patients in group B, with a rise to 25% in the Jewish patients. The rate of T1 tumors in Arab patients increased to 50% in group B Vs 64% in the Jewish patients.

The rate of mastectomies in group A was 68% in the Arab group compared to 52% in the Jewish patients. This dropped to 18% only in the Jewish patients in group B, but hardly changed in the Arab patient group: 60%.

Conclusions: The National Mammographic Screening program brought significant improvement in early detection, more so in the Jewish population then in the Arab population. The influence in respect to shift from mastectomy to breast conservation was dramatic in the Jewish patient group, and practically nil in the Arab patient group.

Efforts to increase awareness to the importance of early detection should continue, with special emphasis on disadvantaged populations,

***The Abstract is based on data collected for the MD thesis of the first author, in progress.**

Breast Surgery In Elderly; Is It Really Safe And Sound ?

Ayal Hassidim MD, Roie Tzadok, Ribhi Abu Dalo MD, Oded Olsha MD, Arye Durst MD, Ohn Sibirsky MD, Petachia Reissman MD, Tal Hadar MD

Department of general surgery, Shaare Zedek Medical center, affiliated with the Hebrew University School of Medicine, Jerusalem, Israel

Background: Prevalence of breast cancer increases with age. Elderly patients are less likely to be offered surgical treatment either due to their comorbidities or age itself. Studies show that surgical treatment should be the common practice in advanced age breast cancer, but this was not established in the very old patient population.

Methods: Retrospective study of female patients who had surgery for breast cancer or for complications of prior surgery between 2011 and 2015 and were 80 years or older. Pre-operative, intra-operative and post-operative records were obtained and data on standard patient safety indicators was collected.

Results: Our study included 58 operations in 55 patients. 8 (14%) were due to recurrent disease or non-adequate margins, 1 (2%) was due to post-operative bleeding. There was one post-operative death. There were complications in 9 (16%) operations 6 of which resulted in hospitalization for seven days or more, compared with average hospitalization of 2.7 days. The average duration of surgery was 78 minutes and 59 drains were inserted. ASA score for patients who experienced complications was significantly higher ($p<0.05$) than in patients who had no complications. The major complications were post-surgical bleeding, falls, transient ischemic attacks, acute renal failure and mental deterioration. No statistically significant association was found between the age of the patients or the duration of the operation and development of complications.

Conclusion: In view of the low complication and mortality rate, age alone should not disqualify patients older than 80 years from breast cancer surgery, even with a high ASA. Prospective studies should be done to determine if there is a benefit in terms of long-term morbidity or survival.

Surgical Management Of The Axilla In Elderly Breast Cancer Patients In The Era Of Z0011

Tal Hadar, Moshe Carmon, Ribhi Abu-Dalo, Ohn Sibirsky, Oded Olsha

Breast Surgery Unit, Department of General Surgery, Shaare Zedek Medical Center, affiliated with The Hebrew University School of Medicine, Jerusalem, Israel

Background: Axillary staging in breast cancer is considered prognostic, with adjuvant treatment determined by biological characteristics. Many elderly patients have no adjuvant treatment. ACOSOG Z0011 was a practice changing study resulting in a shift towards less extensive axillary surgery. We reviewed our practice in axillary management in elderly patients after the publication of Z0011.

Methods: Retrospective chart review of women 75 years and older, who had surgery for breast cancer from 2013-2014 (n=86). Patients with surgery for in breast tumor recurrence were excluded (n=8).

Results: 11 (27%) cases of lumpectomy with SLNB, had intra-operative frozen section examination of lymph nodes. 1/4 cases, which had 3 positive lymph nodes on definite pathological exam in lumpectomy procedures, had completion ALND. The other 3 cases had no completion procedure (2 or less positive nodes). There were 2 level 1 ALND procedures done despite negative frozen section lymph node examination

Conclusions: Among elderly breast cancer patients operated in our institution there are still cases where Z0011 is not implemented. Only a minority did not have an axillary staging procedure, although this would probably not affect decisions regarding adjuvant treatment in this patient population.

Prevention of PTSD by Neurocognitive Training of Emotional Regulation

Naomi Fine, Center for Trauma Research, Shaare Zedek Medical Center, Jerusalem

Michal Ahituv, Center for Trauma Research, Shaare Zedek Medical Center, Jerusalem

Ofer Merin, M.D., Trauma Unit and Department of Cardiothoracic Surgery, Shaare Zedek. Medical Center and Hebrew University Faculty of Medicine, Jerusalem

Arieh Y Shalev, M.D., Professor of Psychiatry Department of Psychiatry, NY Langone Medical Center

Introduction: The immediate aftermath of traumatic events is a period of enhanced neural plasticity, following which some survivors develop post-traumatic psychopathology whereas others recover. Evidence points to impairments in emotional reactivity, emotion regulation, and broader executive functions as critically contributing to the risk for post-traumatic psychopathology upon trauma exposure. Emerging evidence further suggests that the neural systems that underlie emotional reactivity, regulation and broader executive functions remain plastic in adulthood and that targeted training enhances their efficiency, and hypothetically reduces the likelihood of developing PTSD. Hypothetically as well, such intervention may be especially efficient during a window of opportunity that follows trauma exposure. We present a study design that investigates the direct effects of targeted, cognitive-affective remediation training on neurocognitive mechanisms that underlie post-traumatic psychopathology (primary outcome) and explores the amelioration of emerging PTSD symptoms (secondary outcome) at the early aftermath of trauma exposure.

Method: The proposed study design addresses three major challenges to early neurocognitive interventions, feasibility and adequacy: (a) reliably and promptly identify, evaluate, randomize and enroll survivors at risk of chronic psychopathology, (b) offer intense, acceptable, targeted and potentially efficacious neurocognitive intervention, and (c) define and administer control conditions and relevant outcome measurements. Successive phases of the design include screening, identification and initial neurocognitive assessment of survivors at-risk, administering and monitoring Web-based interventions and control conditions (30 minutes per day for 30 days), evaluation of primary and secondary outcomes and their persistence after treatment termination. We will address methodological considerations that underlie our choices of study sample, timing of intervention, measurements, expected outcome and statistical power, intervention and control condition, adherence, interviewers' competency and blindness, and team burnout.

Discussion: The proposed protocol offers a template for targeting causative mechanisms in early prevention of PTSD, evaluating the interventions' effect on targeted, objective measures and subjective report of symptoms.

Auditory responses to stimulation at soft tissue sites before and after fixation of mobile components of the middle ear

Ronen Perez*[1]*, MD, Cahtia Adelman2, PhD, Jean-Yves Sichel*[1] *MD, Haim Sohmer*[3]*, PhD

[1]Department of Otolaryngology-Head and Neck Surgery, Shaare Zedek Medical Center affiliated with the Hebrew University Medical School, Jerusalem, Israel

[2]Speech & Hearing Center, Hebrew University School of Medicine - Hadassah Medical Center, Jerusalem, Israel

[3]Dept. of Medical Neurobiology (Physiology), Institute for Medical Research - Israel-Canada, Hebrew University-Hadassah Medical School, Jerusalem, Israel

Background: In recent years, a new mode of auditory stimulation called "soft tissue conduction" (STC) or non-osseous bone conduction has been described. It is believed that the soft tissue conduction complements the well-established air conduction (AC) and bone conduction (BC) modes of auditory stimulation. On the other hand, since STC stimulation uses the same bone vibrator as in BC, it is possible that STC is simply a form of BC. The present study was conducted in order to investigate this possibility.

Methods: Six sand-rats initially underwent ablation of the left cochlea and opening of the right bulla. This was followed by measurement of auditory nerve and brainstem responses (ABR) thresholds to AC, BC and STC stimuli. AC stimuli were given through an insert earphone, BC through a bone vibrator to the skull and STC by applying the same bone vibrator to the sub-mental area. After baseline threshold measurements, the middle ear ossicles including the stapes footplate and the round window were totally fixated by immobilizing them with super glue (cyanoacrylate), thus eliminating the classical BC mechanisms. After the glue had dried, the AC, BC and STC ABR thresholds were determined again in the presence of the immobilization and compared to baseline measurements.

Results: Initial mean ABR thresholds before and after immobilization of the round window and ossicles in response to AC stimulation were 53.3±6.8 and 91.7 ± 11.3 dB pe SPL respectively. In response to BC stimulation the thresholds were 81.7±6.8 before and 80.8 ± 7.4 dB (instrument settings) after. With STC stimulation at the sub-mental area ABR thresholds were 99.2±2.0 before and 98.3 ± 4.1 dB (instrument settings) after the immobilization. Thus, mean air conduction responses were significantly elevated by 38.4 dB (two tailed paired t-test, $p<0.00001$) (conductive hearing loss), but mean BC and STC thresholds were virtually unchanged following the immobilization (in each, mean thresholds improved non-significantly by less than 0.9 dB; BC $p= 0.61$, STC $p=0.36$).

Conclusion: Even though the two windows were no longer mobile and bulk fluid flow is therefore no longer possible, and a pressure difference across the basilar membrane would not be induced, STC and BC thresholds were not altered. These and additional results from previous experiments provides evidence that STC may not be variant of BC, and that STC activation at low sound intensities may not be based on a passive traveling wave which requires two mobile windows.

Multiple electro-stimulation treatments to the promontory for tinnitus

Ronen Perez*[1] *MD, Chanan Shaul*[1] *MD, Michael Vardi*[2] *M.Sc., Nidal Muhanna*[1] *MD, PhD, Paul R Kileny*[3] *PhD and Jean-Yves Sichel*[1] *MD

[1]Department of Otolaryngology-Head and Neck Surgery, Shaare Zedek Medical Center affiliated with the Hebrew University Medical School, Jerusalem, Israel

[2]EStimME, Tel-Aviv, Israel

[3]University of Michigan Health System, Otolaryngology- Head and Neck Surgery, Ann Arbor, MI USA

Background/aims: Tinnitus is a subjective phantom perception of sounds in the absence of a real external auditory stimulus. While 10-20% of the of the adult population experience chronic tinnitus, 1-3% suffer from its severe form which in most cases includes sleep disturbance, decreased concentration and psychiatric pathology such as anxiety and depression. Unfortunately, to date there isn't a satisfactory treatment modality for this vast number of patients. First reports of suppressing tinnitus using electro-stimulation go back as early as 1801. The objective of the current study was to assess the safety and efficacy of multiple sessions of electro-stimulation by a trans-tympanic needle electrode on the promontory for tinnitus relief.

Methods: Ten patients (8 males, 2 females), mean age 50.1±12 years (range 34-67) with severe unilateral tinnitus completed all stages of the study. Patients with tinnitus duration between 6 months to 3 years were included. The patients underwent three consecutive, alternate day, 30 minute sessions of bi-phasic charge balanced electro-stimulation pulses to the promontory near the round window. The stimulation was delivered by a trans-tympanic needle electrode. The main outcome measures included: 1) Tinnitus loudness reported by visual analog scale (VAS) between 1-10, at baseline, before and after each treatment, and 1, 2, 3 and 4 weeks following the last treatment. 2) Tinnitus Handicap Inventory (THI) questionnaire at baseline and 4 weeks after treatment. 3) Tinnitus specific audiometric tests which included minimum masking level, dominant pitch match and tinnitus loudness at baseline and 4 weeks after treatment. 4) Repeat physical examination throughout the duration of the experiment and basic audiometry testing at baseline and 4 weeks after treatment (for safety assessment).

Results: No long term adverse safety outcomes were noted in physical examination or audiological evaluation. VAS levels decreased by ≥2 levels in 5 patients (50%) and returned to baseline 4 weeks after treatment. The VAS decrease was found significant ($p=0.048$) in those patients. A statistically significant correlation ($p<0.01$, correlation coefficient 0.787) was observed between the VAS level decrease and the duration of tinnitus. In addition, a significant decrease in THI total score as well as in all three sub-categories of the questions (functional, emotional and catastrophic) was noted 4 weeks after treatment. Tinnitus specific tests at that time were unchanged from baseline.

Conclusion: Multiple sessions of electro-stimulation to the promontory appear to be safe and may be beneficial for some tinnitus patients. Further clinical trials are warranted.

Selective Non-Operative Management Of Traumatic Splenic Injury - A Five Years Single Trauma Center Experience

Alon D. Schwarz, Ofer Merin, Petachia Reissman

Trauma Unit, Department of General Surgery, Shaare Zedek Medical Center, Jerusalem

Background: Splenic injuries constitute the most common injuries accompanying blunt abdominal traumas. Over the last century, the management of splenic injuries has evolved from expectant management to mandatory operative intervention and to the current evidence based practice of selective non-operative management (SNOM) in the hemodynamically stable patients. Angioembolization is well established as a minimally invasive intervention that increases the successful non-operative management rate.

Aim: To present our clinical experience with SNOM of traumatic splenic injuries.

Methods: A retrospective study that included 100 cases of traumatic splenic injuries that were treated in the trauma unit of Shaare Zedek medical center between January 2010 and January 2015.

Results: 47 patients (47%) had mild splenic injury (AAST I or II) while 53 patients (53%) had severe splenic injury (AAST III or greater). The management included 21 splenectomies (21%). The successful SNOM rate was 86% with a failure rate of 8.1%. There was strong association between isolated splenic injury and successful SNOM ($p<0.001$). There was no association between the injury grade and the failure rate of SNOM. Cases of delayed splenic rupture occurred up to 13 days following the initial injury.

Conclusions: SNOM is the treatment of choice in traumatic splenic injuries of grades I-IV. Failure of SNOM may occur but in low rate and with minor morbidity and mortality rates.

Obscure Gastrointestinal Bleeding In Patients With Aortic Stenosis (Heyde's Syndrome) - Case Report

Schwarz AD MD, Edden Y MD, Sibirsky O MD, Reissman P PhD

Department of General Surgery, Shaare Zedek Medical Center, Jerusalem

Case Report :

In 1958, EC Heyde MD published 10 cases of calcific aortic stenosis associated with severe gastrointestinal bleeding. The combination of calcific aortic stenosis and iron deficiency anemia due to gastrointestinal bleeding was later described as Heyde's syndrome1. Since that publication some theories were proposed for the pathophysiology of this phenomenon2.

The believed pathophysiology is an acquired deficiency in Von-Willebrand Factor caused by the turbulence flow over the calcified valve and resulting in coagulopathy and causing angiodysplasia along the gastrointestinal tract3.

We present a case of an 81 year old woman with obscure gastrointestinal bleeding and severe aortic stenosis and who was admitted to the surgical department. The patient underwent extensive workup that included multiple upper and lower endoscopies and imaging studies that failed to identify and address the source of bleeding.

After presenting with systemic symptoms and receiving 11 units of blood she was taken emergently to the operating room. An exploratory laparoscopy did not reveal small bowel anatomic abnormalities and an intra-operative enteroscopy was performed. That procedure as well did not demonstrate specific vascular pathology or clear source of bleeding.

Eventually, after the bleeding has stopped spontaneously, she underwent angiographic aortic valvuloplasty successfully and was discharged home in a stable condition without further episodes of gastro-intestinal bleeding.

We believe that Heyde's Syndrome is under-diagnosed since it considered as an extremely rare entity. The aim of this presentation is to bring this syndrome to awareness and present our proposed study for investigating the real prevalence of this phenomenon.

Ultrasound as a primary imaging modality for follow up of Crohn`s disease in pregnant women: initial results

***Aner Keinan*[1], *Kuint Ruth Cytter*[2], *Benjamin Koslowsky*[3], *Eran Goldin*[3], *Ariella Bar-Gil Shitrit*[3]**

[1]Surgery department, [2]Radiology department and [3]Digestive diseases institute

Background: Imaging pregnant women with Crohn`s disease is very challenging. The use of CT and MRI is restricted due to radiation or the inability to inject gadolinium.

Lack of radiation makes the ultrasound (US) imaging study of choice for many medical conditions in pregnancy. However, especially in advanced stages of pregnancy, the bowel is pushed by the uterus and the normal anatomy is altered, which makes the scanning more difficult.

Aim: To evaluate the accuracy and the reliability of ultrasound in the assessment of Crohn`s disease in pregnant women with comparison to post-partum MR/CT enterography.

Materials and methods: In this prospective study (still ongoing), pregnant women with known or suspected Crohn`s disease' were referred from the IBD- MOM clinic (a multi-disciplinary clinic for follow up of pregnant IBD patients) for sonographic assessment of abdominal symptoms (pain, bloating, etc.). The study was approved by the institutional review board with waiver of informed consent.

Patients` demographics, clinical information and imaging findings were collected for all cases. Radiologic findings included: abdomen wall thickness, bowel wall thickness, mucosal irregularity, bowel wall hyperemia and strictures. Mesenteric changes and extra-luminal findings were evaluated as well. US studies were compared with post-partum MR/CT enterography.

Results: 19 patients enrolled in the study. Three of them were scanned more than once. Mean age was 30y±5.8 (range 20-39y). Pregnancy week ranged from 8-32 weeks. 14 patients had known CD disease (in 5 there was a suspicion of CD). Bowel wall changes were noted in 15 patients and changes in the mesentery in 6 patients. The terminal ileum was detected in 15 patients. No correlation was found between the abdomen wall thickness or the week of pregnancy to the quality of imaging of the TI (P=0.23 and p=0.93 respectively).

Till now, 8 women had post-partum CT/MR enterography. In 7 women, findings were correlated with the US findings. In one case an entero-enteric fistula was missed by the US. (5 women will have their MR enterography in the next 2 months.)

Conclusions: These initial results are indicative of the potential of US as a primary tool for follow up of CD in pregnancy. Meticulous scanning is informative in most women throughout the whole pregnancy period.

Does Nurses' Cultural Background Impact Pain Management?

***Annika Schwarz, RN, MA*[1], *Zila Cohen, RN, MA*[2]**

[1]Head Nurse - General Surgery department

[2]Severe Pain Coordinator - Nursing Management

Background: Surgical pain is a known phenomenon that is described extensively in the medical literature. Pain treatment today offers a variety of analgesic agents that are well tolerated and can be tailored to meet individuals' conditions and needs. Pain management is regarded as an integral part of the healing process. Studies have shown that proper post-surgery pain management, decreases the length of hospital admissions, and promotes a better recovery with fewer complications.

Pain is a subjective sensation, may be strongly related to a person's background, upbringing, beliefs and cultural myths.

Shaare Zedek Medical Center is a reflection of the demography of Jerusalem and its neighboring communities. Both nursing staff and patients come from an array of diverse cultures: Jewish, Christians and Muslims, with their various subgroups. Cultural backgrounds may have various practices, myths and perceptions relating to post-surgical pain. The literature describes pain perceptions in relation to culture from the patient's point of view; however, until recently, pain perceptions among nurses in the context of culture have not been discussed.

Aims: The proposed study (2013) intended to explore the staff's cultural perception regarding pain specifically during the post-operation phase, and its impact on pain treatment. Despite the fact that there are protocols for pain management, it appears that patients are not treated accordingly for post-op pain. We hypothesize that there is a correlation between the nurse's perception of pain, and decisions regarding pain management.

Methods: Data was collected via a Likert scale questionnaire to the nursing staff in the various surgical wards. Questions focused on pain perceptions in cultural context. Demographic questions included: country of birth, religion and education.

Results: 60 questionnaires were collected. From the analysis it appears that cultural background, religion and gender are less significant in decisions regarding pain management. Even though, nurses don't tend to consume pain meds for their own light nor severe pain, they tend to dispense pain meds appropriately for patient's pain, light or severe.

In addition, it appears that nurses apply a judgmental approach upon patient's self-report of pain level. Nurses tend to assess patients' pain based on his/ her behavior, conduct, facial expression. This finding is in accordance with universal literature regarding the nurses' personal impression vs patients' self-report.

Staff training, rather than place of birth carries a greater impact on pain management

Conclusion: In order to treat patients appropriately, it is advised to invest in staff training.

Laparoscopic Adrenalectomy Of Large Adrenal Lesions

Halfteck G MD PhD, Sibirsky O MD, Keinan A MD, Reissman P PhD

Department of general surgery, Shaare Zedek Medical center, Jerusalem

Introduction: Laparoscopic adrenalectomy became the procedure of choice for small and benign adrenal lesions. With the experience gained, many surgeons expanded the range of indications for laparoscopic adrenalectomy and nowadays this approach is used for large adrenal lesions and in lesion suspicious for malignancy. However, great controversy exists regarding the oncological safety of this approach and therefore some surgeons still prefer using the open technique.

Purpose: Assess the outcome and the oncological safety of laparoscopic adrenalectomy of large adrenal lesions.

Methods: Retrospective analysis of prospectively collected data of all consecutive patients who underwent laparoscopic adrenalectomy in our department during the years 1995-2014 for lesions of 6 cm. or larger.

Results: Fifty patients out of 230 who underwent laparoscopic adrenalectomy, were included. The main indications for surgery were functional tumors such as pheochromocytoma (15 pts, 30%) and Cushing's syndrome (11 pts, 22%) and non-functional lesions (13 pts, 26%). Two patients had lesion suspicious for malignancy. In all cases the lateral trans-peritoneal approach was employed. Four (7.84%) intra-operative and five (10%) post-operative complications were documented. The latter include high fever, surgical wound infection and stroke. Three (6%) operations were converted to open due to uncontrolled bleeding (2 pts) and hemodynamic instability (1 pt). The final histopathological diagnoses in the majority of patients were adenoma (20 pts, 40%) and pheochromocytoma (13 pts, 26%). Three patients (6%) were diagnosed with adrenocortical carcinoma. During up to 5-year follow-up, no local or distant recurrences were found.

Conclusions: The laparoscopic approach for removal of adrenal lesions larger than 6 cm is safe in respect of intra- and perioperative morbidity and the oncological safety. The true incidence of malignancy in large adrenal lesions appears to be lower than reported in the literature. In high-volume centers the laparoscopic approach should be attempted for large adrenal lesions.

Gastric Cancer Developing After Pancreaticoduodenectomy With Pancreaticojejunostomy: Case Report

Halfteck G MD PhD, Sibirsky O MD, Alberton J MD

Department of general surgery, Shaare Zedek Medical center, Jerusalem

Case report:

A 75-year-old man underwent pancreaticoduodenectomy with pancreaticojejunostomy in June 2008 for Ampulla of Vater cancer. He was followed up in our outpatient clinic. In January 2014 the patient presented with melena and upper GI endoscopy revealed a polypoid mass in the gastroesophageal (GE) junction and signs if bile gastritis. A biopsy revealed high grade dysplasia with foci of intramucosal gastric adenocarcinoma. With a diagnosis of gastric cancer, the patient underwent total gastrectomy in April 2014. The pathologic exam showed an intramucosal well-differentiated adenocarcinoma.

Six cases of gastric cancer occurring after pancreaticoduodenectomy have been reported thus far. However, all patients described underwent pylorus-preserving pancreaticoduodenectomy with pancreaticogastrostomy (PG), and were reported from Japan. Authors have speculated that excretion of pancreatic juices and bile reflux into the gastric cavity can damage gastric mucosa and play a role in the carcinogenic process. However, a causal relationship has not been proved.

The present report describes a rare case of gastric cancer developing 6.5 years after Whipple's procedure for ampullary cancer in a patient undergoing conventional pancreaticoduodenectomy (Whipple's procedure) with pancreaticojejunostomy.

Vascular Access Creation In Elderly Patients

Hijazi J MD2, Shemesh D MD RVT[2], Sibirsky O MD[1], Olsha O MD1 BS, Goldin I MD[2].

Department of Surgery[1] and Hemodialysis Access Center[2]

Shaare Zedek Medical Center, Jerusalem, 91031, ISRAEL

The number of elderly patients requiring hemodialysis is growing rapidly1 and they are more likely to have dialysis via central catheters.2 In our center, patient age has not been a consideration in the decision to construct arteriovenous hemodialysis access, with the oldest patient to have access surgery aged 94 years.

Using pre-operative planning, 88% of accesses constructed in patients aged over 80 were autogenous, with one-year secondary patency of 91.7%, compared with 90% for 220 patients of all ages. 24-month secondary patency was 84% for radial cephalic (forearm) accesses and 88% for brachial cephalic (upper arm) accesses. The average time to first failure was 219 days. 5.5% of patients with native fistula had early failure.3 The mortality rate in our patients aged 80 and older with fistula was 21.3% in the first year, compared with a one year crude death rate of 24.9% in Medicare patients receiving hemodialysis who were 67 years and older.4

Higher mortality rates in hemodialysis patients with central vein catheters supports the use of arteriovenous access for elderly hemodialysis patients to reduce mortality and improve quality of life. They should not be disqualified from access surgery solely on account of age. On the contrary, access surgery should be encouraged as there may be no age limit for this procedure. Our findings support the use of radial cephalic fistula as the initial approach in elderly patients if appropriate vessels are available. This should result in fewer complications without compromising patency, while allowing maximal utilization of available vessels.

Influence Of Helicobacter Pylori And Gastritis On Weight Reduction After Sleeve Gastrectomy

Sibirsky O MD, Yellinek S MD, Mintz A MD, Weiss Y MD, Freund M MD, Reissman P MD, Spira RM MD

Department of general surgery, Shaare Zedek Medical center, Jerusalem

Introduction: Laparoscopic vertical sleeve gastrectomy has become the leading bariatric surgical procedure used to treat morbid obesity. The procedure involves removing about 80% of the cells producing Ghrelin leading to success in weight reduction. It may be that the infection is protective against obesity, because of the Helicobacter Pylori (HP) gastritis-induced decrease production and secretion of the orexigenic hormone Ghrelin. However, recent epidemiological studies have failed to show an association between HP infection and reduced body mass index (BMI)

Methods: A constantly updated data base was used for all morbid obesity patients admitted for laparoscopic sleeve gastrectomy in our department from January 2013-July 2014. The pathology report was reviewed for gastritis and for H. pylori. Updated weight was obtained from the patient personally. Mean FU period was 420 days.

Result: 369 patients underwent laparoscopic sleeve gastrectomy in our institution. The average age was 40 (14-70). There were 137 males and 232 females. The initial average BMI was 42 (34-54) which dropped down to a BMI of 28 at follow up. This correlated to a mean initial weight of 119 Kg and post-operative of 80 Kg in the follow up period.

Review of the pathology specimens showed 128 (35%) specimens were positive for HP (HP+) and 194 were negative. Out of 159 pt. diagnosed with gastritis only 124 (78%) detected HP+. The positive predictive value of HP+ for gastritis is 97%.

The median weight reduction was 41 Kg in the gastritis group versus median of 36 Kg in the non-gastritis group (P=0.031) with a BMI reduction of 14.5 versus 11 (P=0.0013). The median BMI reduction was 15.8 in the HP+ group versus 12 in the HP- group (P=0.0022)

Conclusion: Weight reduction following Sleeve Gastrectomy in patients who had gastritis in the specimen was greater than patients who did not. The identification of Helicobacter Pylori infection of the gastric wall was also indicative of greater weight loss.

Laparoscopic Sleeve Gastrectomy For Siblings Achieve Greater Weight Loss Compared With A Control Group Of Unrelated Individuals That Underwent The Same Bariatric Operation

Sibirsky O MD, Yellinek S MD, Mintz A MD, Weiss Y MD, Freund M MD, Reissman P MD, Spira RM MD

Department of general surgery, Shaare Zedek Medical center, Jerusalem

Background: Many variables involving the success of reducing weight after having bariatric surgery and could be influenced by the family environment. Some patients make the decision to undergo bariatric surgery after another family member has had the operation. This study aimed to evaluate the results of laparoscopic sleeve gastrectomy (LSG) performed for several members in the close family compared with a control group of unrelated individuals

Method: We retrospectively reviewed a prospective cohort of 369 patients who had undergone LSG at our institution between January 2013 and July 2014. We found 17 LSG patients with at least one family relation, defined as blood relations for siblings (7) or parent & child (6) or spouses (4) in the cohort (the LSG-family group from 9 different Jewish families). One family member underwent laparoscopic gastric bypass and excluded. The control group are the rest (n=352). The same surgical procedure was performed for all.

Results: The initial BMI was the same in spite of elevated mean weight and high in LSG-family group that were younger (mean age 24 vs. 40, p=0.0050). Breakdown the LSG-family group for age revealed that siblings (19) were younger than parent & child (36) or spouses (38.5) (p=0.0008). Pathological variables including HP+ and gastritis were the same in both groups. Mean FU was 309 days. When LSG-family group examined as one homogeneous group no difference was observed regarding weight loss comparing the control group.

However, when we analyzed separate sub type of the blood relationships we revealed that siblings showed better results than the control group (without family ties) in terms of TWL (48/40 kg p=0.0485), %WL (42.8/33.3 p=0.0620), ΔBMI (13.4/12.9 p=0.1100), %EBMIL (88/82.7 p=00234). Spouses achieved somewhat intermediate results, and the sub group of parent & child achieved relatively poor results.

Conclusion: Laparoscopic sleeve gastrectomy performed for several members in the same family can results in better success of reducing weight for siblings and less for spouses compared with the control group of unrelated individuals. Further series are needed to verify these results.

Laparoscopic Sleeve Gastrectomy For The Treatment Of Morbid Obese Patients In The 60-70 Age Group

Sibirsky O MD, Kreskas A MSc RN, Tsevi E MSc RD, Mintz A MD, Weiss YHJ MD, Freund M MD, Reissman P MD, Spira RM MD

Department of general surgery, Shaare Zedek Medical center, affiliated with The Hebrew University School of Medicine, Jerusalem, Israel

Background: Bariatric surgery may be considered a preventive strategy for complications of morbid obesity. Alas, it may be used as a tool intendant to treat diseases related to obesity and to improve quality of life. As people age we see more of the later.

Method: We retrospectively reviewed a prospective cohort of 629 patients who have undergone laparoscopic sleeve gastrectomy (LSG) at our institution between March 2012 and February 2015. We reviewed 43 patients (6.8%) who have undergone LSG aged 60-70yrs. The control group consisted of the rest of the cohort (n=586). The same surgical technique was performed in all.

Results: The initial BMI was equivalent -41.6kg/m2 (41.1for the over 60 vs. 41.9). Male to female ratio was equal in the over 60 group (22/21) as compared to a female predominance 67% in the younger age group (193/393). Median FU was 407 days.

The operative procedure was significantly longer in the over 60 group; 60min vs. 54min. (P=0.0199)

Weight loss was significantly lower for the over 60 group; TWL (24.1/38 kg p=0.0001), %WL (20.3/31.3 p=0.0001), ΔBMI (8.9/13.3 p=0.0001), %EBMIL (57.6/76.1 p=0.0001).

The complication rates were comparable. No perioperative mortality occurred.

Conclusion: Laparoscopic sleeve gastrectomy performed in the elderly is not as effective in terms of weight loss but can be performed safely.

Laparoscopic Management Of Enterovesical Fistulas In Crohn's Disease

Sibirsky O MD, Dagan A MD, Reissman P MD

Department of general surgery, Shaare Zedek Medical center, affiliated with The Hebrew University School of Medicine, Jerusalem, Israel

Background: Laparoscopic management of complicated Crohn's disease (CD) by enteric fistulas to the urinary bladder (EVF) reported to have higher conversion rate and postoperative complications. The aim to present our experience with the various surgical procedures employed laparoscopically to treat patients with EVF

Methods: In retrospective study we analyzed all our patients (pts) who underwent elective laparoscopic surgery for EVF during 2003-2014. Clinical data and outcome were recorded.

Results: we investigated twenty-eight patients (pts) with EVF 9-females and 19-males mean age was 27 years. Symptoms of EVF had been presented on average 9 years after the diagnosis of CD, and included usually recurrent urinary tract infection (15), pneumaturia (10). 23 pts suffered from an ileovesical fistulas (IVF), 4 had a fistula between the sigmoid colon and the urinary bladder (SVF) and one had a rectovesical fistula (RVF). 18 pts had one or two additional fistulas like ileocolic fistulas (16) and required complementary procedures that were added depending on the findings.

Usually preoperative diagnosis established before operation but in 3 pts the diagnosis was made incidentally during operation for other pathology. All patients with an IVF underwent an ileocecal resection (ICR) comprised basically resection of the fistula tract, debridement and repair of the bladder. Two segmental sigmoid resections (SSR) were done for 2 SVF pts, and 2 subtotal colectomies (STC) performed for another 2 SVF due to diffuse longstanding colonic disease. One patient with RVF underwent low anterior resection (LAR) and was required conversion to an open procedure. Another 3 pts were also converted (total 14%). The mean operating time was 218±57 min for the majority completed laparoscopically versus 255±83 min for the converted cluster. Postoperatively no mortality occurred. 3 (11%) pts had minor morbidity. Length of stay (mean 9 days) was alike for converted and not converted group. Mean FU 6.6 years. All FU pts (n=20) but one (95%) were well with no symptoms of recurrent fistula and none required additional surgery.

Conclusions: Laparoscopic management of enterovesical fistula associated with complicated CD, is feasible and safe, with acceptable conversion rate, low morbidity and excellent long term results.

Acute Sigmoid Diverticulitis -What Has Changed Over The Last Decade?

Sibirsky O MD, Bar-Nur Y MD, Rivkin L MD, Reissman P MD

Department of general surgery, Shaare Zedek Medical center, affiliated with The Hebrew University School of Medicine, Jerusalem, Israel

Background: Sigmoid Diverticulitis (SD) is a frequent disorder in the western world including Israel. The impression concerning SD in recent years was the younger age of presentation and increased occurrence, disease recurrence and severity over the last decade. The aim of our study was to analyze various changes in SD characteristics over time, based on our patients' data.

Methods: We conducted a retrospective study reviewing all the patients records with the entity of SD collected from our hospital computerized data base, from 1998 to 2014. Various parameters including age of first presentation were analyzed.

Results: 1969 patients were included for study analysis, male 810 (41%), female 1159 (59%). 50% of the patients were admitted during the first 12 years of the study period (1998-2010) and the rest of 50% were hospitalized in the following 4 years (2011-2014). The age of first episode for the entire group ranged from 40-100 years (median 67 mean 66.8±14). When dividing the years sequence (1998-2014) to two groups (early and late) of 1998-2006 vs. 2007-2014 and testing the age of presentation for each group, the mean age increased in the late years from 65 to 69 ($p=0.0015$). In the same manner when examined 2 extreme groups: 1998-2002 vs. 2013-2014, again, the mean age increased from 66 to 69 ($p=0.0450$).

278 out of 1969 patients underwent surgery (14%). The interval duration from first diagnosis to surgery was 0-9 (median 0 mean 0.72±1.57) years. And when we plotted those intervals to correlate against the years over the study period, we noticed that the interval between first diagnoses to the surgery was shortened in recent years ($p<0.0001$, $r2 =-0.28524$). It seems that disease severity and complications did not change during the study period.

Conclusions: As expected, we found that the occurrence of SD has increased in recent years. In contrast, the mean age of first episode of acute SD however, is increasing, and the interval between first diagnoses to the operation is shortening. Possible explanations of these findings will be discussed.

Focal laser may be a misnomer: long-term follow-up of argon laser marks in diabetic maculopathy

Dr. Joel Hanhart, Dr. Tamar Levi Vineberg, Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem, Israel.

Background/aims: Macular argon laser was the main local treatment delivered in diabetic macular edema prior to the advent of intraocular injections and is still offered in selected cases. We aim to take advantage of en-face optical coherence tomography (OCT) to assess the long-term structural changes induced by macular argon laser.

Methods: We reviewed the records of adult diabetic patients who had undergone macular laser treatment at least 4 years prior to swept source OCT volumetric imaging, recording demographic and clinical relevant data.

En-face images were flattened at the RPE (retinal pigment epithelium) plane. We determined for each eye the retinal surface covered by laser marks and determined the maximal diameter of the largest identified lesion at this plane.

We moved the analysed plane upwards defining the level of neurosensory retinal damage and measuring its distance from the RPE.We measured total retinal thickness at the location of the most superficial lesion and expressed the level of neurosensory retinal damage as a percentage of retinal thickness. We moved the analysed plane towards the sclera until we could not see any specific lesion. We defined the distance between the RPE and the deeper plane at which laser marks were detected as the level of choroidal changes.

Results: 21 eyes of sixteen patients were analyzed. The mean age (±SD) was 61.7±15.5 years (range: 36-84). Patients had undergone macular laser 6.5±2.8 years (range 4-13) prior to entering our study. On en-face view, depending on the selected plane, laser marks appeared as hypo- or hypreflective structures.

In 16 eyes the most superficial laser marks were detected at the inner plexiform/inner nuclear layers. The level of neurosensory retinal damage was 159±48 microns over the RPE (62.6±18.3% of the retinal thickness). The deepest level at which laser marks were retrieved was 125±110 microns below the RPE.

A positive moderate correlation was observed between time since laser and the surface of retina covered by laser marks at the RPE (Pearson's correlation coefficient=0.36; p=0.1), the deeper level of detected laser marks (Pearson's correlation coefficient=0.35; p=0.1) and the level of neurosensory retinal damage as a fraction of the retinal thickness (Pearson's correlation coefficient=0.25; p=0.2).

Conclusions: With time, argon laser marks expand horizontally and vertically. The damage induced by argon laser in the neurosensory retina often reaches inner layers. Those long-term changes should be taken into consideration when discussing therapeutic options in diabetic macular edema.

En face Integrated Central Avascular Zone (EFICAZ) scoring: a noninvasive tool for correlating morphological and functional damage in central diabetic macular edema.

Joel Hanhart, Hillel Greifner, Michael J Potter, Morton H. Seelenfreund, Israel Strassman, Roger Zylbermann, Yaakov Rozenman

Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem, Israel.

Background/aims: To describe a new way of assessing diabetic impairment to the macula and to correlate it with functional loss.

Methods: In this retrospective analysis of a consecutive group of patients with diabetic macular edema in at least one eye, compared to a control group of healthy subjects, we included 30 eyes of 16 diabetic adults, and 34 eyes of 17 healthy adults.

Type 1 and Type 2 diabetes patients were included if one or both eyes had central diabetic macular edema. Exclusion criteria comprised any other significant macular pathology and previous macular photocoagulation. Healthy volunteers and diabetic patients being seen as part of their regular care underwent swept source coherence tomography (OCT) fundus imaging. En face Integrated Central Avascular Zone (EFICAZ) was manually determined and measured on images obtained by swept-source optical coherence tomography (OCT). EFICAZ score was then compared between both populations and, for diabetic patients, correlated with best corrected visual acuity, measured by Snellen chart. The main outcomes measures were EFICAZ score and best corrected visual acuity

Results: In healthy subjects, a moderate correlation was found between age and EFICAZ score (Pearson's coefficient=0.45, P=0.01). In age-matched populations (mean age of 63±3.8 years for healthy subjects and 62.7±8.9 years for diabetic patients; P=0.9), EFICAZ score was significantly higher in diabetic than non-diabetic eyes (2.92±1.10 mm2 versus 1.86±0.53 mm2; $P < 0.01$).

In diabetic patients, correlation between the size of EFICAZ and visual acuity (Pearson's correlation coefficient = -0.72, $P < 0.001$) was stronger than between OCT measured central subfield retinal thickness and visual acuity (Pearson's correlation coefficient = -0.02, N.S).

Conclusions: EFICAZ score increases with age in normal subjects. It is significantly larger in diabetic than in non-diabetic subjects. It offers a better way to determine visual acuity than OCT measurement of central retinal thickness. This new approach, which takes into account several factors involved in diabetic maculopathy, could be useful in monitoring response to therapy. It can easily be combined with other modalities.

Imaging the suprachoroidal space in vivo: a new technique developed at Shaare Zedek Medical Center

Dr. Joel Hanhart, Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem, Israel.

Background/aims: Until recently, the suprachoroidal space (SCS) could only be visualized on histology. It was observed in vivo by ultrasonography in pathologic conditions only. With the advent of new imaging modalities, focus has gone deeper in the study of the choroid in health and disease. The SCS is expected to be a route for drug delivery in the treatment of retinal conditions. In this study, we compare enhanced depth imaging (EDI) and non-EDI swept source OCT (SS-OCT) in their ability to capture the SCS.

Methods: In this prospective, interventional case series, twenty volunteers with a minimum age of 18 years without any ocular pathology and refractive error below ±2 diopters underwent SS-OCT foveal scanning, with and without EDI. Masked averaged B-scan lines were analyzed for presence of the SCS. When the SCS was seen, the percentage of the scan on which this structure could be unequivocally observed was measured. Scores obtained from the images taken with or without EDI were then compared.

Results: 37 eyes were analysed, since three eyes of three different patients were eliminated, as the outer border of the choroid was insufficiently delineated with both modalities.

The SCS was not detected at all on 14 pictures (37.8%) obtained by non-EDI SS-OCT and 9 pictures (24.3%) obtained by EDI SS-OCT. When the SCS was detected with both modalities, it was observable on 27.2±24.2% of the scan without EDI and 40.4±30.3 of the scan with EDI ($p < .001$)

Conclusions: EDI SS-OCT enables a more frequent and extensive visualization of the SCS than non-EDI SS-OCT. This new approach could be considered as the most accurate modality to currently visualize the SCS in vivo. The technique is easy to use in further research on the SCS, a structure arousing growing interest.

Exceptional hazard in the inflation of heart shaped balloons

***Brosh Koby MD*[1], *Bekenstein Yehonadav*[2], *Goldman Tamar*[2], *Rozenman Yaacov MD*[1], *Strassman Israel MD*[1].**

[1]Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem 91031, Israel.

[2]Racah Institute of Physics, the Hebrew University of Jerusalem, Jerusalem 91904, Israel.

Purpose: To report eight cases of blunt ocular injury due to heart shape balloon burst while being inflated and to propose underlying mechanism of injury.

Methods: Retrospective reports of eight cases are presented. Additionally, in order to verify the injury mechanism we conducted an experiment in which four heart shaped balloons and four spherical balloons were inflated until burst occurred. High speed camera capturing twenty thousand frames per second recorded the burst.

Results: All eight cases suffered significant ocular trauma such as traumatic hyphema, berlin's edema, Permanent mydriasis, angle recession, Iris transillumination defect, photophobia, vitreous hemorrhage and retinal hole. Moreover, we compared spherical balloon burst to heart shape balloon burst. In all four heart shaped balloons the bursts originated along the saddle point. Furthermore, the tear progressed symmetrically splitting the balloons into two large rubber parts. In all of these cases backward whiplash of the two balloon parts was observed. In contrast, spherical balloons began to burst at a random point, dividing the balloon into several small pieces, lacking the aforementioned whiplash motion.

Conclusion: We strongly advise Eyewear protection during the inflation of heart shaped balloons in order to prevent any more ocular damage from this cause.

Chemical burn induced stromal demarcation line

Koby Brosh, MD*[1]*. Yaacov Rozenman MD*[1]*.

[1]Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem Israel.

Purpose: A stromal demarcation line is a well-known sign after collagen cross-linking. It has been proposed that this line is the transition zone between cellular and acellular stroma, and thus it might reveal the depth of photochemical changes in the corneal stroma. We report 2 cases of a similar demarcation line after chemical alkali burns. To the best of our knowledge, this is the first report of a stromal demarcation line after a chemical burn.

Observation: Two patients presented to the emergency department after an ocular alkali burn. At presentation, both had total corneal erosion, corneal edema, and limbal ischemia. After 12 to 15 days, a stromal line was apparent by both slit-lamp examination and anterior segment optical coherence tomography. The stromal demarcation lines disappeared approximately 3 months after the injury.

Conclusions: A stromal demarcation line may appear not only after collagen cross linking but also after a chemical burn. The line depth may be associated with the severity of the injury, and therefore, may have prognostic significance. Patients with chemical burns should be examined for evidence of a stromal line in the corneal stroma.

Analysis Of 109 Consecutive Explanted Breast Implants - Correlation Between Suspected Implant Rupture And Surgical Findings

Maisel Lotan A, Retchkiman M, Tuchman I, Binenboym R, Gronovich Y

Department of Plastic & Reconstructive Surgery, Shaare Zedek Medical Center, Jerusalem, Israel.

Introduction: The use of breast implants is on the rise due to the increase in breast reconstructive and aesthetic surgery. Implant rupture is a possible complication, and is mostly asymptomatic. Assessment modalities for implant rupture include patient's symptoms, breast examination and imaging studies, with magnetic resonance imaging (MRI) being the gold standard for rupture detection. Final diagnosis is made during surgery.

Methods: We conducted a prospective analysis regarding medical history, physical examination, imaging and surgical findings on fifty seven women after breast augmentation or post mastectomy reconstruction (109 implants) who were admitted to our department between February 2010 and February 2015 with suspected implant rupture. Whenever unilateral rupture was suspected, implants were replaced bilaterally. We correlated implant rupture with implant specifications, medical history, symptoms and physical examination at presentation, ruptured implant side, imaging and surgical and pathological findings.

Results: Seventy four explanted implants were preoperatively suspected of rupture, clinically or by imaging. More than a third of suspected implants were intact and unjustifiably explanted. This number was reduced with ultrasound (US) or MRI evaluation (false positive - US 26% and MRI 18%). MRI evaluation was found to be the most accurate modality both for diagnosing and excluding implant rupture (PPV 82%, NPV 100%).

Patient's age, comorbidities, smoking, medications, presenting symptoms, implant duration and volume did not have a significant correlation with implant rupture. 61% of ruptured implants were left sided ($p<0.04$).

Conclusions: Our study confirmed preexisting data regarding the importance of imaging diagnosis, with MRI being the most accurate modality for both diagnosing and ruling out implant rupture. Interestingly, our study showed that MRI was accurate in detecting all intact implants, unlike lower detection rates reported in previous studies, thus preventing unnecessary explantation.

Another unique finding was that left sided implants were significantly more prone to rupture than right sided ones. As iatrogenic damage is known to be the most common cause of implant rupture, with most surgeons being right handed, awareness during surgery must be sharpened, with further investigation required for potential causes of this unexpected finding.

Implant duration or volume and clinical impression of rupture did not correlate with increased rupture rate.

Our study emphasized the importance of understanding the causes of rupture and the need for evidence based indications regarding imaging and replacement of implants.

Improvement of facial scars using autologous fat graft and 1540nm nonablative erbium laser

Yoav Gronovich, MD, MBA; Adi Meisel-Lotan, MD; Meir Retchkiman, MD; Rami Binenboym, MD; Nirit Eizenman, MD; Izhak Tuchman, MD.

Department of Plastic Surgery, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Facial scars are a devastating problem both aesthetic and functional. Many treatments have been proposed for improvement of scars. Among the advanced treatments are the use of nonablative laser which facilitate the synthesis and deposition of collagen in the dermis. Other advanced treatments include fat grafting. This method helps to reshape the scar by volumetric effect of the fat cells, and improve its contour by the adipose derived stem cells that accompany the fat transfer. Combination of these two methods can be synergistic and of better result than each one alone (1-3).

Purpose: We present our experience with 15 consecutive cases of facial scars using fat grafting and resurfacing with 1540 nm nonablative erbium laser. We wish to emphasize the main advantages of this treatment combination.

Methods and materials: We began using this combination of treatment in January, 2014, since when fifteen patients (8 females), median age 42 years (range 16-59) were treated for facial scars using autologous fat graft and nonablative 1540nm erbium laser. The causes of the scars included trauma (73%) and acne. Two thirds of the scars were new (less than 30 days old). In all of the cases treatment included fat injection to the surface of the scar, using Coleman technique, and a series of five treatments of 1540nm erbium laser (ICON TM Cynosure; Westford, MA, USA) beginning a month later. Patients were evaluated both before and after each treatment, and a follow up of 6 month was done.

Results: In all of the cases, the treatment was uneventful with no side effects. The scars were improved both in texture and appearance. Patient satisfaction was high in all of the cases.

Conclusion: The combination of autologous fat grafting with fractional non ablative laser for scars is a safe and efficient treatment that improves scar appearance and texture.

Osmotic tissue expander for convenient reconstruction - experience with 30 consecutive cases

Yoav Gronovich, MD, MBA; Adi Meisel-Lotan, MD; Meir Retchkiman, MD; Rami Binenboym, MD; Nirit Eizenman, MD; Izhak Tuchman, MD.

Department of Plastic Surgery,Shaare Zedek Medical Center, Jerusalem, Israel

Background: Tissue expander is a major reconstructive modality. Its main disadvantages includes: inconvenient long period of inflation accompanied with deformation of the surrounding tissue. Osmotic expander was developed in order to eliminate some of these limitations. It is a self-filling device which absorbs fluids in order to achieve tissue expansion faster (1-3).

Aim: We present our experience with 30 consecutive cases of tissue reconstruction using osmotic expanders. We wish to emphasize its main advantages and limitations.

Methods: The present study was launched in May, 2008, until April, 2015, since when thirty patients, median age 27 years were reconstructed using an osmotic expander (total of 41 expanders). The reasons for using tissue expander included large congenital nevi (67%) and scars. Body areas treated included: scalp (30%), neck (16%), shoulder (7%), back (7%), chest (3%), breast (3%), upper extremities (17%) and lower extremities (17%). In 74% of the patients one osmotic expander was used for each patient, in 20%, two osmotic expanders were used, in 3%, three osmotic expanders were used and in 3%, four expanders were used.

Results: In all of the cases, the operative and post-operative management was uneventful. During the expansion period, there were 2 outpatient clinical visits. The average expansion time was 9 weeks. In 10% of the patients, there was partial extrusion of the expander. In all other cases there was no complication and final aesthetic results were satisfying.

Discussion: Osmotic expander is an advanced modality for tissue reconstruction. The final shape and size are precisely predictable. Its initial small size allows for a small surgical incision and a simple and short overall operating time. The expansion period is shorter and more convenient for the patient. Its main disadvantage includes the inability to control the filling rate and the need to remove the expander in case of damage to the overlying tissue.

Conclusion: Osmotic expander is a reliable tool for tissue expansion. It allows for a satisfying aesthetic result in a shorter period of time and with less inconvenience to the patient.

The benefits for post-operative acute pain protocol

Zila Cohen, MA, RN, Severe Pain Coordinator, SZMC

Background: Pain, the fifth vital sign, causes discomfort and suffering to patients. Adequate pain treatment leads to a better recovery, shortens length of admission as well as raises patient's satisfaction from the overall medical care. Patients undergoing a surgical procedure are more susceptible to suffer acute pain and its consequences. In order to improve pain management, health organizations have introduced pain treatment protocols for acute as well as chronic pain. In 2001, the MOH nursing department has published a national guideline for a routine, initiated pain assessment for every admitted patient.

This study aims to evaluate the implementation of the protocol for acute pain (2012) and its impact on patient's length of stay. We hypothesize that Implementation of the acute pain protocol will decrease length of stay as well as the amount of PRN pain medications. In addition implementation of the acute pain protocol will increase the use of constant analgesia to patients.

Method: Chart review of surgical patients in S"Z, post operative (day 0-discharge) was performed, focusing on three major factors: number of admission days, average VAS during the first 5 post-op days, the cost of prn pain meds administered during the first 5 post-op days.

Prior to the protocol implementation, a chart review of 70 patients that underwent common surgeries without complications was performed.

A year later, following the implementation of the acute pain protocol the same chart review was performed. Data was analyzed separately for each type of surgery before and after the implementation of the acute pain protocol.

Results: In patients that underwent hemicolectomy surgery, the chart review showed that in accordance with the hypotheses, there was significancy, ($p<0.05$) for days of admission and average VAS during the first 5 post-op days.

In patients that underwent sigmoidectomy surgery, the chart review showed that ,in accordance with the hypotheses, there was significancy, ($p<0.01$) for the average VAS during the first 5 post-op days as well as the prn meds' cost during days 4 and 5.

Conclusion: It appears that post acute pain protocol implementation has achieved its initial goal in reducing days of admission as well as cost reduction in prn pain meds. In addition, acute pain protocol has enforced a better standard of care in treating acute post op pain.

Two infants with osteomyelitis of the odontoid process

***Asael Lubotzky*[1], *Ruth Cytter Kuint3, Eliyahu Raccah*[1], *Orli Megged*[1,2]**

Department of Pediatrics [(1)] and Infectious Diseases Unit [(2)], Department of Diagnostic Imaging [(3)], Shaare Zedek Medical Center affiliated with Hadassah-Hebrew University Medical School, Jerusalem, Israel,

Objective: To report clinical, laboratory, and radiological manifestations of two infants with osteomyelitis of the odontoid process.

Background: Acute osteomyelitis is not uncommon in children. The major mechanism is hematogenic spread of infection. The long bones, most likely because of their unique blood circulation and anatomy, have a predilection for infection from bacteremia. Vertebral osteomyelitis is uncommon, and osteomyelitis of the Dens (odontoid process) has rarely been reported in the pediatric population.

Methods: The medical records of two infants diagnosed with Dens osteomyelitis were reviewed. Data regarding clinical, laboratory, and imaging studies were collected.

Results: Both infants had fever which resolved spontaneously prior to their admission. They were both non-toxic appearing with persistent neck stiffness and torticollis. White blood count and C-reactive protein were only mildly elevated in both cases. Blood cultures were negative. Magnetic resonance imaging (MRI) revealed the diagnosis in both cases.

Discussion: Osteomyelitis of the dens in adults have sometimes been hematogenous in origin, but the majority of cases resulted from direct extension from epidural abscess or parapharyngeal / retropharyngeal abscess. In children, there are only rare case reports of this entity. Osteomyelitis of the Dens is rare and poses danger of atlantoaxial dislocation and extension of the infection to the epidural space, if not promptly diagnosed and treated.

Conclusions: We report two cases of Dens osteomyelitis. These cases emphasize the need to consider C1-C2 osteomyelitis in differential diagnosis of neck stiffness and torticollis in infants, and highlight the usefulness of MRI in diagnosing this clinical condition.

Lower Basal Insulin Dose - Better Control in Type 1 Diabetes

David Strich

Pediatric Endocrinology, Shaare Zedek Medical Center

Introduction: There is no valid evidenced-based recommendation for the optimum basal insulin dose in Type-1 Diabetes Mellitus when supplied either by continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI). We studied this previously by evaluating the dose associated with successful fasting. Another way of looking at this is by evaluating the association between basal insulin dose and HbA1c. To this end we performed a retrospective study of 89 children and young adults with T1DM.

Patients and Methods: 89 (mean age 14.67±4.8 years (range 3-29)) patients were enrolled. 46 were treated with CSII and 43 with MDI (glargine as basal insulin). Basal insulin used was either downloaded from the insulin pump or taken as the dose registered in the chart. Glucose data were downloaded from patients glucometers. Mean time between data download and HbA1c determination was 0.9 ± 0.78 months. We divided the patients by quartiles according to HbA1c and determined the average basal insulin for each quartile. The second and third quartiles were joined and are presented together in the graph.

Results: The basal insulin dose of 18 patients who had the lowest HbA1c (average of 6.49± 0.34) was 0.28±0.08u/kg/d.

Conclusion: With lower basal insulin levels lower HbA1C was achieved despite the same total bolus dose. The optimal basal dose as determined by this study is similar as shown for fasting individuals of similar age.

In euthyroid humans younger than 40 years, thyrotropin enhances thyroxine conversion to triiodothyronine.

David Strich

Pediatric Endocrinology, Shaare Zedek Medical Center

Introduction: About 80% of T3 production is due to extra thyroidal conversion of T4 to T3 by two deiodinases (D1 and D2). TSH has been shown to enhance deiodinase activity in thyroid cell cultures. There is clinical evidence that this effect is relevant in-vivo in children. It is not known if this effect is significant in adults.

Methods: free T3 (FT3), free T4 (FT4) and TSH levels from 861,475 sera taken from patients age 1 year or greater were studied. Initial exclusions were: missing data for either TSH or one of the thyroid hormones and TSH greater than 7.5 mIU/l. Samples from patients taking, or who had taken, thyroid medications or/and drugs that may interfere with thyroid hormone activity were then removed by crossing data from electronic patient files. The 27,940 samples that remained after all exclusions were stratified by age and analyzed in order to investigate relations between TSH, FT4 and FT3 in the euthyroid or near-euthyroid state.

Results: For each increasing TSH quartile, FT3 and the FT3/FT4 ratio increased and FT4 decreased significantly (for both FT3, FT4 and FT3/FT4 ratio, $p<0.05$ for every TSH quartile when compared with the1st quartile, except FT3 in the 30-40 age group). Beyond age 40, increasing TSH was associated with lower FT3 and FT4 ($P<0.05$ in the 40-60 age group for both and for FT4 in the 60-80 age group), the FT3/FT4 ratio does not change between the TSH quartiles.

Conclusion: Increasing TSH levels are expected to be higher as FT4 and FT3 levels decrease. Surprisingly, within the euthyroid range, as TSH increases FT3 levels increase but FT4 levels decrease. This phenomenon occurs only in the young (below 40) age groups and disappears later. The change in these relations may reflect a decrease in T4 to T3 conversion with age, which may be one component of the ageing process.

Intrapartum fetal heart rate patterns of trisomy 21 fetuses: A case control study

Koren I[a], ***Michaelson-Cohen R***[b], ***Chen D***[c], ***Michaeli J***b, ***Schimmel M***[a], ***Tsafrir A***b, ***Shen O***[b,d]

[a] Pediatric Medicine Shaare Zedek Medical Center

[b] Obstetrics and Gynecology Shaare Zedek Medical Center

[c] Tel Aviv University Sackler school of medicine

Background: To determine whether there are specific characteristic intrapartum heart rate patterns for fetuses with trisomy 21(T21).

Methods: Intrapartum fetal heart rate (FHR) tracings of T21 fetuses were compared to those of euploid fetuses in a retrospective, observational, matched, case-control study. The study group consisted of 42 fetuses with T21 and 42 matched euploid controls. Matching was designed to accommodate possible confounders. The sign test and McNemar's test were used for categorical variables. The paired t test was used for comparison between quantitative variables.

Results: Intrapartum baseline FHR of fetuses with T21 was found to be slightly decreased compared to controls (122.5 vs 129.05 beats per minute, p = 0.028). No differences were detected in the presence of periodic changes, or FHR variability between the groups.

Conclusion: When evaluating intrapartum FHR of fetuses with T21, decreased baseline FHR can be expected.

Perfusion index as a screening tool for Patent Ductus Arteriosus

Itamar Nitzan, Cathy Hamerman , Daniel fink , Meir Nitzan, , Robert Koppell , Ruben Bromiker

Pediatrics, Shaare Zedek Medical Center

Background: ductus arteriosus (DA) is a blood vessel connecting the pulmonary artery and the aorta in the fetus. The DA closes in the days after birth. In some premature neonates the DA fails to close and is referred to as Patent Ductus Arteriosus (PDA). Gold standard for PDA evaluation is echocardiography. Photopletysmography is the change in the amount of light that passes throw the tissue between systole and diastole. Perfusion Index (PI) is the amplitude of the photopletysmography wave divided in its baseline. PI was suggested as a screening tool for conditions affecting perfusion, like PDA

Objective: To evaluate PI in neonates with and without PDA.

Methods: Preterm neonates who had hemodynamic significant PDA where assessed for PI, with a Photopletysmograph built in Jerusalem college of technology (JCT) Preterm neonates with no PDA where examined as controls.

Results: 46 preterm neonates were assessed, 20 with PDA (avg GA 29 W, day of life 18, weight 1.45 KG) and 26 with closed duct (avg GA 29 W, day of life 17, weight 1.44 KG). PI was higher in neonates with PDA (1.88 ±0.5 right hand, 1.79 ±1.0 foot) than in neonates without PDA(1.46 ±0.4 right hand, 1.24 ±0.4, foot)) (P=0.015, P=0.004)

Discussion: earlier studies showed that PI correlates with perfusion in adults. In our study we saw that neonates with hemodynamic significant PDA have higher PI, although PDA is considered to be a hypoperfusion state. Possible explanation for this finding can be that in hemodynamic significant PDA there is retrograde blood flow in diastole that lowers the blood volume in the extremities during diastole, and though makes the difference in blood volume between systole and diastole higher. This difference in blood volume is reflected in higher PI.

Conclusion: Perfusion index (PI) is higher in preterm neonates with hemodynamic significant PDA than in normal preterm neonates. PI can be a simple and valuable tool for screening and following after PDA in premature neonates, as all premature neonates are continuously monitored by photopletysmography.

PANCA and ASCA in > 400 children with IBD-unclassified (IBDU), Crohn's Colitis and Ulcerative Colitis (UC) - a longitudinal report from the Porto pediatric IBD group of ESPGHAN

Liron Birimberg-Schwartz[1], David Wilson[2], Kaija-Leena Kolho[3], Katarzyna Kardowsha-Bochenek[4], Nadeem A. Afzal[5], Chris Spray[6], Claudio Romano[7], Paolo Lionetti[8], Almuthe C. Hauer9, Christine Martinez-Vinson[10], Gabor Veres[11], Dan Turner[1,12] on behalf of the Paediatric IBD Porto group of ESPGHAN

[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]University of Edinburgh; [3] University of Helsinki; [4]Department of Pediatric Gastroenterology, Medical University, Warsaw, Poland; [5]University Hospital Southampton; [6]University Hospitals Bristol; [7]University of Messina, [8]University of Florence, Meyer Children Hosp; [9]University Hospital for Pediatrics and Adolescent Medicine of the Medical University of Graz, [10]Department of Pediatric Gastroenterology and Nutrition, Robert Debré Hospital; [11]Semmelweis University; [12] The Hebrew University of Jerusalem, Israel

Background: Serology can help differentiate Crohn's disease (CD) from Ulcerative Colitis (UC), but the real clinical challenge is differentiating Inflammatory Bowel Disease Unclassified (IBDU) from isolated Crohn's colitis (CC). No study to date has evaluated ANCA and ASCA in pediatric IBDU as compared with CC. In this largest study to date, we aimed to explore the diagnostic utility of serological profiles in these subgroups.

Methods: This was a multicenter retrospective longitudinal study including 406 IBD children from 19 centers affiliated with the Porto IBD-working group of ESPGHAN (mean age 10.5 ± 3.9, 221 (54%) males); 118 (29%) with CC, 142 (35%) with UC and 146 (36%) with IBDU. Follow-up period was 2.8 [IQR 1.6-4.2] years.

Results: The most prevalent serologic profile in IBDU was pANCA-/ ASCA- 37(41%) followed by pANCA+/ ASCA- (34%) and pANCA-/ ASCA+ (17%). Serologic combinations had a high PPV but very low NPV to differentiate IBDU from either CC or UC (Table 1). UC patients with pANCA+/ASCA- had less often mild disease at diagnosis than those negative for this profile (36 (62%) vs 22 (38%), p=0.033) and had more severe disease course (25 (80%) vs 6 (20%), p=0.026).

Conclusions: In this first comparison of serology in IBDU and isolated CC, serology seems less accurate than previously reported when comparing UC vs. CD. Moreover, whereas serology profile was predictive of severe disease course in UC, this was not demonstrated in CC, questioning the utility of serology testing in clinical practice of children with CC.

Table 1:

	Sensitivity %	Specificity %	PPV %	NPV %
IBDU vs. CC (pANCA-/ ASCA+)	33%	83%	96%	13%
IBDU vs. UC (pANCA+/ ASCA-)	65%	66%	94%	38%
CC vs UC				
pANCA+/ASCA-	65%	77%	55%	79%
pANCA-/ ASCA+	33%	97%	90%	40%

CC, Crohn's colitis; UC, ulcerative colitis; IBDU, Inflammatory Bowel Disease Unclassified

Prenatal diagnosis of biliary atresia

Shen O[a*], Nagar H[b], Rabinowitz R[1], Jacobovich E[c], Chen Dd, Granot E[c,e]

[a] Department of Ob/Gyn, Shaare Zedek Medical Center

[b] Department of pediatric surgery, Shaare Zedek Medical Center

[c] Department of pediatrics, Kaplan Medical Center

[d] Tel-Aviv Sackler School of Medicine, Tel-Aviv University

[e] Department of pediatrics, Shaare Zedek Medical Center

Background: Biliary atresia (BA) is a progressive fibro-obliterative disease of the extra-hepatic biliary tree that presents in the neonatal period with biliary obstruction, and is the most common indication for liver transplantation in the pediatric population. Prenatal ultrasound series have yielded conflicting results concerning a possible association between BA and prenatal nonvisualization of the gallbladder (PNVGB). This retrospective case series was performed to assess the association between BA, PNVGB and other sonographic signs.

Methods: We identified all BA patients who underwent a Kasai procedure by a single pediatric surgeon and/or follow up by a single pediatric gastroenterologist. Images and/or video recordings were scrutinized for sonographic signs of BA on the second trimester anomaly scan.

Results: Twenty five charts of children with BA and high quality prenatal images were retrieved. 6/25 (24%) of cases analyzed had PNVGB or a small gallbladder on the prenatal scan. Two cases had biliary atresia splenic malformation syndrome (BASM). None of the cases had additional sonographic markers of BA.

Discussion: BA has traditionally been divided into an embryonic form, characterized by multiple malformations, many of which can be diagnosed prenatally, and a perinatal form, which was considered to have its pathogenesis rooted in the perinatal period. Our study suggests that an additional embryonic variant exists, which is characterized by PNVGB in the second trimester. This may have important implications for prenatal diagnosis, and for research of the disease's etiology and pathophysiology.

Abnormal shape of the cavum septi pellucidi: An indirect sign of partial agenesis of the corpus callosum on prenatal ultrasound

***Shen O*[a], *Gelot AB*[c], *Moutard ML*[c], *Jouannic JM*[c], *Sela HYa*, *Garel C*[c].**

[a]Dpt Ob/Gyn. Shaare Zedek Medical Center Jerusalem

[c]Hôpital Trousseau, Paris, France.

Objective: To describe a new indirect prenatal sonographic sign of partial agenesis of the corpus callosum (pACC). The presence of this sign, an abnormally shaped cavum septi pellucidi was assessed.

Methods: 71 cases of pACC were analyzed retrospectively. Images from cases seen at 2 referral centers between September 2006 and April 2014 were reviewed by the authors.

When the lateral dimension of the cavum septi pellucidi (CSP) was greater than its anterior-posterior (AP) length in the axial transthalamic plane, the CSP was considered to be abnormal. The incidence of this sign was assessed, as were the following variables: gestational age on referral, indication for referral, the abnormal segment/s of the corpus callosum (CC), the presence of indirect signs of callosal agenesis (ACC), the presence of additional cerebral and extracerebral anomalies.

Results: In 33/71(46%) cases there were one or more indirect signs of callosal abnormality. In 19/56(34%) cases with a measurable CSP and in 12/23(52%) cases with isolated pACC and no indirect signs, the CSP was abnormal. In 15/19(79%) with an abnormal CSP, there were no indirect signs of pACC.

Conclusions: In a significant proportion of cases of prenatally detected pACC, the shape of the CSP is abnormal. This should be considered an additional indirect sign of pACC, which is frequently the only clue to the diagnosis. When observing this sign in a screening context, pACC should be considered, and an attempt to directly visualize the CC in the midsagittal plane is suggested.

The availability of calcineurin inhibitors and infliximab in acute severe colitis have reduced colectomy rates in 283 children admitted during 1990-2012

***Sapir Choshen*[1, 2], *Anne Griffiths*[7], *Helen Finnamore*[3], *Marcus KH Auth*[3], *Eyal Shteyer*[1,2], *David Mack*[4], *Jeffrey Hyams*[5], *Neal Leleiko*[6], *Dan Turner*[1,2]**

[1]The Juliet Keidan Institute of Pediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, Jerusalem, Israel [2]The Hebrew University of Jerusalem, Israel [3]Alder Hey Children's NHS Foundation Trust, Liverpool, UK [4]Children's Hospital of Eastern Ontario IBD Centre and Department of Pediatrics, University of Ottawa, Ottawa, Canada [5]Connecticut Children's Medical Center, Hartford, CT [6]Alpert School of Medicine at Brown University, Hasbro Children's Hospital/Rhode Island Hospital, Providence, Rhode Island, USA[7]SickKids Hospital, University of Toronto, Toronto, Canada

Background: One third of children admitted with acute severe colitis (ASC) fail intravenous corticosteroids (IVCS) and require salvage therapy. While colectomy was originally the only available salvage treatment, cyclosporine and then tacrolimus (Cys/Tac) have been introduced since 1996, followed by infliximab (IFX) in 2004, as second line medical treatment prior to colectomy. However, no data to date have shown whether these interventions actually managed to reduce colectomy rates, during the admission or thereafter.

Aim & Methods: We aimed to explore trends in colectomy rate in pediatric ASC before and after the introduction of Cys/Tac and IFX, using the largest pediatric cohort of ASC to date. 283 children treated with IVCS for ASC during 1990-2012 were included (from the prospective (n=128) and retrospective (n=99) OSCI studies and another 55 retrospectively reviewed patients from Jerusalem and Liverpool). Patients were followed for 1 year (46% males, age 12.1±3.9 years, disease duration 2 (IQR 0-14) months, baseline PUCAI 69±13 points). Data accrual were similar in the 3 cohorts, collected using the same standardized case report forms at admission, 3 days and 5 days thereafter, at discharge and at 1 year. Colectomy rates were compared between 3 periods: 1990-1996 (era1: pre medications; n=68), 1997-2004 (era2: Cys/Tac and colectomy; n=45), 2005-2012 (era3: IFX, Cys/Tac and colectomy; n=170). No child in our cohort has been treated with IFX prior to 2005.

Results: Total 1-year colectomy rates were 40/68 (59%) during era1, 17/45 (38%) during era2, and 31/170 (18%) during era3 (P<0.001). Since IVCS failure rates was different between the eras, we then focused on those failing IVCS. Of the 283 children, 89 children (31%) failed IVCS treatment and required second line therapy during admission (44 primary colectomy, 9 Cys/Tac and 22 IFX; total colectomy 56). The 3 era groups were similar in 12 pre-treatment basic variables at admission (e.g. PUCAI, CRP, albumin, disease duration etc.) except for age and ESR. The rate of colectomy in those requiring salvage therapy during the admission was significantly reduced from 100% (51/51) in era 1, to 62% (8/13) in era2 and 33% (14/42) in era3 (p<0.001). At 1 year after discharge, 123 children (43%), were treated with second line therapy (44 primary colectomy, 12 Cys/Tac and 53 IFX; total colectomy 88). The rate of colectomy was again significantly reduced from 100% (40/40) of children requiring salvage therapy in era1 to 77% (17/22) in era2 and 51% (31/61) in era3 (p<0.001).

Conclusion: We show for the first time that the introduction of Cys/Tac and then infliximab sharply reduced the need for colectomy during admission and 1-year thereafter in pediatric ASC.

Corticosteroid Dosing in Pediatric Acute Severe Ulcerative Colitis: a Propensity Score Analysis

***Sapir Choshen*[1, 2]*, Helen Finnamore*[3]*, Marcus KH Auth*[3,] *Tali Bdolah-Abram*[2]*, Eyal Shteyer*[1,2]*, David Mack4, Jeffrey Hyams*[5]*, Neal Leleiko*[6]*, Anne Griffiths*[7]*, Dan Turner*[1,2]

[1]The Juliet Keidan Institute of Pediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, Jerusalem, Israel

[2] The Hebrew University of Jerusalem, Israel

[3] Alder Hey Children's NHS Foundation Trust, Liverpool, UK

[4] Children's Hospital of Eastern Ontario IBD Centre and Department of Pediatrics, University of Ottawa, Ottawa, Canada

[5] Connecticut Children's Medical Center, Hartford, CT

[6] Alpert School of Medicine at Brown University, Hasbro Children's Hospital/Rhode Island Hospital, Providence, Rhode Island, USA

[7] SickKids Hospital, University of Toronto, Toronto, Canada

Background: We aimed to explore the optimal dosing of intravenous-corticosteroids (IVCS) using a robust statistical method on the largest pediatric cohort of acute severe colitis (ASC) to date.

Methods: 283 children treated with IVCS for ulcerative colitis were included and followed for 1 year (46% males, age 12.1±3.9 years, disease duration 2 (IQR 0-14) months, baseline PUCAI 69±13 points). Confounding by indication was addressed by matching high and low IVCS dose patients according to the propensity score (PS) method, using three cutoffs (1mg/kg methylprednisolone to 40mg/day, 1.25mg/kg to 50mg/day and 2mg/kg to 80mg/day).

Results: The median IVCS dose in the entire cohort was 1.0 mg/kg (IQR 0.8-1.4) and 44 mg/day (32-60). 94/283 children were matched in the low-dose cutoff (1mg/kg), 218/283 were matched in the middle cutoff (1.25mg/kg), and 86/283 in the high dose cutoff (2mg/kg). No differences were found in 25 pretreatment baseline variables in the three cutoffs, implying successful matching. There were no statistical differences in the outcomes of the two lower cutoffs (including need for salvage therapy during admission and by 1 years, admission duration, and day-5 PUCAI<35 points; all P>0.05). In the high cutoff, the higher doses were somewhat better but this benefit reversed in a sensitivity analysis excluding one center. High doses were not associated with better outcome also in a PS-weighted regression model on the entire cohort.

Conclusion: Our data support current guidelines that doses of IVCS higher than 1-1.5mg/kg/d (maximum 40-60mg/d) are not justified in ASC.

Low Intereferon Relative-Response To Cytomegalovirus Is Assosiated With Low Likelihood Of Intreuterine Transmission Of The Virus

Y. Eldar-Yedidia, M. Bar-Meir, M. Hillel, G. Abitbol, E.Broide, R. Falk, M. Assous and Y. Schlesinger

Research Laboratory of Infectious Diseases, Shaare Zedek Medical Center, affiliated to the Hebrew University Medical School, Jerusalem, Israel.

Introduction: Congenital Cytomegalovirus (CMV) is a very common intrauterine infection which can cause severe mental and hearing impairments. Notably, only 40% of primarily infected women transmit CMV to the fetus. CMV-specific T-cell response has a role in CMV disease but individual immune heterogeneity precludes reliable correlation between measurable T-cells response and intrauterine transmission.

Study aim: To establish a correlation between maternal T cells response and fetal CMV transmission using an individual normalized immune response.

Methods: We analyzed IFN-y secretion upon whole blood stimulation from primary CMV-infected pregnant women, with either CMV-peptides or PHA-mitogen.

Results: We established a new normalization method of individual IFN-g response to CMV, by defining the ratio between specific-CMV response and non-specific mitogen response (defined as IFN-g relative response, RR), aiming to overcome high person-to-person immune variability. We found a unique subpopulation of women with low IFN-g RR, strongly correlated with absence of transmission. IFN-y RR lower than 1.8% (threshold determined by ROC analysis) reduces the pre-test probability of transmission from 40% to 8%, revealing an unexpected link between low IFN-g RR and non-transmission.

Conclusion: In pregnant women with primary CMV infection, low IFN-g RR is associated with low risk of transmission.

Interferon Signaling Genes And Cmv Intrauterine Transmission

***Y. Smith*[1], *Y. Eldar-Yedidia*[2], *Y. Kotler*[3], *S. Pundak*[3], *M. Hillel*[2] *and Y. Schlesinger*[2]**

[1]Genomic Data Analysis, Hadassah-Hebrew University Medical School. [2]Research Laboratory of Infectious Diseases, Shaare Zedek Medical Center, Hebrew University Medical School. [3]Genfron Ltd, Jerusalem, Israel.

Introduction: CMV intra-uterine transmission occurs in only 40% of pregnancies with primary maternal infection, and the mechanism(s) involved in transmission are not clearly understood. Currently the only reliable method to diagnose fetal infection is invasive amniocentesis. Therefore, there is an urgent need for an early and non-invasive assay which can predict transmission of the virus.

Methods: A mathematical model for stimulation of interferon (IFN) signaling genes in response to CMV infection based on data from five published array-datasets, led us to suggest seven biomarker genes for predicting intrauterine-transmission of CMV. Validation of our prediction-model was performed by qRT- PCR on PBMC's RNA samples from 26 pregnant women with primary CMV infection. Transmission was determined by qRT- PCR of CMV in amniotic fluid or newborn urine.

Results: Combined analysis of data of IFN signaling genes before and after CMV stimulation from five GEO microarray datasets revealed two distinct sub-populations; those with high basal expression and low rise upon stimulation and those with low basal expression and high rise upon stimulation. This phenomenon may reflect a more efficient immune response with a robust increase during acute infection and a rapid decline to low basal state thereafter. Seven of these genes were selected for analysis of the expression of the IFN signaling genes on 26 pregnant women with primary CMV infection who were viremic (minimum of 200 CMV copies/ml blood). We found that women with high basal expression of the tested genes were significantly more likely to transmit the virus to the fetus.

In our cohort, the IFN signaling genes levels predicted transmission with a sensitivity of 92.3% (95% CI: 72, 92), specificity of 100% (95%CI: 80, 100), PPV of 100% (95% CI: 78, 100) and NPV 92.9% (95% CI: 74, 93).

Conclusions: Low basal expression of the assayed IFN signaling genes is associated with low likelihood of maternal fetal infection. Further research with larger cohort might facilitate the clinical utilization of our data.

Carbon Dioxyde (CO2) Monitoring in Ventilated Neonates #1

Kugelman A, Golan A, Riskin A, Shoris I, Ronen M, Qumqam N, Bader D, Bromiker R

NICU, Shaare Zedek Medical Center

Monitoring vital signs in newborns admitted to intensive care is essential for an appropriate management. Most signs are regularly monitored by non-invasive methods, including heart and respiratory rates, oxygen saturation, blood pressure. Ventilated neonates need frequently blood gases in order to evaluate the effectiveness of ventilation. The cumulative amount of blood needed for these tests is huge, which prompts the need of frequent transfusions to treat this iatrogenic anemia and replace the blood lost.

Non invasive methods have been developed to monitor CO2, such as end tidal CO2 and transcutaneous CO2.

Objective: To compare the time spent within a predefined safe range of CO2 (30-60 mmHg) during conventional ventilation between infants who were monitored with distal end-tidal CO2 (dETCO2, or capnography) and those who were not.

Study design: For this randomized, controlled multicenter study, ventilated infants with a double-lumen endotracheal tube were randomized to 1 of 2 groups: the open (monitored) group, in which data from the capnograph were recorded, displayed to the medical team, and used for patient care, and the masked group, in which data from the capnograph were recorded. However, the measurements were masked and not available for patient care. dETCO2 was compared with PaCO2 measurements recorded for patient care.

Results: Fifty-five infants (25 open, 30 masked) participated in the study (median gestational age, 28.6 weeks; range, 23.5-39.0 weeks). The 2 groups were comparable. dETCO2 was in good correlation ($r = 0.73$; $P < .001$) and adequate agreement (mean ± SD of the difference, 3.0 ± 8.5 mmHg) with PaCO2. Compared with infants in the masked group, those in the monitored group had significantly ($P = .03$) less time with an unsafe dETCO2 level (high: 3.8% vs 8.8% or low: 3.8% vs 8.9%). The prevalence of intraventricular hemorrhage or periventricular leukomalacia rate was lower in the monitored group ($P = .02$) and was significantly ($P < .05$) associated with the independent factors dETCO2 monitoring and gestational age.

Conclusion: Continuous dETCO2 monitoring improved control of CO2 levels within a safe range during conventional ventilation in a neonatal intensive care unit.

Carbon Dioxyde (CO2) Monitoring in Ventilated Neonates #2

Kugelman A[1,2], Bromiker R[3], Riskin A[1], Shoris I[1], Ronen M[4], Qumqam N[3], Bader D[1], Golan A[5].

NICU, Shaare Zedek Medical Center

Monitoring vital signs in newborns admitted to intensive care is essential for an appropriate management. Most signs are regularly monitored by non-invasive methods, including heart and respiratory rates, oxygen saturation, blood pressure. Ventilated neonates need frequently blood gases in order to evaluate the effectiveness of ventilation. The cumulative amount of blood needed for these tests is huge, which prompts the need of frequent transfusions to treat this iatrogenic anemia and replace the blood lost.

Non invasive methods have been developed to monitor CO2, such as end tidal CO2 and transcutaneous CO2.

Background and objective: High-frequency ventilation (HFV) is a powerful tool for CO2 elimination, and thus requires careful monitoring of CO2 . Our aim was to assess the diagnostic accuracy (correlation, agreement, and trending) of continuous distal capnography (dCap) with PaCO2 in infants ventilated with HFV.

Design: This was a prospective, observational, multicenter study. dCap was compared with simultaneous PaCO2 ("gold standard") drawn from indwelling arterial line for patient care in term and preterm infants ventilated with HFV. dCap was obtained via the side-port of a double-lumen endotracheal-tube by a Microstream capnograph with specially designed software for HFV.

Results: Twenty-four infants participated in the study (median [range] gestational age [GA]: 26.8 [23.6-38.6] weeks). Analysis included 332 measurements. dCap was in correlation ($r=0.70$, $P<0.001$) but with less than adequate agreement (mean difference ± SD of the differences: -11.7 ± 10.3 mmHg) with PaCO2 . Comparable findings were found in the subgroup of infants <1,000 g (n=240 measurements). Correlations were maintained in severe lung disease. Changes in dCap and in PaCO2 for consecutive measurements within each patient were correlated ($r=0.63$, $P<0.001$). Area under the receiver operating curves (ROC) for dCap to detect high (>60 mmHg) or low (<30 mmHg) PaCO2 was 0.83 (CI: 0.76-0.90) and 0.88 (CI: 0.79-0.97), respectively; $P<0.001$.

Conclusion: Our prospective study suggests that continuous dCap in infants ventilated with HFV may be helpful for trends and alarm for unsafe levels of PaCO2 . dCap is only a complimentary tool and cannot replace PaCO2 sampling because the agreement between these measurements was less than adequate

Acute Nonspecific Abdominal pain in teenage female in the Pediatric Emergency Department

Dr. Mati Ormianer, Dr. Giora Weiser, Dr. Matti Arlichman, Dr. Oren Ledder

Pediatric Emergency Medicine, Shaare Zedek Medical Center

Introduction: Nonspecific Abdominal Pain (NSAP) refers to abdominal pain for which organic pathology is not suspected by the attending physician following reasonable diagnostic investigations. This diagnosis is more common in childhood, particularly in female adolescents. Adolescent females with NSAP frequently present to a hospital emergency department and often undergo multiple investigations and require significant analgesia during at times prolonged admissions, with no organic diagnosis obtained.

Objectives: Describe the nature and length of emergency presentations, and requirement of analgesia of adolescent females with NSAP.

Study Design: Retrospective case matched study of females aged 12-18 years presenting to the SZMC PED with a final diagnosis of NSAPcompared to patients from the same demographic with a final diagnosis of acute appendicitis (AA). History of presenting illness, physical examination, lab results, imaging studies and analgesia requirements were collected from thorough chart review.

Results: 270 patients (180 with NSAP, 90 with AA). Ethnicity, weight Z-score, chronic abdominal complaints and non -RLQ abdominal sensitivity were statistically different between the two cohorts ($p<0.05$). AA group had significant differences in heart rate, anorexia, nausea, vomiting, RLQ abdominal sensitivity, signs of peritonitis and leukocytosis ($p<0.05$). Imaging studies were more frequently performed in the NSAP group compared to the AA group 288 to 128 respectively. Gynecology consult was more frequently provided in NSAP (115 (64%) vs AA 20 (22%) ($p<0.001$). Length of stay in the pediatric emergency department (PED) was longer in the NSAP group(10.7 hours vs 4.1 hours ($p<0.001$)). 54.4% of AA received analgesia versus 45.0% of NSAP ($p=0.143$). A total of 75 dosages of analgesics were given in AA patients versus 128 given to NSAP ($p=0.154$). Opioid analgesics were given to 31.1% of AA versus 18.3% of NSAP ($p=0.018$).

Conclusions: NSAP patients are typically of higher weight z-score and have more frequent chronic abdominal complaints compared to AA patients. They have less anorexia, nausea and vomiting, RLQ sensitivity, signs of peritonitis and leukocytosis.

NSAP patients consumed more PED resources such as multiple imaging studies and specialists consults. NSAP patients had a more prolonged PED stay to the time of diagnosis than AA patients. NSAP patients required similar amounts of analgesia, although the AA group received more opioids.

Studying the variation in the personal nutritional composition and proving that awareness to a low variation leads to better compliance for carbohydrate counting and consequently better glucose monitoring in children treated for type 1 diabetes.

***Ravid Kol*[1], *Prof. David Zangen*[2]**

[1]Shaare Zedek Medical Center,

[2]Division of Pediatric Endocrinology, Hadassah Hebrew University Medical Center

Introduction: The optimal treatment of juvenile diabetes is based on insulin accordance with carbohydrate counting (CC). However, the actual compliance to CC is low due to the concern of having to remember the amount of carbohydrates in many sorts of foods.

The hypothesis: A) The variety of sorts of food in each individual is relatively limited, B) achieving awareness of this limited variety may increase the Compliance of CC and improve control of diabetes.

Goals: Examine whether for each individual there is a limited and fixed repertoire of types of meals/foods.

Examine whether individual meals repertoire awareness will increase the capability of the patients to remember the amount of carbs in these meals.

Examine whether the use of an individual foods binder improves glucose monitoring of patients after six months.

Methods: 26 patients with type 1 diabetes between the ages of 6-23 years enrolled in a prospective clinical study, at the Juvenile Diabetes clinics of Hadassah Medical Center. The patients filled out an FFQ (food frequency questionnaire) and an individual food diary, to determine their various types of individual foods.5 patients dropped out for various reasons. 21 patients were followed for 6 months.

An individual foods binder with quantification of carbohydrates was made for each of the 21 patient.

After 6 months of use, a comparison of post and pre- intervention %HbA1c values was made.

Testing the knowledge of carbohydrate content of the individual food sorts included in the individual binder was preformed telephonically at the end of the study.

Results: After reviewing data from 26 food diaries and 26 FFQ, we found that the average amount of food types that are eaten regularly in the FFQ was 42, as well as an average of 22 food types per patient in the food diaries.

After 6 months of use, a comparison of post-study %HbA1c values was made to pre-study %HbA1c values. The %HbA1c of baseline decreased significantly by an average of 0.28 after 6 months of intervention, with a p-value of 0.0275.

Testing the knowledge of carbohydrate content of the individual sorts of food (included in the provided binder) at the end of the study, did not find a correlation between the difference in %HbA1c and an improved knowledge.

Conclusions and Discussion: Patients have a relatively limited and fixed repertoire of individual types of foods - 22! A passive recall (FFQ) finds probably an artificial and therefore a higher variety when compared to a simple diary.

The use of an individual foods sorts and carbohydrate counting binder significantly improves the %HbA1c of patients after six months.

No correlation was found between the difference in %HbA1c and the better capability of carbohydrate counting of the individual variety of foods included in the personally provided binder. This may be explained by the need for larger COHORT and / or longer duration of follow-up.

Once versus twice daily mesalazine to induce remission in pediatric ulcerative colitis: a randomized controlled trial

Dan Turner, Baruch Yerushalmi, Michal Kori, Efrat Broide, Yael Mozer, Ron Shaoul, Kaija-Leena Kolho, Eyal Steyer, Hussein Shamali, Oren Ledder, Shlomi Cohen, Sarit Peleg, Avi On, Arie Levine

Pediatric Gastroenterology, Shaare Zedek Medical Center

Background: Several trials in adults have suggested that once daily dosing of 5ASA may be as or more effective than twice daily dosing in ulcerative colitis (UC). There are no similar studies in children. In this 9-week induction investigator-blinded randomized controlled trial we aimed to compare the effectiveness and safety of once vs. twice daily Pentasa in paediatric UC.

Methods: Children, 4-18 years with a PUCAI of 10-55 points were eligible for enrolment if they were not treated with effective 5ASA dose, in 13 centers in Israel and Finland. Children were randomized into two arms: once (OD) and twice (BID) daily Pentasa using a weight-based dosing table (max 3gr/d) and computer generated randomization table. Primary outcome was week 6 mean PUCAI score, which has a high concordance with sigmoidoscopy in children. Physicians who completed the PUCAI were blinded to the treatment allocation as was the persons analyzing the data. Six visits were schedules until week 9 when safety was assessed. Missing data were imputed using the LOCF method; analyses were performed using the modified ITT approach.

Results: 86 children were randomized and 3 were excluded (1 withdrew consent before receiving study drug, 1 Crohn's and 1 C. Difficile). 83 were analyzed: 43 in the OD and 40 in the BID groups (mean age 14±2.7 years, range 7-18, 43 (52%) males, 51 (62%) extensive colitis). 31 (38%) dropped due to disease aggravation, 7 (8%) lost to follow-up, and 45 (54%) completed the primary visit. There was no difference in completion rates between the OD (28 (65%)) and BID (28 (70%)) arms; p>0.2. Mean PUCAI scores at weeks 2, 3, 6 and 9 were similar between the OD vs. BID arms (24±17 vs 21± 16, 19±17 vs. 17±17, 23±20 vs. 19±20, and 22±21 vs. 20±20; all P>0.2). The proportion of children in remission (PUCAI<10) at week 6 and 9 was similar between the OD and BID groups (13 (30%) vs 16 (40%); p=0.35 and 15 (35%) vs. 17 (43%); p=0.48, respectively). The proportion of children who responded (βPUCAI≥20) was similar at both weeks 6 and 9 (25 (60%) vs 25 (63%); p=0.78, and 25 (60%) vs. 22 (55%); p=0.68, respectively). IMPACT QOL questionnaire at week 6 was similar between the OD (70±12 points) and BID (75±13) arms; p=0.14. Mean reported compliance with treatment was 94% in the OD vs 89% in the BID arms; p=0.17. There were no differences in the mean values of CRP, albumin, hemoglobin, ESR and calprotectin (performed in 17 children) at week 6 (all p>0.1). Most adverse events were related to disease aggravation and the rate of serious adverse events was similar (P>0.2); there were 9 events possibly related to the study medication with similar occurrence (4 vs. 5).

Conclusion: In this first randomized controlled trial in children, there were no differences in effectiveness, safety and compliance when prescribing Pentasa once or twice daily for inducing remission in active UC.

Treatment options and outcomes of pediatric inflammatory bowel disease unclassified (IBDU) compared to other IBD subtypes: a retrospective multicentre study from the IBD Porto group of ESPGHAN

***Liron Birimberg-Schwartz*[1]*, *Marina Aloi*[2]*, *Stephan Buderus*[3], *Iva Hojsak*[4], *John M. Fell*[5], *Jiri Bronsky*[6], *Gigi Veereman*[7], *Sibylle Koletzko*[8], *Ron Shaoul*[9], *Erasmo Miele*[10], *Dan Turner*[2,11], *Richard K. Russell*[12] on behalf of the Pediatric IBD Porto group of ESPGHAN**

*Equal contribution

[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]Sapienza University of Rome, Rome, Italy; [3]St.-Marien-Hospital, Department of Pediatrics, Bonn, Germany ; [4]Children's Hospital Zagreb, Zagreb, Croatia; [5]Chelsea and Westminster Hospital, London, United Kingdom; [6]Dept. of Paediatrics, Charles University and University Hospital Motol, Prague, Czech Republic; [7]Free University Brussels, Brussels Belgium; [8]Ludwig Maximilians University, Munich, Germany; [9]Rambam Medical Center, Haifa, Israel; [10]University of Naples "Federico", Naples, Italy; [11]The Hebrew University, Jerusalem, Israel; [12]Yorkhill Hospital , Glasgow, United Kingdom.

Background: Inflammatory bowel disease unclassified (IBDU) is the rarest IBD subtype with treatment based on extrapolation from ulcerative colitis (UC) and Crohn's disease (CD) studies. We compared IBDU treatment choices to other colonic IBD's and explored long-term outcomes.

Methods: This was a multicentre retrospective longitudinal study of 23 centres of paediatric IBD with isolated colitis, including a mild ileitis consistent with backwash.

Results: 797 children (median age 11.6 years, range 2-18.4) were included: 250 CD, 287 UC and 260 IBDU (median follow-up 2.8 [IQR 1.6-4.2] years). IBDU differed from UC with lower corticosteroid (CS) [154 (59%) vs. 204 (71%), p=0.004] and higher exclusive enteral nutrition (EEN) use [26 (10%) vs. 2 (0.6%), p<0.0001]. Compared to CD, IBDU patients received less EEN and immunomodulators (IM) [26 (10%) vs. 93 (37%), p<0.0001 and 67 (26%) vs. 129 (52%) p<0.0001, respectively] but more aminosalicylates [228 (88%) vs. 159 (64%), p<0.0001]. Biologic treatment was significantly higher in CD [82 (34%)] than in IBDU and UC [24 (12%) and 47 (17%), respectively; p<0.0001]. At last follow-up, 135 (69%) IBDU patients had remission/mild disease activity compared to 100 CD (46%, p<0.0001), and 174 UC (64%, p=0.3). 4 of 194 (2%) IBDU patients underwent surgery, compared to 22/270 (8%) UC (p=0.009) and 20/238 (8%) CD (p=0.008).

Conclusions: Children with IBDU have a lower medication burden and lower surgery rates than other IBD subtypes. The disease course at follow-up is generally mild, supporting an initial trial with 5-ASA before using more aggressive therapies.

Development and validation of diagnostic criteria for IBD-Unclassified (IBDU) in children: a multicenter longitudinal study from the Paediatric IBD Porto group of ESPGHAN

***Liron Birimberg-Schwartz*[1], *David M. Zucker*[2], *Amichay Akriv*[2], *Salvatore Cucchiara*[3], *Fiona Cameron*[4], *Iza Łazowska*[5], *Lambri Yianni*[6], *Siba Paul*[7], *Claudio Romano*[8], *Sanja Kolaek*[9], *Stephan Buderus*[10], *Anders Pærregaard*[11], *Johanna C.Escher*[12] , *Dan Turner*[1,2] on behalf of the Paediatric IBD Porto group of ESPGHAN**

[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]The Hebrew University of Jerusalem, Israel; [3]Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, Italy; [4]Yorkhill Children's Hospital, Glasgow, [5]Medical University of Warsaw, Poland; [6]University Hospital Southampton NHS Foundation Trust, Child Health, Southampton, Hampshire, UK; [7] Bristol Royal Hospital for Children, United Kingdom; [8]Pediatric Gastroenterology and Endoscopy, University of Messina, Messina, Italy; [9]Children's Hospital, Medical Center "Sestre Milosrdnice" Zagreb University Medical School, Croatia; [10]St.-Marien-Hospital, Department of Pediatrics, Bonn, Germany; [11]Department of Paediatrics, Hvidovre University Hospital, Copenhagen, Denmark; [12]Erasmus MC, Rotterdam, Zuid Holland, Netherlands

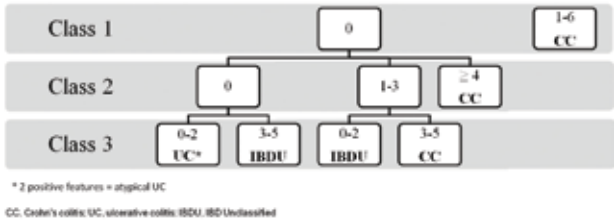
Background: There are no available criteria by which to classify and diagnose Inflammatory Bowel Disease Unclassified (IBDU). We aimed to derive and validate diagnostic criteria of IBDU in children, using both judgmental approach and mathematical modeling on the largest IBDU cohort ever constructed.

Methods: This was a multicenter retrospective longitudinal study from 23 centers affiliated with the pediatric IBD Porto-group of ESPGHAN. Both a hypothesis driven approach and mathematical modeling (CART analysis) were utilized for creating the classification algorithm.

Results: 749 IBD children were enrolled- 236 (32%) with Crohn's colitis (CC), 272 (36%) with ulcerative colitis (UC) and 241 (32%(with IBDU (mean age 10.9±3.6 years, 53% males). Median follow-up was 2.8 years (IQR 1.7-4.3). A set of 23 features were clustered in 3 classes according to their accepted frequency in UC: 6 class 1, 12 class 2 and 5 class 3 features. According to the chosen hypothesis driven judgmental algorithm (Figure 1): ≥1 class 1 feature, ≥4 class 2 features or ≥3 class 3 features with 1-3 class 2 features - diagnose as CC. When having no class 2 features with ≤2 class 3 features- diagnose as UC. All the remaining combinations should be diagnosed as IBDU. This algorithm differentiated UC from CC and IBDU with 80% sensitivity (95% CI (71-88)) and 84% specificity (95% CI (77-89)). The algorithm also differentiated between CC from IBDU and UC with 78% sensitivity (95% CI (67-87)) and 94% specificity (95% CI (89-97)).

Conclusions: The validated algorithm can adequately classify children with colonic IBD into CC, UC and IBDU, thus enabling the standardization of the diagnostic criteria of IBDU.

Figure 1:



Therapeutic Hypothermia: Effect on respiratory condition in neonates.

Itamar Nitzan, Shmuel Goldberg, Cathy Hamerman, Francis Mimouni, Ruben Bromiker

Pediatrics, Shaare Zedek Medical Center

Background: Moderate Therapeutic Hypothermia (MTH) is used for neuroprotection in term neonates with neonatal encephalopathy. Hypothermia decreases metabolic requirements, cardiac output and respiratory rate, and shifts the hemoglobin-oxygen dissociation curve leftward, towards higher affinity.

Methods: This is a retrospective study including all neonates treated with MTH (33.5β C) in the Neonatal Intensive Care Unit (NICU) of the Shaare Zedek Medical Center (SZMC) from January 2008 until September 2015. We collected data from NICU records on neonates respiratory and medical condition including: arterial blood saturation as measured by pulse oximeter (SpO2), arterial blood saturation as measured by co oximeter (SaO2), respiratory support, and desaturations, from birth until 24 hours after rewarming.

Results: Thirty neonates' records were evaluated. Twelve neonates suffered respiratory deterioration (needed higher respiratory support or had new onset desaturations with no change in the level of ventilatory assistance during the 24 hours after rewarming versus 3 with respiratory deterioration in the 24 hours before rewarming (p=0.016). SpO2 declined from 96.9% (+2.9) before rewarming to 95.2% (+ 2.6) after rewarming (p<0.001).

Discussion: Our study shows that neonates who underwent MTH require higher FiO2 and their SpO2 decrease after rewarming. Possible explanations for these findings include: shifting of the hemoglobin-oxygen dissociation curve towards higher affinity, and lower metabolic requirements and oxygen consumption during MTH. The fact that more than third of the neonates deteriorated after rewarming supports the second explanation.

Conclusions: During MTH neonates have higher SpO2 and they require less oxygen. After rewarming the clinician should expect, and monitor for possible respiratory deterioration.

These results raise the possibility of using MTH as an option for rescue treatment for respiratory insufficiency unresponsive to conventional treatment. Further animal studies and human prospective studies are needed to assess these conclusions.

Item generation and reduction of the TUMMY index, a newly derived patient reported outcome (PRO) for pediatric ulcerative colitis

Liron Marcovitch[1, 2*], Anat Nissan[2*], David Mack[3], Anthony Otley[4], Seamus Hussey[5], Michael Kappelman[6], Beth Mclean[6], Nick Croft[7], Farah Barakat[7], Anne M. Griffiths[8], Dan Turner[1,2]

[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]Hebrew University of Jerusalem, Jerusalem, Israel; [3]CHEO, Ottawa, Canada; [4]IWK Health Centre, Halifax, Canada; [5]National Children's Research Centre and University College Dublin, Dublin, Ireland; [6] UNC Health Care, North Carolina, USA; [7]Barts and the London School of medicine, UK; [8] The Hospital for sick children, Toronto

Goal: Under the qualification program of the FDA and EMA, we aimed to develop a Patient Reported Outcome (PRO) measure of signs and symptoms for pediatric ulcerative colitis (UC) (i.e. the TUMMY index).

Background: The TUMMY will be used as an outcome measure in pediatric clinical trials - composite with endoscopic assessment i.

Methods: We performed concept elicitation qualitative interviews with 44 children with UC (age 12.2 ± 3.6, range 4-18 years; 47% males; 23% with moderate-severe disease) and 30 caregivers, in Israel, England, Ireland, Canada and the USA, thus ensuring cultural diversity. Interviews were centered at exploring signs and symptoms reflecting the colitis and which are important to patients. Items were rank ordered by the interviewees according to the frequency of endorsement and importance, graded on a 1-5 scale.

Results: There was a general agreement between the scoring of children and their caregivers. The following items were identified in decreasing order of weights (importance X frequency): abdominal pain (3.9), rectal bleeding (3.6), stool frequency (3.0), stool consistency (3.0), general well-being (2.9), urgency (1.9), and nocturnal stools (1.6). Children 13-18 years comprehended adult vocabulary, 8-12 years comprehended simple vocabulary and younger children had poor understanding and thus their disease may be more accurately scored by a caregiver-reported questionnaire.

Conclusions: In this first stage of the TUMMY development, items were generated and ranked by input purely from patients. These items are now being explored for optimal vocabulary and response options.

Long-term outcome of neonates with suspected Hirschsprung's disease but normal rectal biopsy

Daniel Graph MD[1], Oleg Kharenko MD[1], Jacob Waxman MD[1], Tanya Frankel Bsc[1], Dan Turner MD PhD[1,2], Oren Ledder MD[1,2]

[1]Shaare Zedek Medical Center, Jerusalem, Israel,

[2]The Hebrew University of Jerusalem, Israel

Background and Objectives: Hirschsprung's disease (HD) must always be considered in very-early onset constipation. While HD has a well described clinical course, little is known about those neonates in whom HD was excluded. We aimed to describe the long-term clinical outcomes of neonates with clinical suspicion of HD which was excluded by rectal suction biopsy.

Methods: This is a single center double cohort comparative study. Neonates who underwent rectal mucosa biopsy for suspected HD were age and gender-matched with healthy controls. A survey relating to clinical outcomes, stooling patterns and other gastrointestinal-related conditions was sent to parents. Pathology slides were re-reported by an experienced histopathologist blinded to the clinical data.

Results: A total of 51 neonates were included (25 case, 26 control; 41% male, median time of follow-up 4.25 years (IQR 2.7-6.9).). Nine (36%) of the case group required prolonged laxative use for constipation during the first year of life compared with 0 (0%) of controls (P<0.001). This difference was maintained at the end of follow-up with 5 (20%) vs 0(0%) respectively (p=0.02).Case neonates were significantly more likely to be hospitalized or be diagnosed with a chronic gastrointestinal-related condition than controls (33% vs 12%, p=0.01; and 19% vs 8%, p=0.04respectively).

Conclusions: Neonatal constipation is associated with long term gastrointestinal related disorders and should be considered clinically significant even when the diagnosis of HD is excluded. Neonates with early onset abnormal stooling patterns should be monitored with adequate pediatrician or pediatric gastroenterologist follow-up.

Utility of Proposed Modified Simple Endoscopic Score in Upper Gastrointestinal Crohn's Disease

***Oren Ledder*[1], *Peter Church*[2], *Anne Griffiths*[2], *Javier Martin de Carpi*[3], *Johanna Escher*[4], *M L Mearin*[5], *Batia Weiss*[6], *Raanan Shamir*[7], *Baruch Yerushalmi*[8], *Ron Shaoul*[9], *George Alex*[10], *Daniel Lemberg*[11], *Dan Turner*[1]**

[1]Instutute of Pediatric Gastroenterology, Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Israel; [2] Division of GI/Hepatology/Nutrition, SickKids Hospital, University of Toronto; Canada; [3]Department of Pediatric Gastroenterology, Hospital Sant Joan de Déu, Barcelona, Spain; [4]Department of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands; [5]Departments of Pediatrics, Leiden University Medical Center and Free University Medical Center, Amsterdam, the Netherlands; [6]Department of Pediatric Gastroenterology, Tel Hashomer Medical Center, Tel Aviv, Israel; [7]Department of Pediatric Gastroenterology, Schneider Medical Center, Petach Tikva, Israel; [8]Department of Pediatric Gastroenterology, Soroka Medical Center, Beer Sheba, Israel; [9]Department of Pediatric Gastroenterology, Rambam Medical Center, Haifa, Israel; [10]Department of Pediatric Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Australia; [11]Department of Pediatric Gastroenterology, Sydney Children's Hospital, Sydney, Australia

Objectives and study: With more frequent performance of upper endoscopy (EGD), upper gastrointestinal (UGI) inflammation in Crohn's disease (CD) patients has become increasingly recognized. UGI CD is associated with earlier onset and more severe disease. Recognition of UGI CD may assist in predicting disease course and directing appropriate therapy. Descriptive colonoscopy findings in CD are well standardized, however this is not so in the UGI. Lack of standardization limits the ability to implicate clinical significance of UGI CD. We empirically applied the Simple Endoscopic Score for CD (SES-CD) in the UGI for the first time, using the same indices as that for colonoscopy. The study aimed to assess the utility of the UGI SES-CD and its clinical significance in pediatric CD.

Methods: We used prospectively recorded data of pediatric CD patients collected for the ongoing ImageKids study. All patients underwent an EGD during the enrollment phase with a full clinical assessment within 2 weeks of the EGD. SES-CD items were scored in real time during upper endoscopy at each region (esophagus, stomach body, antrum and duodenum) with maximum total UGI SES-CD of 48. Demographics, clinical findings, biochemical markers, weighted Pediatric Crohn's Disease Activity Index (wPCDAI) and physician global assessment (PGA) were also recorded.

Results: 94 children were enrolled at time of analysis (52 male; mean age 11.4 years ±3.0; range 3.3-17.3 years). Mean time from diagnosis to enrollment and endoscopic assessment was 2.4 years (±2.1; range 0-8.2). Mean wPCDAI 17.2 (±14.3; range 0-52.5). Median UGI SES-CD was 0 ± 3 (range 0-17). 44% had UGI SES-CD score ≥1, the majority of whom had endoscopic pathology identified in the duodenum (32%) with the least frequently involved region being the esophagus (9%). The major contributor to overall score in the esophagus, stomach body and antrum was "affected area" with less contribution from ulcer scores. In the duodenum these scoring features occurred in comparable frequencies. Narrowing was not identified in any region. There was a poor but significant correlation of UGI SES-CD with ESR and wPCDAI (r=0.2, r=0.2 P=<0.05). There was no correlation between UGI SES-CD and age of diagnosis, clinical manifestations (including abdominal pain), other biochemical markers or specific Crohn's therapy used. Patients with perianal CD had higher UGI SES-CD score [Median (IQR) 3 (±5) vs 0 (±3); p=0.01].

Conclusion: UGI SES-CD is an easily reported objective scoring system which may standardize reporting of endoscopic features of UGI CD.

UGI findings were present in almost half of patients in this cohort.

There is a lack of correlation between UGI findings and symptomatology, further supporting the recommendation of routine UGI endoscopy at IBD diagnosis rather than limiting EGD to patients with UGI symptoms.

Disclosure of interest: The ImageKids study is funded by an IIS grant from Abbvie. The authors declare no conflict of interest relating to this work

Rapid infliximab infusion in children: a multicenter cohort study

***Raffi Lev-Tzion*[1], *Amit Assa*[2], *Baruch Yerushalmi*[3,4], *Avishay Lahad*[5], *Oren Ledder*[1,6], *Dan Turner*[1,6]**

[1]Juliet Keidan Institute of Pediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, [2]Institute of Gastroenterology, Nutrition and Liver Disease, Schneider Children's Medical Center, [3]Pediatric Gastroenterology Unit, Soroka University Medical Center, [4]Faculty of Health Sciences, Ben-Gurion University, [5]Pediatric Gastroenterology, Hepatology and Nutrition Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, [6]Hebrew University of Jerusalem Faculty of Medicine

Background/Aims: A significant drawback of infliximab administration is the requirement that patients spend 3-4 hours in a dedicated infusion center. While a number of adult studies have found rapid infusion to be safe, pediatric data continues to be scarce. We report our experience with a 1-hour rapid infusion protocol, prescribed in three pediatric IBD units over a period ranging from 6-20 months.

Methods: 1-hour infliximab infusions were administered to children with IBD who fulfilled the following criteria: 1) They had received at least 4 standard duration infusions with no infusion reactions; 2) There was no recent dose increase; 3) No more than 10 weeks had elapsed since the previous infusion. Standard duration infusions were administered over the course of approximately 3 hours for the first 3 infusions, and approximately 2 hours for subsequent infusions. Premedication administration was left to the discretion of each individual center. Patients were followed prospectively and all infusion reactions were recorded in patients' charts.

Results: 85 children with IBD received infliximab infusions (69 CD, 9 UC and 7 IBD-U); mean age 15.4±2.9 years, 55.3% males, and median disease duration 23 (IQR 48-12) months. 50 children qualified for the rapid infusion protocol. 448 standard duration infusions and 311 rapid infusions were administered. 57/85 (67%) patients received concomitant immunomodulators. 7 infusion reactions (1.6%) occurred during standard duration infusions and 3 (0.96%) occurred during rapid infusions (p=0.54).

Conclusion: Consistent with adult data, our results indicate that 1-hour infliximab infusions in selected pediatric IBD patients offer a safe alternative to traditional 2-3 hour infusions. By decreasing the time patients and their parents need to spend in the infusion center, rapid infliximab infusion can mitigate an important obstacle to patient acceptance of infliximab therapy.

Intermittent Vancomycin And Gentamicin As Exclusive Therapy For Infantile Onset Inflammatory Bowel Disease

***Raffi Lev Tzion**[1], *Oren Ledder*[1], *Eyal Shteyer*[1, 2], *Dan Turner*[1, 2]**

[1]Juliet Keidan Institute of Pediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, [2]The Hebrew University of Jerusalem, Jerusalem, Israel

Background/Aims: Very Early Onset Inflammatory Bowel Disease (VEO-IBD) is a unique subtype of IBD and many patients are resistant to standard therapy, particularly those with infantile onset. Infantile-onset IBD is also often associated with monogenic etiologies. While children with both PSC and IBD treated with vancomycin have been reported to incidentally show improvement in IBD as well, vancomycin has never been studied as exclusive therapy for VEO-IBD.

Methods: We report here our experience using oral vancomycin and gentamicin (V&G) to successfully treat two patients with infantile-onset IBD refractory to standard treatments.

Results: Patient 1, with severe Crohn's colitis, presented at 5 months with hematochezia and subsequent diarrhea, failure to thrive and elevated inflammatory markers. Colonoscopy revealed aphthous ulcerations in the rectosigmoid and cecum with granulomas. Investigation for immune deficiency and interleukin-10 defects was negative. Treatment with corticosteroids, exclusive enteral nutrition, sulfasalazine and infliximab was unsuccessful; he had an allergic rash on azathioprine. At the age of 14 months he fully responded (PUCAI=0) within 5 days to oral V&G following 6 months of chronically active disease (PUCAI 20-85). Over the next 14 months he received no maintenance treatment; he had 2 exacerbations which were successfully treated with 2 week courses of V&G. Seven months after completing the third course, he continues to be in complete clinical remission with no medications.

Patient 2 had intermittent hematochezia starting at 8 months of age. At 2.5 years she presented with bloody diarrhea along with elevated transaminases and GGT. Colonoscopy demonstrated pancolitis and liver biopsy was consistent with PSC. Investigation for immune deficiency and interleukin-10 defects was negative. She was refractory to 5-ASA. Over the next 7 months she received three courses of oral V&G with prompt and complete remission each time of both her colitis symptoms and her liver markers, including normalization of CRP. She was continued on vancomycin only, but her inflammatory markers rose and salazopyrine was added with rapid normalization. At last follow-up she is in complete clinical remission with normal transaminases and GGT and calprotectin.

Conclusion: We have reported the first two cases of infantile-onset IBD successfully treated with only oral antibiotics, using intermittent courses of vancomycin and gentamicin. The treatment also resulted in normalization of liver enzymes in a patient who had concurrent PSC. Both antimicrobial and immunomodulatory effects, including stimulation of regulatory T cells, may play a role in the mechanism of action. As infantile-onset IBD is often difficult to treat, our findings represent a potential treatment and should be further investigated in controlled trials

Mild inhibition of alanine-glyoxylate aminotransferase translation as a possible treatment of primary hyperoxaluria type I

R Lyakhovetsky[1], ***Y Frishberg***[1], ***BB Beck***[2], ***R Belostotsky***[1]

[1]Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel[2].Institute of Human Genetics, Cologne, Germany

Background: Primary hyperoxaluria type 1 (PH1) is a kidney stone disease, often leading to ESRD, caused by absence, deficiency or mistargeting of the liver peroxisomal alanine-glyoxylate aminotransferase (AGT), encoded by AGXT. The most frequent PH-1 linked mutation, G170R, responsible for 30% of PH1 cases in Caucasians, results in aberrant mitochondrial localization rather than catalytic inactivity of the protein. This phenomenon is followed by excessive production of oxalate by the liver, and insoluble calcium oxalate crystals eventually coalesce into kidney stones. Retargeting AGT into peroxisomes by pharmacological modulation of its' maturation and folding, has long been perceived as a possible therapeutic method. Yet, numerous attempts over the years failed to rescue AGT mutants. We propose mild translation inhibition as a novel approach to improve localization and function of AGT mutants.

Methods: We employ a known translation inhibitor, the anti-amoebic FDA-approved drug emetine that has recently been shown to improve folding and function of misfolded mutants of other proteins. We applied various emetine treatment regimens to cultured CHO cells overexpressing either the wtAGT or AGT that bears the G170R mutation (G170R-AGT).

To ensure selective and specific discrimination between the mitochondrial (major) and the peroxisomal (minor) subpopulations of mutated AGT we developed the GlowAGT assay based on the recently described "self-assembly split GFP" approach. Briefly, the GFP protein is divided into a short moiety (GFP11- "the tag") which is used to label the protein of interest, and a large moiety (GFP1-10, "the detector"). If these moieties are co-expressed in the same subcellular compartment, they associate spontaneously, reconstituting a fluorescent GFP molecule. If they are located in different compartments, there is no fluorescence. We tagged wtAGT and G170R-AGT with GFP11 and added a peroxisome-targeting sequence to the GFP1-10 "detector".

Results: wtAGT but not G170R-AGT was detectable by GFP fluorescence, although both variants were detectable by indirect immunofluorescence. Long-term treatment with low concentrations of emetine showed statistically significant increase of fluorescent subpopulation of G170R-AGT in treated cells. This increase was inversely correlated to the levels of both GlowAGT components. GlowAGT fluorescence was exclusively co-distributed with the peroxisomal staining in all cases. Importantly, we were able to show decrease of oxalate secretion by emetine-treated upcyte® G170R AGT-bearing hepatocytes.

Conclusions: We have developed and successfully applied GlowAGT as a unique self-assembly split-GFP-based assay for detecting peroxisomal subpopulation of AGT. Using GlowAGT we show that mild translation inhibition by emetine is a novel therapeutic approach for PH1 caused by AGT misfolding/mislocalization. Those results were confirmed in G170R-hepatocytes, suggesting clinical relevance of the treatment.

Mutations in HAO1 encoding glycolate oxidase cause isolated glycolic aciduria rather than primary hyperoxaluria

Ruth Belostotsky[1], ***Avraham Zeharia1***, ***Roman Lyakhovetsky***[1], ***Ruth Bargal***[1] ***and Yaacov Frishberg***[1,2]

[1]Division of Pediatric Nephrology, Shaare Zedek Medical Center, [2]The Hebrew University School of Medicine, Jerusalem, Israel,

The primary hyperoxalurias are a group of recessive disorders manifesting as calcium oxalate kidney stone disease. Oxalate overproduction is facilitated by perturbations in the metabolism of glyoxylate and glycolate. Type 1 primary hyperoxaluria (PHI) is caused by the deficiency of alanine:glyoxylate aminotransferase. Hyperoxaluria and glycolic aciduria are regarded as the hallmarks of PHI. The genetic basis of PH-unrelated glycolic aciduria in a boy with extremely high urinary glycolate levels was investigated. The combination of glycolic aciduria with normal urinary oxalate excretion led us to assume that the patient has nonfunctional glycolate oxidase (HAO1). DNA sequencing of HAO1 revealed a homozygous c.814-1G>C mutation in the invariant -1 position of splice acceptor site. Since HAO1 is a liver-specific enzyme, the effect of this novel mutation on splicing was validated by an in-vitro hybrid-minigene approach. We confirmed the appearance of an abnormal splice variant within the transfected cells. The proband and his brother had in addition a triple-A-like syndrome characterized by anisocoria, alacrima and achalasia. Homozygous mutations in GMPPA encoding guanosine diphosphate mannose pyrophosphorylase were recently found to be responsible for the triple-A-like syndrome in this kindred. It is unlikely that either of the proband's symptoms are attributable to his variant in HAO1 as his brother had a similar phenotype without glycolic aciduria or homozygous mutations in HAO1.

Our results pinpoint the expression of defective splice variant of glyoxylate oxidase as the cause of isolated asymptomatic glycolic aciduria which concurs with the HAO1 deficient mice. Our observation has contributed to the development of a novel approache, namely substrate reduction, for the treatment of primary hyperoxaluria type I.

Primary Hyperoxaluria Type 3: a novel gene, theAshkenazi-Jewish allele and the phenotype

Ruth Belostotsky and Yaacov Frishberg

Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem 91031, Israel

Primary hyperoxalurias are autosomal recessive disorders characterized by the accumulation of calcium oxalate, primarily in the kidney. To determine the etiology of a yet uncharacterized type of primary hyperoxaluria an international cohort of 15 non-PHI/PHII patients from 8 unrelated families was selected. SNP microarray analysis did not reveal any suspicious locus. The only family characterized by a LOD score of 2, was a non-consanguineous family of Ashkenazi-Jewish (AJ) descent having 5 affected offspring. All affected children shared two heterozygous regions with a total length of 60Mbp, implying a compound-heterozygous pattern. One of these regions partially intersected with a heterozygous region shared by two affected siblings of another AJ family. Given that 4 out of 8 families in this cohort were of AJ descent we assumed that they share a common allele. To investigate this assumption we developed a heterozygosity mapping approach which allowed us to detect in all AJ families the fragments of the common allele on chromosome 10. The intersection of all fragments resulted in a shared region of 0.6 Mbp. Within this region we detected the gene HOGA1, bearing mutations in both alleles in all individuals from our cohort. All patients of AJ origin carry the c.943_945delAGG deletion. We predicted that this uncharacterized gene encodes the 4-hydroxy-2-oxoglutarate aldolase. This assumption was confirmed by bioinformatic analysis and comparison with the characteristics of the protein from bovine liver. 4-hydroxy-2-oxoglutarate aldolase is involved in the catabolism of hydroxyproline to glyoxalate. The latter is the substrate for oxalate synthesis which explains the phenotypic consequences of these mutations.

The Metabolic Basis Of Primary Hyperoxaluria Type 3

Ruth Belostotsky[1], ***James Pitt***[2] ***and Yaacov Frishberg***[1]

[1]Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel

[2]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Australia

Perturbations in glyoxylate metabolism lead to the accumulation of oxalate and give rise to primary hyperoxalurias, recessive disorders characterized by kidney stone disease. Loss-of-function mutations in HOGA1 are responsible for primary hyperoxaluria type III (PHIII). HOGA1 encodes a mitochondrial 4-hydroxy-2-oxoglutarate (HOG) aldolase which cleaves HOG to pyruvate and glyoxylic acids in the 4-hydroxyproline catabolic pathway. We investigated hydroxyproline metabolites in the urine of patients with PHIII using gas chromatography - mass spectroscopy. Significant increases in concentrations of 4-hydroxy-2-oxoglutarate and its precursor and derivative 4-hydroxyglutamate and 2,4-dihydroxyglutarate, respectively, were found in all patients as compared to carriers of the corresponding mutations or healthy controls. These data confirm that HOGA1 mutations result in loss of function and that accumulating HOG can exit mitochondria. Despite a functional block in the conversion of hydroxyproline to glyoxylate (immediate oxalate precursor) the production of oxalate increases. To explain this apparent contradiction we propose a model of glyoxylate compartmentalization in which cellular glyoxylate is normally prevented from contact with the cytosol where it can be oxidized to oxalate. We propose that HOGA1 deficiency results in the accumulation of 4-hydroxy-2-oxoglutarate in the mitochondria and its transport into the cytosol where it is converted to glyoxylate by a different cytosolic aldolase. In vitro studies using a non-PH3 human hepatocyte cell line demonstrated significant HOG aldolase activity in cytosolic fractions. No HOGA1 protein was detected in the cytosolic fraction indicating that it contains other enzyme(s) with HOG aldolase activity. Aldolase enzymes are known to have broad substrate specificity and several cytosolic aldolases could fill this role.

Our data provide a diagnostic tool for screening larger cohorts for PHIII and shed light on glyoxylate metabolism and the pathogenesis of primary hyperoxalurias.

Progressive renal failure in infancy: a manifestation of a new mitochondrial cytopathy: mutations in the mitochondrial seryl-tRNA synthetase cause HUPRA syndrome

Ruth Belostotsky,[1] Efrat Ben-Shalom,[1] Choni Rinat,[1] Rachel Becker-Cohen,[1] Sofia Feinstein,[1] Sharon Zeligson,[2] Reeval Segel,2 Orly Elpeleg ,[3] Suheir Nassar,[4] and Yaacov Frishberg1*

[1]Division of Pediatric Nephrology, Shaare Zedek Medical Center, [2]Institute of Medical Genetics, Shaare Zedek Medical Center, Jerusalem 91031, Israel; [3]Hadassah, Hebrew University Medical Center; [4]Makassed Hospital, Jerusalem 91194 , Israel

An uncharacterized multi-systemic mitochondrial cytopathy was diagnosed in 2 infants from an inbred Arab kindred living in a single village. The most significant clinical findings were tubulopathy (hyperuricemia, metabolic alkalosis), progressive renal failure in infancy and pulmonary hypertension (HARP syndrome). Analysis of the consanguineous pedigree suggested that the causative mutation is in the nuclear DNA. Using genome-wide SNP homozygosity analysis, we identified a homozygous identity-by-descent region on chromosome 19 and detected the pathogenic mutation c.1169A>G (p.Asp390Gly) in SARS2, encoding the mitochondrial seryl-tRNA synthetase. The same homozygous mutation was later identified in a third infant with HARP syndrome. The carrier rate of this mutation among inhabitants of this Arab isolate was found to be 1:15. The mature enzyme catalyzes the ligation of serine to two mitochondrial tRNA isoacceptors: tRNASerAGY and tRNASerUCN. Analysis of amino acylation of the two target tRNAs, extracted from immortalized peripheral lymphocytes derived from two patients, revealed that the Asp390Gly mutation significantly impacts on the acylation of tRNASerAGY but not of tRNASerUCN. Marked decrease in the expression of the non-acylated transcript and the complete absence of the acylated tRNASerAGY suggest that this mutation leads to significant loss of function and that the uncharged transcripts undergo degradation.

Loss-of-function of PCDH12 underlies recessive microcephaly mimicking intrauterine infection*

Adi Aran*[1]*, Nuphar Rosenfeld*[2]*, Ranit Jaron*[2]*, Paul Renbaum*[2]*, Shachar Zuckerman*[2]*, Hila Fridman*[2]*, Sharon Zeligson*[2]*, Reeval Segel*[2]*, Yoav Kohn*[3]*, Lara Kamal*[4]*, Moien Kannan*[4]*, Yoram Segev*[5]*, Eyal Mazaki*[6]*, Ron Rabinowitz*[6]*, Ori Shen*[6]*, Ming K. Lee*[7]*, Tom Walsh*[7]*, Mary-Claire King*[7]*, Suleyman Gulsuner*[7]*, Ephrat Levy-Lahad*[2]*.

[1]Neuropediatric Unit SZMC, [2]Medical Genetics, SZMC, [3]Eitanim Psychiatric Hospital, [4]Bethlehem University, [5]MRI Unit, SZMC, [6]Obstetrics and Gynecology Department, SZMC, [7]Medical Genetics, University of Washington, Seattle, WA

Objective: To identify the genetic basis of a recessive syndrome characterized by prenatal hyperechogenic brain foci, congenital microcephaly, hypothalamic midbrain dysplasia, epilepsy, and profound global developmental disability.

Methods: Identification of the responsible gene by whole exome sequencing and homozygosity mapping.

Results: Ten patients from four consanguineous Palestinian families manifested in utero with hyperechogenic brain foci, microcephaly, and intra-uterine growth retardation. Postnatally, patients had progressive severe microcephaly, neonatal seizures, and virtually no developmental milestones. Brain imaging revealed dysplastic elongated masses in the midbrain-hypothalamus-optic tract area. Whole exome sequencing of one affected child revealed only PCDH12 c.2515C>T, p.R839X, to be homozygous in the proband and to co-segregate with the condition in her family. The allele frequency of PCDH12 p.R839X is <0.00001 worldwide. Genotyping PCDH12 p.R839X in three other families with affected children yielded perfect co-segregation with the phenotype (probability by chance is 2.0x10^(-12)). Homozygosity mapping revealed that PCDH12 p.R839X lies in the largest homozygous region (11.7 MB) shared by all affected patients. The mutation reduces transcript expression by 84% (p<2.4x10^(-13)). PCDH12 is a vascular endothelial protocadherin that promotes cellular adhesion. Endothelial adhesion disruptions due to mutations in OCLN or JAM3 also cause congenital microcephaly, intracranial calcifications, and profound psychomotor disability.

Conclusion: Loss of function of PCDH12 leads to recessive congenital microcephaly with profound developmental disability. The phenotype resembles Aicardi-Goutières syndrome and in utero infections. In cases with similar manifestations but no evidence of infection, our results suggest consideration of an additional, albeit rare, cause of congenital microcephaly.

Medical decisions of pediatric residents turn riskier after a 24-hour call with no sleep

***Adi Aran*[1], *Netanel Vasertile*[1], *Itai Gross*[2] , *Joseph Mendelovic*[1], *Yehuda Pollak*[1]**

[1]Shaare Zedek Medical Center; [2]Hadassah Medical Center.

Background and Objectives: Despite a gradual workload reduction during residency, 24-hour calls are still an integral part of most training programs. While sleep deprivation increases risk propensity, the impact on medical risk taking has not been studied.

This study aimed to assess clinical decision making and psychomotor performance of pediatric residents following limited nap time during a 24-hour call.

Methods: Neurocognitive battery (IntegNeuro, BRC) and a medical decision questionnaire were completed by 44 pediatric residents at two time points: after a 24-hour call and following 3 nights with no calls (night-sleep ≥ 5 hours). To monitor sleep, residents wore actigraphs and completed sleep logs.

Results: Nap time during shift was < 1 hour in 14 cases (32%), 1-2 hours in 16 cases (35%) and 2-3 hours in 14 cases (32%). Residents who napped less than one hour chose the riskier medical option in 50% of cases compared with 36% when answering the same questionnaire after 3 nights with no calls (p=0.002). This effect was not found in residents who napped 1-2 hours (no change in risk taking) or 2-3 hours (4% decreased risk taking; difference between groups, p= 0.001). Risk taking tendency inversely correlated with sustained attention scores (Pearson = -0.433, p=0.003). Sustained attention was the neurocognitive domain most affected by sleep deprivation (effect size = 0.29, p = 0.025).

Conclusion: This study suggests that residents napping less than an hour during a night shift are prone to riskier clinical decisions. Hence, enabling residents to nap at least 1 hour during shifts is recommended.

A novel post-streptococcal antibody, anti-protein disulfide isomerase, in patients with Sydenham's chorea

Adi Hersh, Hilla Ben-Pazi and Adi Aran

Neuropediatric unit, Shaare Zedek Medical Center

Background: Rheumatic fever (RF) is a post-streptococcal autoimmune disorder characterized by inflammation of the joints, heart valves and CNS. Serological markers of recent streptococcal infection have an important role in the diagnosis of rheumatic fever and its CNS manifestation - Sydenham's chorea (SC). Anti-streptolysin O (ASLO), and Anti-deoxyribonuclease B (ADB) are commonly used post-streptococcal markers but their specificity and sensitivity are lacking, especially in cases of isolated SC that might present months after the streptococcal infection. Anti-protein disulfide isomerase (Anti-PDI) is a recently described post-streptococcal antibody that has been associated with autoimmunity and a longer duration in the serum after a streptococcal infection.

Objectives: To assess the role of anti-PDI in the diagnosis of children with SC and to explore the association between anti-PDI, and clinical symptoms.

Methods: Serum samples of 32 children with SC and 81 matched controls, admitted to the pediatric emergency room due to abdominal pain, were assessed for titers of anti-PDI and ASLO. Severity of chorea in patients was assessed using the unified chorea rating scale (UCRS) and associations with post-streptococcal antibody titers were explored.

Results: Anti-streptolysin -O and anti-PDI titers were higher in patients with SC (ASLO= 616 ± 385 IU/ml; anti-PDI= 31.3 ± 33.1 U/ml) compared with control group (ASLO- 386 ± 353 IU/ml, p=0.003; anti-PDI- 16.2 ± 22 U/ml, p=0.007). ASLO ≥ 650 IU was found in 26% of patients and 13.6% of controls (p=0.06) Anti-PDI ≥ 40 U/ml was found in 33% of patients and 12.6% of controls (p=0.006).

High titers of at least one post-streptococcal antibody (either ASLO≥650 or anti-PDI≥40) were found in 50% of SC patients compared with 22% of controls (p=0.002), while high titers of both antibodies were found in 10% of patients and 3.6% of controls (p=0.01). Severity of chorea motor symptoms was correlated with ASLO titers (pearson=0.522, p=0.007) and positive anti-PDI status (≥10 U) was associated with moderate to severe chorea motor symptoms (UCRS score ≥11, p=0.02)

Conclusions: Measurement of both ASLO and anti-PDI antibodies improve sensitivity and specificity of serological evaluation in children with SC. Patients with severe motor symptoms have higher anti-streptococcal antibodies. Further studies are needed to assess the role of anti-PDI in the diagnosis and pathogenesis of SC.

A novel post-streptococcal antibody, anti-protein disulfide isomerase, in patients with Sydenham's chorea

Adi Hersh, Hilla Ben-Pazi and Adi Aran

Neuropediatric unit, Shaare Zedek Medical Center

Background: Rheumatic fever (RF) is a post-streptococcal autoimmune disorder characterized by inflammation of the joints, heart valves and CNS. Serological markers of recent streptococcal infection have an important role in the diagnosis of rheumatic fever and its CNS manifestation - Sydenham's chorea (SC). Anti-streptolysin O (ASLO), and Anti-deoxyribonuclease B (ADB) are commonly used post-streptococcal markers but their specificity and sensitivity are lacking, especially in cases of isolated SC that might present months after the streptococcal infection. Anti-protein disulfide isomerase (Anti-PDI) is a recently described post-streptococcal antibody that has been associated with autoimmunity and a longer duration in the serum after a streptococcal infection.

Objectives: To assess the role of anti-PDI in the diagnosis of children with SC and to explore the association between anti-PDI, and clinical symptoms.

Methods: Serum samples of 32 children with SC and 81 matched controls, admitted to the pediatric emergency room due to abdominal pain, were assessed for titers of anti-PDI and ASLO. Severity of chorea in patients was assessed using the unified chorea rating scale (UCRS) and associations with post-streptococcal antibody titers were explored.

Results: Anti-streptolysin -O and anti-PDI titers were higher in patients with SC (ASLO= 616 ± 385 IU/ml; anti-PDI= 31.3 ± 33.1 U/ml) compared with control group (ASLO- 386 ± 353 IU/ml, p=0.003; anti-PDI- 16.2 ± 22 U/ml, p=0.007). ASLO ≥ 650 IU was found in 26% of patients and 13.6% of controls (p=0.06) Anti-PDI ≥ 40 U/ml was found in 33% of patients and 12.6% of controls (p=0.006).

High titers of at least one post-streptococcal antibody (either ASLO≥650 or anti-PDI≥40) were found in 50% of SC patients compared with 22% of controls (p=0.002), while high titers of both antibodies were found in 10% of patients and 3.6% of controls (p=0.01). Severity of chorea motor symptoms was correlated with ASLO titers (pearson=0.522, p=0.007) and positive anti-PDI status (≥10 U) was associated with moderate to severe chorea motor symptoms (UCRS score ≥11, p=0.02)

Conclusions: Measurement of both ASLO and anti-PDI antibodies improve sensitivity and specificity of serological evaluation in children with SC. Patients with severe motor symptoms have higher anti-streptococcal antibodies. Further studies are needed to assess the role of anti-PDI in the diagnosis and pathogenesis of SC.

Copy number variations in cryptogenic cerebral palsy

Reeval Segel, Hilla Ben-Pazi, Sharon Zeligson, Aviva Fatal-Valevski, Adi Aran, Varda Gross-Tsur, Nira Schneebaum-Sender, Dorit Shmueli, Dorit Lev, Shira Perlberg, Luba Blumkin, Lisa Deutsch, and Ephrat Levy-Lahad.

Neuropediatric Unit SZMC, Medical Genetics, SZMC

Aims: To determine the prevalence and characteristics of copy number variations (CNVs) in children with cerebral palsy (CP) of unknown etiology, comprising approximately 20% of the CP population.

Methods: Fifty-two participants (age 10.5±7.8 years; Gross Motor Function Classification System scale 2.8±1.3) with non-progressive pyramidal and/or extrapyramidal signs since infancy and no identified etiology were enrolled. Individuals with evidence of acquired causes were excluded. Participants underwent neurologic and clinical genetic examinations before the genomic testing. Chromosomal microarray analysis to detect CNVs was performed using the Affymetrix platform. CNVs identified were classified as pathogenic, likely pathogenic, likely benign, or benign. Only pathogenic and likely pathogenic CNVs were defined as clinically significant.

Results: Thirty-nine CNVs were found in 25 of 52 participants (48%). Sixteen participants (31%) had clinically significant CNVs: 10 pathogenic and 6 likely pathogenic, of which 7 were not previously associated with motor disability. Nine participants had likely benign CNVs. Clinically significant

CNVs were more frequently de novo (12/16; p<0.001) including in 5 of 8 individuals who had a first- or second-degree relative with a major neurologic disorder. Dysmorphic features and non-motor comorbidities were more prevalent in individuals with clinically significant CNVs (p< 0.05 for both).

Conclusion: CNVs, most frequently de novo, are common in individuals with cryptogenic CP. We recommend CNV testing in individuals with CP of unknown etiology.

Sexual dichotomy of gonadal function in Prader-Willi Syndrome from early infancy through the fourth decade.

Hirsch HJ, Eldar-Geva T, Bennaroch F, Pollak Y, Gross-Tsur V. (2015)

Neuropediatric Unit, Shaare Zedek Medical Center

Study question: At what age does the type of hypogonadism, namely hypothalamic or primary gonadal defect, become established in men and women with Prader-Willi syndrome (PWS?

Summary answer: The type of hypogonadism becomes established only in late adolescence and early adulthood.

What is known already: The etiology of hypogonadism in PWS is heterogeneous and the clinical expression is variable. Primary testicular failure is common in PWS men, while combinations of ovarian dysfunction and gonadotrophin deficiency are seen in women.

Study design, size, duration: This is a prospective study of a cohort of 106 PWS patients followed for a mean duration of 4.5 years. Serial blood samples were obtained and assayed for gonadotrophins, inhibin B, anti-Mullerian hormone (AMH), dehydroepiandrosterone sulfate (DHEAS), testosterone (males), and estradiol (females). Results were compared with normal reference values obtained from the literature. For

The purpose of this study, we defined the following age groups: infants, 1 year; children 1-10 years; adolescents 11-20 years and adults >20 years.

Participants/materials, setting, methods: Study participants were 49 males (aged 2 months to 36 years) and 57 females (aged 1 month to 37 years) with genetically confirmed diagnoses of PWS (deletions 60, uniparental disomy 54, imprinting center defect 2) followed in the Israel national multidisciplinary PWS clinic.

Main results and the role of chance: Serum LH levels were in the normal range (1.0-6.0 mIU/ml) for 7/10 adult men, and high in 3, while FSH (normal range 1.0-6.1 mIU/ml)was elevated (34.4+11.5mIU/ml) in 6 and normal (3.5+1.6 mIU/ml) in 4men. Testosterone was low (5.7+3.4 nmol/l) compared with the normal range of 12.0-34.5 nmol/l in the reference population in all men >20 years AMH showed a normal decrease with age, despite low testosterone levels. Inhibin B was normal (241+105 pg/ml) in infant boys,

but low or undetectable in most adult men. Hormonal profiles were more heterogeneous in women than in men. Estradiol was consistently detectable in only 7/13 adult women. Inhibin B was lowor/undetectable in all PWS females although occasional samples showed levels within the normal range of 15-95 pg/ml. Vaginal bleeding was reported to occur for the first time in eight women at a median age of 20 years (13-34 years), but only one had regular monthly menses. The type of hypogonadism (primary or secondary) in PWS can be determined only after age20 years.

Limitations, reasons for caution: The study cohort was heterogeneous, showing variability in BMI, cognitive disability and medical treatment.

Wider implications of the findings: Demonstration of the natural history of reproductive hormone development in PWS suggests that androgen replacement may be indicated for most PWS boys in mid-adolescence. Recommendations for hormone replacement in PWS women need to be individually tailored, serial measurements of inhibin B should be performed, and contraception should be considered in those women who may have the potential for fertility.

Energy expenditure, physical activity and maximal oxygen uptake in adults with Prader-Willi syndrome

Itai Gross, Harry J Hirsch, Naama Constantini, Shachar Nice, Yehuda Pollak, Larry Genstil, Talia Eldar-Geva and Varda Gross Tsur

Neuropediatric Unit, Shaare Zedek Medical Center

Background: Prader-Willi Syndrome (PWS) is the most common syndromal cause of life threatening obesity. Strict adherence to a low-calorie diet and regular physical activity prevent extreme obesity. Unexpectedly, direct measurement of maximal oxygen uptake (VO2 max), the “gold standard” for assessing aerobic exercise capacity, has not been described in PWS.

Objectives: Assess aerobic capacity by direct measurement of VO2 max in adults with PWS, and in age and BMI-matched controls (OC). Compare the results with values obtained by indirect prediction methods.

Methods and Patients: 17 individuals (12 males) ages: 19-35 (28.6±4.9), BMI: 19.4-38.1 (27.8±5) kg/m2 with genetically confirmed PWS who exercise daily and 32 matched OC (22 males) ages: 19-36 (29.3 ±5.2), BMI: 21.1-48.1 (26.3±4.9) kg/m2. All filled out a medical questionnaire and performed strength and flexibility tests. During a graded exercise test on a treadmill VO2 max was determined by measuring oxygen consumption.

Results: VO2 max (24.6±3.4 vs 46.5±12.2 ml/kg/min, $p<0.001$) and anaerobic threshold (20±2 and 36.2±10.5 ml/kg/min, $p<0.001$), maximal strength of both hands (36±4 vs. 91.4±21.2 kg, $p<0.001$) and flexibility (15.2±9.5 vs. 26±11.1 cm, $p=0.001$) were all significantly lower for PWS compared to OC.

Conclusions: Aerobic capacity, assessed by direct measurement of VO2 max, is significantly lower in PWS adults, even in those who exercise daily, compared to OCs. Indirect estimates of VO2 max are accurate for OC, but unreliable in PWS. Direct measurement of VO2 during a graded exercise test is preferred, when tailoring a personal training plan and when planning clinical studies of exercise in PWS.

Irisin and the Metabolic Phenotype of Adults with Prader-Willi Syndrome

Harry J. Hirsch, M.D.[1*], ***Itai Gross, M.D***[2,*], ***Yehuda Pollak, Ph.D.***[1,3], ***Talia Eldar-Geva, M.D., Ph.D.***[4,5], ***Varda Gross-Tsur, M.D.***[1,4*]

[(1)]Israel Multidisciplinary Prader-Willi Syndrome Clinic, Neuropediatric Unit, Department of Pediatrics, Shaare Zedek Medical Center, Jerusalem, [(2)]Department of Pediatrics Hadassah Hospital, Ein Kerem, Jerusalem, [(3)]The School of Education, The Hebrew University, Jerusalem, [(4)]The Hebrew University Faculty of Medicine, Jerusalem, and [(5]Reproductive Endocrinology and Genetics Unit, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Jerusalem, Israel

Context: Hyperphagia, low resting energy expenditure, and abnormal body composition contribute to severe obesity in Prader Willi syndrome (PWS). Irisin, a circulating myokine, stimulates "browning" of white adipose tissue resulting in increased energy expenditure and improved insulin sensitivity. Irisin has not been previously studied in PWS.

Objectives: Compare plasma and salivary irisin in PWS adults and normal controls. Examine the relationship of irisin to insulin sensitivity and plasma lipids.

Design and Study Participants: A fasting blood sample for glucose, lipids, insulin, leptin, adinopectin, and irisin was obtained from 22 PWS adults and 54 healthy BMI-matched volunteers. Saliva was collected for irisin assay in PWS and controls.

Results: Fasting glucose (77±9 vs 83±7mg/dl, p=0.004), insulin (4.1±2.0 vs 7.9±4.7μU/ml, p<0.001), and triglycerides (74±34 vs 109±71mg/dl, p=0.007) were lower in PWS than in controls. Insulin resistance (HOMA-IR) was lower (0.79±0.041 vs 1.63±1.02, p<0.001) and insulin sensitivity (QUICKI) was higher (0.41±0.04 vs 0.36±0.03, p<0.001) in PWS. Plasma irisin was similar in both groups, but salivary irisin (64.5±52.0 vs 33.0±12.1ng/ml), plasma leptin (33.5±24.2 vs 19.7±19.3ng/ml) and plasma adinopectin (13.0±10.8 vs 7.6±4.5μg/ml) were significantly greater in PWS (p<0.001). In PWS, plasma irisin showed positive Pearson correlations with total cholesterol (r=0.58, p=0.005), LDL-cholesterol (r=0.59, p=0.004), and leptin (r=0.43, p=0.045). Salivary irisin correlated negatively with HDL-cholesterol (r=-0.50, p=0.043) and positively with LDL-cholesterol (r=0.51, p=0.037) and triglycerides (r=0.50, p=0.041).

Conclusions: Salivary irisin was markedly elevated in PWS although plasma irisin was similar to levels in controls. Significant associations with plasma lipids suggest that irisin may contribute to the metabolic phenotype of PWS.

Prader-Willi syndrome can be diagnosed prenatally

Gross N, Rabinowitz R, Gross-Tsur V, Hirsch HJ, Eldar-Geva T.

[1]Reproductive Endocrinology and Genetics Unit, Department of Obstetrics and Gynecology,

[2]Ultrasound Unit, Department of Obstetrics and Gynecology,

[3]Neuropediatric Unit, Department of Pediatrics, all in Shaare Zedek Medical Center, Jerusalem, Israel;

[4]The Hebrew University School of Medicine, Jerusalem, Israel

The aim of this study was to characterize the fetal phenotype of a cohort of individuals with confirmed diagnoses of Prader Willi syndrome (PWS), a severe multi-system genetic disorder, diagnosed by a specific methylation test. We interviewed mothers of 106 individuals with PWS to obtain information about the pregnancy of their affected child. For 47 pregnancies of children younger than 10 years, we also reviewed the obstetric ultrasound and detailed obstetric history from medical records. We compared the PWS pregnancies with those of the sibling closest in age and with the general population. McNemars, Chi- square and Fisher exact tests were used for statistical analyses. Decreased fetal movements, small for gestational age (SGA), asymmetrical intrauterine growth (elevated head/abdomen circumferences ratio) and polyhydramnios were found in 88%, 65%, 43% and 34%, respectively (P<0.001 vs. siblings and P<0.0001 vs. the general population for all measurements). No severe morphological abnormalities were found. A combination of 2, 3 and 4 abnormalities was found in 27%, 29% and 24% of pregnancies, respectively. Fourteen out of 15 umbilical artery Doppler studies were within the normal range (93%). The rare combination of asymmetrical intrauterine growth and polyhydramnios was found in 34% of PWS pregnancies) p<0.0001 vs. the general population). Prenatal genetic screening for PWS by methylation testing is indicated when any combination of polyhydramnios, SGA or asymmetric intrauterine growth, with normal Doppler studies is present, particularly when asymmetrical intrauterine growth and polyhydramnios coexist.

Condensation: Prenatal genetic screening for Prader-Willi syndrome is indicated when any combination of polyhydramnios, small for gestational age/asymmetrical intrauterine growth, reduced fetal movements and normal Doppler studies is present.

The Association between Legg Calvé Perthes Disease and attention deficit hyperactivity disorder (ADHD)

Berman J. (MD thesis), Aran A, Lebel E. (units of pediatric neurology & pediatric orthopedics)

Background: Legg-Calve-Perthes' disease (LCPD) is suspected to have association with attention deficit hyperactivity disorder (ADHD). Previous studies have demonstrated inconsistent results regarding this association. Since ADHD is relatively common (childhood prevalence is 5-10%) its association with LCPD is not easily ascertained. Objective: To assess the prevalence of ADHD in children with LCPD and their closest sibling in order to elucidate the genetic and environmental relationships between these disorders. Patients and methods: 16 children diagnosed with LCPD, and 13 siblings were evaluated. Diagnosis of ADHD was based on neurologic evaluation (DSM criteria) and computerized Test of Variables of Attention (TOVA) test. Sleep disturbances were evaluated by the Pediatric Daytime Sleepiness Scale (PDSS), and quality of life was measured by the Child Health Questionnaire Parent Form 50 (CHQ-PF50) and Pediatric Outcomes Data Collection Instrument (PODCI). Results: Sixteen children with LCPD (age = 9.1 ± 3.3, 75% males) were compared with their closest sibling (age = 9.3 ± 2.6, 30% males). TOVA scores of children with LCPD (-3.79 ± 2.6) and their siblings (-3.6 ± 4.04) were lower compared with the general population (0 ± 1.8, $p<0.0001$), both in the ADHD range (≤ -1.8). Quality of life scores in the physical domain of the CHQ were lower in children with LCPD (78.8 ± 11.3) compared with their siblings (86 ± 8.3, P = 0.027). There were no sleep disturbance differences between groups. Discussion: Our findings in a small cohort of children with LCPD and their siblings support an association between LCPD and ADHD, and suggest that ADHD symptoms are involved in the pathogenesis of LCPD. A routine screening for ADHD in all children with LCPD is recommended.

Bone Mineral Density and Lean Muscle Mass Characteristics in Children with Gaucher disease Treated with Enzyme Replacement Therapy or Untreated

Liron Dar MD*, Deborah Elstein PhD, Ari Zimran MD, Ehud Lebel MD**

Gaucher Clinic and the Department of Orthopedic Surgery**, Shaare Zedek Medical Center, affiliated with the Hebrew University Hadassah School of Medicine, Jerusalem Israel

Background: Although Bone Mineral Density (BMD) characteristics as measured by dual energy x-ray absorptiometry (DXA) are standard indices of risk of bone fragility and osteoporosis in adults with Gaucher disease, there is only limited information regarding changes in BMD in pediatric patients with Gaucher disease. Moreover, the possibility that there may be a disease-specific impact on either Lean Muscle Mass (LMM) or Fat Fraction (FF) as in some other disorders of bone in children has never been explored.

Objective: Characterization of BMD, LMM and FF composition in children with Gaucher disease, some of whom have been exposed to Gaucher-specific enzyme replacement therapy (ERT) because of symptomatic findings and others who have remained untreated because they are as yet asymptomatic as per Gaucher Clinic policies.

Patients &Methods: All glucocerebrosidase-deficient pediatric (>3 years) patients with type 1 (non-neuronopathic) disease were included. All underwent DXA as a total-body scan and results were analyzed for BMD, FF and LMM (body surface absorption minus fat and bone area). Participants were characterized by background factors: age, gender, genetic diagnosis, body dimensions, and treatment status.

Results: In all, 48 pediatric patients (24 males; aged 3-16 years) underwent DXA scans. Thirteen were homozygote for the N370S mutation (usually associated with milder disease) and were not receiving ERT. The remaining 35 were N370S heterozygous with one mutation associated with more severe manifestations; 26 were receiving ERT. Forty-one (85%) patients were underweight according to calculated BMI. Treated patient had significantly higher average (age-adjusted) whole body BMD values ($p=0.005$). Among treated heterozygotes, there was a strong positive linear correlation between age and bone and soft tissue values ($R=0.706$ for whole body BMD, $R=0.5$ for lumbar spine BMD, and $R=O.713$ for LMM), representing gradual and steady growth. These findings were closely aligned with those of the untreated homozygous patients (i.e., less affected) children. The nine untreated heterozygous patients showed slower accumulation of BMD and LMM. Linear regression curves of age and FF among treated females had moderate strength ($R=0.268$) but was weaker in treated males ($R=0.049$). Also, a weak correlation was found in the whole cohort between FF and age ($R=0.05$), demonstrating that FF is not increased during growth. Age-adjusted values of BMD (Z-scores for whole body, lumbar spine, femoral neck) were low among all patients, representing lower than normal skeletal dimensions and/or delayed bone-age in this population. Duration of treatment was significantly correlated with whole-body BMD ($R=0.399$, $p<0.05$). No correlation was demonstrated between age at the beginning of treatment and bone/soft tissue values.

Discussion & Conclusions: This is a first study to consider these three components of body composition in Gaucher disease. As the availability of early administration of ERT invariably improves the outlook for a healthier adulthood, normal bone-mass, well developed musculature, and average fat-mass should be the targets of future interventions in Gaucher disease especially in children. This study evaluates a relatively large pediatric cohort with Gaucher disease. Nevertheless, diversity of genetic mutations, the reliance on a single DXA evaluation, variable durations of ERT and of other background factors, are limitations of this study. BMD showed steady accumulation, but on average, was below expected values for age/gender. This is the first study that demonstrates true relative to expected values for BMD and LMM among pediatric patients with Gaucher disease. As maturation of patients with Gaucher disease (as in other chronic diseases) is delayed, further studies, especially those including periodic evaluation of each patient over time, and adjustment for bone-age (and other evaluators of growth) are needed. Data are slowly accumulating because of worldwide use of Gaucher disease registries and this is to be encouraged. Recording (minimally) of BMD and LMM should become part of routine evaluation of children with Gaucher disease: such data would supply substantial support for decision-making regarding interventions such as ERT, dietary consumption, physical activity, and medications.

Interleukin (IL)-1 Inhibition for Patients with Colchicine Resistant/Intolerant Familial Mediterranean Fever (FMF)

Philip J Hashkes, MD, MSc

Pediatric Rheumatology Unit, Shaare Zedek Medical Center

Background: There is no proven treatment alternative for the 5-10% of FMF patients whose disease is resistant to colchicine. Since pyrin has an important role in IL-1ь regulation we hypothesized that IL-1 inhibition would decrease the number of FMF attacks in these patients.

Methods: We performed studies of two IL-1 inhibitors in patients with at least 1 FMF attack per month despite colchicine therapy. The first, a randomized, double-blind, alternating treatment phase 2 study of rilonacept, a soluble decoy receptor that "traps" IL-1, was performed in patients ≥4 years of age. Patients received in randomized order one of 4 treatment sequences that included two 3-month courses of rilonacept at 2.2 mg/kg (max 160 mg) by weekly SC injection and two 3-month courses of placebo. The primary outcome was the difference in the frequency of FMF attacks between rilonacept and placebo courses analyzed by signed rank tests and Bayesian methods. The second a 3-month open label pilot study of canakinumab, a humanized IL-1ь antibody, was performed in children between the ages of 4-17 days. Patients received three 2 mg/kg (max 150 mg) SC injections, given every 4 weeks, with an increase of the dose to 4 mg/kg in the event of an attack during the first month. Following the end of the treatment period, patients were followed until day 144 or until an attack occurred, whichever occurred first. Patients then resumed canakinumab therapy and were entered in a long-term extension. The primary outcome during the first three months was the proportion of patients with >50% reduction in FMF attack rate during the treatment vs. pretreatment period, time-adjusted per 28 days.

Results: Study 1: Fourteen patients were randomized, 8 males and 6 females, mean (±SD) age 24.4±11.8 yrs (range 4.5-47.3; 4 patients <18 yrs.), with 3.1±2.0 attacks per month at baseline. Among the 12 patients who completed at least 2 treatment courses, the mean number of attacks per month was 0.77 on rilonacept vs. 2 on placebo (median difference, -1.74 [95% CI, -3.4 to -0.1]; P=0.027). The risk ratio by Bayesian analysis was 0.45±0.13 in favor of rilonacept (equal-tail 95% credible interval of 0.26-0.77). Patients on rilonacept also had significantly more treatment courses without attacks (29% vs. 0%, P=0.004), courses with >50% decrease in attacks compared to baseline (75% vs. 35%, P=0.006), and improved physical aspects of quality of life (P=0.01). The duration of attacks did not significantly differ between the treatment arms (median difference 1.2 days, P=0.32). Injection site reactions were significantly more frequent with rilonacept (P=0.047) but no differences were seen in other adverse events, including infections.

Study 2: Seven patients (median age 9.5 yrs.; range 6.8-14.9 yrs.) were enrolled. Six of 7 (86%) patients had a >50% reduction in their FMF attack rate. The median attack rate decreased from 2.8 per 28 days at baseline to 0.3 (-89%). Five mild and 3 moderate attacks were experienced by 4 patients; 2 patients had their dose uptitrated. Five of 7 patients experienced an attack during follow up after treatment (median 25 days, range 3-34). There were no drop-outs during the long-term extension (median 29 months, range 25-37). The attack rate was further decreased to 0.05 attacks per patient month. 4 patients were able to decrease their colchicine dose to 1 mg/d and 3 patients decreased the frequency of canakinumab injections to every 6 weeks. There were no severe adverse events, including during the long-term extension.

Conclusion: IL-1 inhibition appears to be an effective and safe option for treatment of patients with colchicine resistant/intolerant FMF.

Exposure of Non-Medical Personnel to Traumatic Experiences in the ED

Deganit Kobliner, RN MPH and Amran Jaber, RN MPH,

Emergency Department, SZMC

Background: Housekeeping, cleaning and other ancillary staff are an integral part of the ED, and it would be impossible to maintain an efficiently operating ED without their support.

Generally the people that perform this type of work are from diverse and often marginal ethnic backgrounds, with limited, if any, formal education. During the course of their daily work in the ED, these employees are exposed to traumatic sights and experiences, including patients suffering serious injuries from stabbings, gunshot wounds, accidents, and the like. Such personnel are routinely called upon to clean pools of blood, collect and dispose of used emergency medical waste, and transport corpses to the hospital morgue. While ED medical staff, doctors, nurses, and students receive intensive training, debriefing, and support in dealing with exposure to medical trauma, the untrained and less-educated ancillary staff, who are significantly less equipped to handle such experiences, are not provided with any tools or support to deal with these challenges.

Methods: This paper intends to explore the benefits of an interventional program specifically designed for ancillary staff utilizing the following approach:

A.Current sensitivity to traumatic events will be measured by a questionnaire mapping out emotional reactions to traumatic experiences. The questionnaire will be prepared and distributed to ED ancillary staff.

B.The questionnaire will be followed-up by 3-session group meetings addressing psychological tools for trauma exposure.

C.Post intervention will be evaluated via questionnaire. We suggest that an interventional program will significantly impact the ability of ancillary staff to deal with traumatic sights and experiences. Similarly, we believe that employees participating in an interventional program will experience an increased feeling of organizational commitment as well as personal empowerment.

Conclusions: Significant correlation was found between the degree of trauma and the extent of problem-focused coping:

The greater the trauma, the stronger the coping. Significant correlation was found between the degree of trauma and the extent of coping by detachment: The greater the trauma, the stronger the coping. No significant correlation was found between the degree of trauma and the extent of emotion-focused coping. The primary methods of coping with the difficulties encountered were either by (i) direct confrontation and problem-focused coping or (ii) by avoiding the difficulty by means of 'disengagement'.

Patients' experiences during hospital admission

Ahuva Spitz, RN,MPA [1], Gali Weiss, RN,MA [2]

[1]Research Coordinator - Nursing Department, [2]Deputy Director General, Head Nurse

Background: The nurses' mission statement in Shaare Zedek hospital regards highly professionalism in conjunction with empathic caring attitude towards patients. Indeed the philosophy of delivering patient care with a warm and caring attitude is well embedded in the overall nursing practice. Patients experiences and perceptions regarding their admission is a challenge to measure since experience is a subjective impression, related to cultural background, previous experience and sometimes difficult to verbally pinpoint.

Aim: This paper intends to find out whether there are differences in perceptions regarding patients' experiences during hospital stay from the patients' prism compare with the nurses' perceptions.

Method: An original Likert scale questionnaire was created by a group of nurses. The tool, of 2 versions, contained questions about patients' experiences during hospital stay covering different aspects such as: nurses' attitude, nurses' professional conduct, communication, hospitality etc. The patient's version included an open question to describe the last admission experience. During 2014-15 96 patients and 140 nurses were recruited.

Results: There was a positive similarity between nurses' perceptions and patients' perceptions in regards to hospital stay's experiences. It appears that nurses more than patients, regard nurses' attitude significant in contributing to patients' experiences. Patients however, more than the nurses, think that nurses' professionalism (conduct, patient education and sensitivity) are of greater importance in contributing to the experience.

Conclusion: Every nurses' meeting or conference, addresses patients experiences during admission as a routine educational activity in promoting positive experiences.

The Merge: Bikur Holim Hospital-Shaare Zedek Medical Center

Ahuva Spitz, RN MPH [4], Tzippy Sivan, RN MA [3], Sara Goldberg RN MA [2], Gali Weiss RN MA[1]

[1]Deputy Director General, Head Nurse [2]Deputy Head Nurse [3]Maternity ward supervisor [4]Research Coordinator-Nursing Department

During Dec, 2012, after years of uncertainty and economic instability, Bikur Holim hospital was merged into Shaare Zedek Medical center. The merging process involved a complex undertaking on many different levels: medical, logistics and nursing. As well documented in the literature, a merge between health organizations generates major changes in the infrastructure of the merged organization. It forces cultural adaptation to the new organization. A challenging process that requires careful planning as well as following the employees' reactions and adaptation skills to the new organization. This paper focuses on the merge from the nurses' perspective. Nurses from Shaare Zedek were transferred to work in Bikur Holim while nurses from Bikur Holim were transferred to Shaare Zedek. Many nurses remained working in Bikur Holim under Shaare Zedek's management.

Aim: Following nursing staff in reference to the merge, personal thoughts and expectations from the merge as well as nursing standard of care.

Method: The research was done in 2 parts: quantitative and qualitative analysis.

In the first part, questionnaires were given to the Bikur Holim nursing staff at T0, T6, and T12. The questionnaire contained 3 parts (Likert scale). Perceptions of the original organization- Bikur Holim, perceptions regarding the merge and perceptions regarding quality of care. In addition there were 2 open-ended questions: what will contribute to the merge and what would they like to preserve from Bikur Holim. The qualitative part included 10 in-depth interviews with nurses. Thematic analysis was conducted.

Results: It appears that despite the economic upheavals in Bikur holim hospital, the nursing staff was committed to stay working there. The nurses described a unique familial atmosphere that connected them to the place. At T12, the nurses felt that the merge advanced their career (69%), they are proud to be part of Shaare Zedek's organization (84%) and are grateful to continue working for Shaare Zedek medical center (92%). The qualitative analysis of the in-depth interviews, revealed a deeper understanding of standard of nursing care as well as the unique familial atmosphere among the staff. In addition it shed light on the merging process itself for future mergers to occur.

Conclusion: Every nurses' meeting or conference, addresses patients experiences during admission as a routine educational activity in promoting positive experiences.

A survey for Diabetes probability

Rachel Kuznitzov RN,BA[1] ,Ahuva Spitz RN,MPA[2]

[1]Diabetes Coordinator Nursing Department, [2]Research Coordinator Nursing Department

Background: The WHO (World Health organization) has declared Diabetes as epidemic. To decrease its prevalence, recent guidelines by the ADA (American Diabetes Association) include education as a preventive measure along with dietary recommendations and lifestyle modification.

Many countries around the world chose to raise the awareness concerning healthy lifestyle in various ways such as: limiting smoking to a designated areas, periodic population screening, education etc. The ADA designated the 14/11 as the national diabetes day (the birthdate of Dr. Fredrick Banting who discovered the insulin) during that day there are various workshops and promotional activities to raise people's awareness about diabetes and its prevention. For the first time, on Nov 18th, 2015, we designated a diabetes day in Shaare Zedek medical center.

Aim: Our aim was to raise diabetes awareness among staff and visitors. Nurses and dieticians were giving out information about diabetes' signs and symptoms, complications as well as diet tips and glucose checks.

Method: Quantitative analysis was performed on a questionnaire that was given out to the participants randomly. The survey evaluated probability for diabetes based on questions such as: diabetes in the family, presence of other illness, BMI, waist circumference and physical activity. In addition there were questions about self-health report as well as health efficacy.

Results: 343 questionnaires were answered. 59% were Shaare Zedek's staff members. 66% assessed themselves as healthy. 66% evaluated that they are able to keep a healthy life style, however only 44% admitted to doing so. In addition, there was a negative correlation between diabetes probability and self-health assessment. Shaare Zedek's staff evaluated themselves healthy more so than non-Shaare Zedek's employees. Shift workers evaluated themselves healthier than non-shift workers. Diabetes probability was found lower among Shaare Zedek's employees in comparison with non-Shaare Zedek's employees.

Conclusion: Even though the hospital's staff showed lower diabetes probability, it is strongly advised to educate staff members about healthy life style so that they will be able to enjoy good health, perform their duties diligently and inspire their patients.

Shift Handover in the Intensive Care Unit

Chaya Broyer RN,MA

Head Nurse-ICU

Shift handover is the transferring of information and responsibility between the outgoing and incoming nursing staff. The information is vital to the continuity, safety and quality of patients' care. However, there is no consensus regarding the required information to be reported. Diversity in information transfer depends on the nurses' seniority, expertise, thought process, fatigue, etc. These variables are embodied in a mental model, a tool describing the subjective reality. Mental model is reflected by concept mapping- a graphic depiction of concepts and their connections.

Aims: 1. To compare mental models of the outgoing nurse, the incoming nurse and ICU expert nurses. 2. To examine how variables that impact information transferred are perceived by the incoming nurse.

Methods: A descriptive observational study was performed. Nurses were trained in concept mapping techniques. 40 morning shift handovers in the ICU were recorded and transcribed; of which concept maps were constructed. During the handover, a form including characteristics of patient, nurse and handover was completed. Thirty minutes post handover, the incoming nurse completed a concept map based on the information that she had received. Simultaneously, two expert ICU nurses were requested to create concept maps on the same patient based on the patient's chart. The three concept maps were compared using IHMC CMAP TOOL software.

Results: It appears that there is a significant decrease in the transferred information from the outgoing nurse to the expert nurses and the incoming one. The outgoing nurse's mental model is the most comprehensive compared to the incoming nurse's mental model which is the simplest, focusing on immediate tasks.

Conclusion: The understanding that there are different perceptions in shift handover can lead to changes in the handover process thus enhancing standard quality care for complicated patients.

In Vitro Fertilization & Preimplantation Genetic Diagnosis decision making among *BRCA1/2 mutation carriers*

Dr. Pnina Mor
Noga Clinic, SZMC

Background: Women and men who are BRCA mutation carriers, and are considering having a family, are faced with difficult and confusing decisions. Some parents sacrifice childbearing, others consider elective termination of a pregnancy when the foetus has been shown to have a BRCA mutation, and still others find preimplantation genetic diagnosis (PGD) and in vitro fertilization(IVF) treatment the acceptable solution. BRCA carriers considering PGD are challenged with the difficult decisions. Preimplantation genetic diagnosis, the possibility of terminating pregnancies that contain embryos that carry the BRCA mutation and the use of hormone treatment to preserve pregnancies are issues that challenge BRCA mutation carriers.

Objective: The purpose of this study is to provide the first research-based report on the decisions of genetically at-risk couples who chose PGD to prevent the transmission of the known BRCA mutation to their child(ren) or who had made a decision not to use IVF and PGD.

Method: Using a convenience sample, validated instruments were used in this study to report on the uptake of IVF & PGD in BRCA mutation carriers of childbearing age attending the NOGA clinic at the Shaare Zedek Medical Center between the years 2009-2014. We evaluated the predictors of uptake of IVF & PGD in BRCA mutation carriers, such as; socio-demographic characteristics (such as: age; employment, level of education, personal and family cancer history, religious affiliation), and their perceived risk. In addition we determined if there are outcome differences (e.g. decisional regret, decisional satisfaction, and the impact of event) between BRCA mutation carriers who decided not to do IVF & PGD and those that decided to do IVF & PGD.

Results: Participants included 80 healthy married couples who are of childbearing age (25-35), of which one has been genetically tested and known to be a BRCA mutation carrier, attending the NOGA clinic from 2009 and had been offered IVF and PGD. Fifty seven couples chose not to undergo IVF & PGD; 23 couples chose IVF & PGD, underwent the process and completed pregnancies. There were no significant differences in socio-demographic characteristics, decisional regret, satisfaction or impact of event. The group that underwent IVF & PGD had higher rates of previous infertility (O.R. 12.22, $p<0.1$). Personal risk assessments were evaluated. The PGD group estimated their risk for ovarian cancer compared to the general population of the same age range significantly higher; (O.R. 3.62, $p<0.05$).

Conclusion: A "working understanding" of the reality and lives of BRCA mutation carriers will advance the medical profession, will inevitably empower BRCA mutation carriers, and perhaps ease reproductive decision making among BRCA1/2 mutation carriers.

Breastfeeding the first hour after birth - Do Midwifes make a difference?

Dr. Pnina Mor
Noga Clinic, SZMC

Background: There is an abundance of literature establishing that early breastfeeding has a range of health promotion benefits. Breast milk contains all the vitamins 'nutrients as well as antibodies for the newborn's first six months thus promoting optimal growth and development. The World health Organization (WHO) currently recommends a global public health recommendation of 10 basic guidelines promoting breastfeeding exclusively in maternity departments as well as implementing practices that protect, promote and support breastfeeding. It aims to ensure that all maternity wards, whether independent or in a hospital, become centers for breastfeeding support (WHO 2012). The World Health Organization recommends that infants start breastfeeding within one hour of life, are exclusively breastfed for six months, with timely introduction of adequate, safe and properly fed supplementary foods while continuing breastfeeding for up to two years of age or beyond. The midwife accompanying the laboring woman throughout the labor and delivery process has a significant role in inspiring positively on the birthing woman and her environment.

Purpose: To compare the differences between compliance to breastfeeding within the first hour after birth (consistent with the WHO recommendations) following the accompanying midwife's intervention to spontaneous breastfeeding in the delivery room.

Methods: A quantitative longitudinal study using a convenient sample was used. Women who delivered a vaginal delivery were recruited in the labor and delivery unit during their first hour post-partum. The women were divided into 2 groups randomly; those who received recommendations and counselling promoting the importance of breastfeeding from their accompanying midwife and the control group that did not receive breastfeeding counselling.

Findings: A positive correlation between advocating the importance of breastfeeding during the first hour after birth by the accompanying midwife and breastfeeding in the delivery room ($p<0.00$, c2-6.28) was significant. Logistic regression was used to predict compliance to breastfeeding during the first hour after birth followed by counselling from the accompanying midwife. Women who received counselling by their accompanying midwife were twice as likely to breastfeed (2.02) than those who did not receive counselling. Similarly women who participated in childbirth preparatory courses were almost twice as likely (1.89) to breastfeed during the first hour after birth.

Discussion and Results: Promoting advocacy towards breastfeeding appears to increase breastfeeding compliance thus leading to a healthier society. We recommend educational breastfeeding updates to midwife and their role in promoting early breastfeeding in the delivery process.

Using Participatory Action Research Techniques, Healthy BRCA Mutation Carriers Design a Model of Care

Dr. Pnina Mor

Noga Clinic, SZMC

Objectives: To define the needs and establish approaches to improving the wellbeing of healthy BRCA gene mutation carriers using participatory action base.

Methods: 23 healthy carriers were recruited from a genetic clinic at a Jerusalem, (Israel) medical center. A series of 9 focus groups were led by the researcher and a trained group moderator, using participatory action research (PAR) techniques in qualitative research.

Results: Through their narratives, carriers described dilemmas that affect and sometimes radically change life perspectives. They identified the constant threat of illness, knowledge the mutation can be passed on to children, need for heightened surveillance, and difficulty in making decisions regarding risk-reducing surgeries and other risk-reducing measures, as ongoing sources of stress. Inconsistent and inaccurate information from healthcare providers, barriers to reimbursement for approved screening studies and prophylactic procedures, and a lack of psychosocial support were named as major healthcare issues. They suggested a "one-stop" center to provide expert care and smooth bureaucratic barriers to screening and preventative procedures. Carrier inputs were presented in parallel focus groups for health care professionals who manage care for healthy carriers, and a multispecialty outpatient clinic for healthy carriers (NOGA) was opened as a result of this work. The clinic provides improved access to imaging surveillance; expert medical consultation; counselling by a nursing coordinator, psychologist, and sexologist; and medical information. Study findings strengthened interdisciplinary connections among participating nurses, genetic counsellors, and physicians, and supported a holistic health promotion model.

Conclusions: The primary study outcome was inception of a one-stop multidisciplinary clinic incorporated into an existing healthcare setting. The clinic provides medical and psychosocial services, including improved access to imaging surveillance, as well as expert medical consultation and counselling.

Grip strength in in healthy Israeli adults: comparison to internationally reported normative data

Danit Langer[1,2] MSc, Miri Tal-Saban[1] PhD, Tal Mazor-Karsenty[1] PhD, Hanna Melchior[2] MSc

[1]School of Occupational Therapy, Hadassah and the Faculty of Medicine. Hebrew University, [2]Occupational Therapy Department Shaare Zedek Medical Center

Background: Reference values are essential when evaluating the normality of an individual's grip strength (GS) relative to the healthy population. Normative data for GS have never been described for Israel.

Objectives: This study had two primary objectives. The first was to establish normative data for GS for the adult population in Israel. The second objective was to compare the results of this derived Israeli normative data to internationally reported measures. Two published studies were used for comparison. One study consolidated data from twelve different studies that originated from eight different countries. The other study was limited to data from Australia.

Methodology: 574 healthy adult volunteers had their grip strength tested. This study was conducted over a three-year period (2013-2015). Testing with regard to position and technique was performed in accordance with recommendations of the American Society of Hand Therapists. Grip strength was determined using the Jamar dynamometer from the average of three trials for each hand. Normative data was established based on age, handedness and sex. More specifically, to allow comparison to international data, the age was subdivided in both 5 and 10 year intervals. The results from this study were then compared to international standards using a one sample t-test.

Results: Looking first at Israeli normative data, across ages and handedness, males were 45% stronger than females. Right-handed people were on average 9% stronger on their right compared to their left side. Left-handed people had the similar average strength on both side. Compared to the Australian data, Israeli men were 3% weaker and Israeli women were 15% weaker. When the data was subdivided based on age, the Israeli population was weaker but statistical significance was reached only for men below the age of 30 and for women below the age of 60. When the Israeli data was compared to the consolidated norms, Israeli men were 10% weaker and women were 23% weaker.

Conclusion: Normative data for grip strength was established for the Israeli population and compared to internationally published data. The lower grip strength of the Israeli population we speculate may be related to the lower demands placed on the hands for "white-collar" occupations relative to manual labor. It may also be related to lower average population size, weight or hand girth when comparing the populations.

Validity of the Israeli Version of the Patient-rated Wrist Evaluation Questionnaire

Hanna Melchior[1], MSc & Danit Langer[1,2], MSc

[1]Department of Occupational Therapy, Shaare Zedek medical Center; [2]School of Occupational Therapy of Hadassah and the Faculty of Medicine Hebrew University.

Background: In the past decade, the client centered approach has become widely accepted, expanding the use of patient rated questionnaires in practice and research. There are several self rated questionnaires for evaluating hand function. The Disability of Arm Shoulder and Hand (DASH) evaluates the whole upper extremity and is the only questionnaire that has been translated into Hebrew. In hand therapy there is a need for an evaluation focusing specifically on the hand. The Patient-rated Wrist Hand Evaluation (PRWHE) Questionnaire is commonly used in hand therapy.

Purpose: The purpose of this study was: a) to translate the PRWHE for use in Israel; b) to test the validity of the Israeli version; c) to establish Israeli standards of the PRWHE in a healthy population.

Methods: The original PRWHE was translated forwards and backwards and face validity was established by inviting experts and patients to participate in the panel review of the questionnaire. 32 patients who were receiving treatment for a variety of hand conditions (study group) and 120 healthy volunteers (control group) participated in the study. Both groups completed the Hebrew PRWHE and Hebrew DASH questionnaires. Test-retest was calculated on 13 participants.

Results: The results of the normative data analysis demonstrated no age or gender effect for the PRWHE while a small age effect ($F=3.007$, $p<.05$) and gender effect ($t= -2.276$, $p<.05$) for the DASH questionnaire. A significant difference was found in the PRWHE score between study and control group ($t=9.04$, $p<.001$) where the study group reported more disability. The results of the Cronbach's Alpha test for the PRWHE demonstrated excellent internal consistency ($\beta = .974$). High criterion validity was found with the DASH ($r=.845$, $p<.001$). As for test-retest reliability a high significant was found ($r=.928$, $p<0001$).

Conclusions: The Israeli version of the PRWHE was found to be a valid tool in the present sample. The high correlation between the DASH and PRWHE suggest that therapists should use only one of the questionnaires for a single client. Nevertheless these results should be interpreted with caution due to a small sample.We also found that the average score of the control group reflected some difficulty in hand related tasks. These findings are similar to previous reports of DASH scores in healthy populations.

Pneumococcal bacteremia elicits the highest WBC counts in a direct comparison with micro-organisms

1.Joshua Manor, M.D., Ph.D, Pathology Department, 2.Yonit Wiener-Well1, M.D., Infectious Diseases unit, 3.Chezi Ganzel, M.D.

Department of Hematology, Shaare Zedek Medical Center in Jerusalem, Israel.

Background: Initial assessment in the clinical practice of a septic patient is still frequently assisted by the peripheral blood count. In this work we compared the immunogenicity of streptococcus pneumoniae (S. pneumoniae) to other micro-organisms by comparing white blood cells (WBC) counts at time of bacteremia or fungemia arising from different pathogens.

Methods: A retrospective database of 8315 positive patient-unique blood cultures and their respective WBC counts at the time of blood infection was constructed. Data was collected from patients admitted to Shaare Zedek Medical Center between 2001 and 2014.

Results: S. pneumoniae's WBC counts were associated with the highest counts distribution compared with the rest of the micro-organisms, e.g., 53, 49, and 30% higher than Staphylococcus aureus, Enterobacteriacea and anaerobes, respectively. Between the 5th and 95th percentiles of all WBC counts, a 28 x 109 WBC cells/μL threshold can be used to exclude all other causative agents. In extremely abnormal counts, an increased prevalence of S. pneumoniae was observed among the young, compared to an increase in Enterobacteriaceae prevalence among elders.

Conclusions: Our database highlights the higher immune response elicited by S. pneumoniae. Our comprehensive counts database provides a window for blood counts distribution elicited by 28 different micro-organisms.

The potential of curcumin in combination with direct acting antivirals to treat Hepatitis C virus infection

Oshri Yosefov[1], Ateret Davidovich[1], Shimon Steingart[2], Yoav Lurie[3], and Meital Gal Tanamy[1]

[1]Molecular Virology Lab, Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel. [2]Patholohy Institute, [3]Liver Unit, Digestive Disease Institute, Shaare Zedek Medical Center, Jerusalem, Israel.

Background: Hepatitis C virus (HCV) is a major public health problem with over 180 million people infected worldwide. It causes hepatitis, cirrhosis, liver failure and is the leading cause for Hepatocellular carcinoma (HCC). With the recent approval of powerful HCV specific direct acting antivirals (DAAs), it is the only human tumor virus that can be completely eradicated from the cells. However, many challenges remain, such as limited implementation of the DAAs due to their high cost and lower efficacy in treating non-genotype 1 HCV infections. Moreover, epidemiological studies show that sustained virological responses (SVR) following anti-HCV treatment reduce but not eliminate tumor development. Curcumin have been shown to positively affect cancer and inhibit HCV entry. We hypothesize that treatment with curcumin in combination with DAAs will enhance HCV eradication.

Methods: First we have evaluated cytotoxicity of C3 curcumin and Viekirax/ Exviera treatment. Human hepatocytes were treated with the combination treatment and curcumin/ DAAs alone and cell viability was evaluated by XTT assay. For evaluating the therapeutic potential of Viekirax/ Exviera in combination with C3 Curcumin, hepatocytes infected with different HCV genotypes were treated with the combination treatment and curcumin/DAAs alone and immunostained for the detection of infected cells. In addition, virus production was evaluated following treatment.

Results: The non-cytotoxic working concentration of curcumin determined by XTT assay is 5uM. Our studies strongly support the enhanced efficacy of DAAs in combination with curcumin compared to each treatment alone for the eradication of different HCV genotypes, including genotype 3a which is considered more difficult to treat. The production of virus infection was significantly reduced upon treatment with Viekirax/ Exviera in combination with curcumin. Eradication of HCV was observed following 4 days of combination treatment with Viekirax/ Exviera and curcumin, where treatment with Viekirax/ Exviera alone did not show virus eradication at day 8 following treatment.

Conclusion: The findings of this study highlight the potential of curcumin to synergize with DAAs to enhance treatment efficacy and lower treatment duration that may subsequently lower treatment cost, the most important limiting factor in treating HCV with DAAs.

Alcohol Use Disorder and Cross-Cutting Symptom Measures Amongst Soldiers Who Present to Shaare Zedek Medical Center

Dr Meydan Ben Ishai[1], Dr David Rave[2] , Dr Cornelius Gropp[3] , Dr Joseph Mergui[3] , Dr Sol Jaworowski[3]

[1]Yosef Tal Hospital, [2]Department of Infectious Diseases, Shaare Zedek Medical Center, [3]Department of Consultation-Liaison Psychiatry, Shaare Zedek Medical Center.

Background: Alcohol consumption in Israel has increased over the last 20 years (1). Alcohol use disorder (AUD) was found in 16% of a cohort of soldiers who presented to Shaare Zedek Medical Center (SZMC) between 2008-2011 for psychiatric assessment (2).

Aims: To compare AUD and mental health functioning in soldiers referred to the emergency room (ER) with a group of young people who had recently completed their military service.

Methods: The study group consisted of 28 consecutive patients who had been seen for psychiatric consultation in SZMC ER as soldiers between 2008-2011, and subsequently followed up between 2013-2014; the control group consisted of 25 soldiers who presented to the same general hospital ER between 2013-2014 for assessment of somatic complaints. We compared demographic factors for AUD and other psychiatric illnesses between groups. Following informed consent, all subjects provided demographic information and completed the AUDIT questionnaire (3) (a screening instrument for AUD) and the CCSM (4) (a screening questionnaire for emotional functioning).

Results: We found no significant difference in prevalence of AUD between the groups. We did find a significant difference in CCSM scores when compared with occupation status - soldiers had a significantly higher score than students, employed and unemployed persons.

Conclusions: Our study shows a correlation between military service and higher CCSM scores, which may represent the perceived stress associated with military service in Israel. ER staff should pay special attention to the level of stress manifested by soldiers who present for medical assessment. This population may be more vulnerable to suffer from stress related medical disorders.

Sponsored by: