A DOUBLE BLIND, PLACEBO CONTROLLED, CROSSOVER TRIAL OF MINOCYCLINE IN CHILDREN WITH FRAGILE X SYNDROME
Leigh M1, Nguyen D2, Winarni T3, Hessl D4, Rivera S5, Chechi T1, Kennedy A1, Kapur R1,2

Purpose of Study: The purpose of this study was to determine the efficacy and tolerability of minocycline as a targeted treatment for children with fragile X syndrome (FXS). Minocycline decreases matrix metalloproteinase 9 levels and rescues dendrite spine abnormalities in the fragile X knock out mouse. Prior open label human studies suggest benefits.

Methods Used: Children with FXS ages 3.5–16 years of age were randomized to receive minocycline or placebo. After three months, participants were crossed over to minocycline or placebo as appropriate for the following three months. Investigators and participants were blinded to the randomization. Outcome measures including the Clinical Global Impressions-Improvement (CGI-I) Scale, Visual Analogue Scale (VAS) for behaviors, and the Aberrant Behavior Checklist (ABC) were administered at baseline, 3 months and 6 months.

Summary of Results: This preliminary analysis focuses on 40 individuals, mean age 8.64 ± 3.46 years. There was a significantly greater improvement in CGI-I scores with minocycline treatment compared to placebo (p=0.0274). The VAS showed a trend for greater improvement on minocycline when compared to placebo for the three behaviors identified by care-givers (p=0.2875, p=0.1296, 0.0551). The ABC Composite score also showed a trend towards greater improvement on minocycline (p=0.0628) when compared to placebo. No serious adverse events occurred and there was no significant difference in side effects during the minocycline period when compared to the placebo period.

Conclusions: Preliminary analysis supports the potential efficacy of minocycline treatment for FXS; however, there also seems to be a significant placebo effect. Treatment with minocycline for 3 months has been well tolerated. The trial is ongoing and updated data for a goal of 50 patients will be presented. Larger, multi-center trials are indicated to further examine these results.

MAPPING GLUCOSE TRANSPORTER-1 POSITIVE NERVE FIBERS IN THE TRANSITIONAL ZONE OF HIRSCHSPRUNG DISEASE
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Purpose of Study: Hirschsprung Disease (HSCR) is a malformation of the distal intestinal tract that causes functional obstruction due to an absence of enteric ganglion cells. HSCR is treated by resection of the aganglionic bowel. Prior open label human studies suggest benefits.

Methods Used: Children with FXS ages 3.5–16 years of age were randomized to receive minocycline or placebo. After three months, participants were crossed over to minocycline or placebo as appropriate for the following three months. Investigators and participants were blinded to the randomization. Outcome measures including the Clinical Global Impressions-Improvement (CGI-I) Scale, Visual Analogue Scale (VAS) for behaviors, and the Aberrant Behavior Checklist (ABC) were administered at baseline, 3 months and 6 months.

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Conclusions: Preliminary analysis supports the potential efficacy of minocycline treatment for FXS; however, there also seems to be a significant placebo effect. Treatment with minocycline for 3 months has been well tolerated. The trial is ongoing and updated data for a goal of 50 patients will be presented. Larger, multi-center trials are indicated to further examine these results.
metastatic status in human SCC. Mouse cells overexpressing miR-9 had increased expression of the AbbC1a, a chemoresistance gene, and were resistant to Docetaxel induced cell death. Docetaxel increased the transcriptional response of the pro-survival signaling pathway nuclear factor-kappa B (NFkB) in a dose-dependent manner with higher reporter activity in miR-9 overexpressing cells. siRNA inhibition of β-catenin abrogated AbbC1a expression.

Conclusions: Our results suggest that miR-9 is an oncogenic microRNA in skin SCC and involved in metastasis and chemoresistance.

**4 DIFFERENTIAL BRAIN, HORMONE, AND SATIETY RESPONSES TO GLUCOSE AND FRUCTOSE INGESTION**

Page K.1, Arora J.2, Belfort-DeAguia R.3, Constable RT.1, Sherwin R.2
1University of Southern California, Los Angeles, CA; 2Yale University, New Haven, CT and 3Yale University, New Haven, CT.

Purpose of Study: Increases in fructose consumption parallel the rise in obesity. Central administration of fructose provokes feeding in rodents, whereas centrally administered glucose produces satiety. Imaging studies in humans show that food intake results in deactivation of the hypothalamus and striatum, brain regions that regulate appetite and reward processing. Moreover, glucose but not fructose ingestion would produce different responses in brain regions that regulate feeding.

Methods Used: 20 healthy volunteers underwent 2 fMRI sessions with ingestion of a fructose or glucose drink in a blinded, random-order crossover design. Subjects had baseline acquisitions including pulsed arterial spin labeling and BOLD sequences to determine regional cerebral blood flow (CBF), markers of neural activation, and functional connectivity (FC), respectively. Subsequently, they drank 75 g of either sugar followed by a 60-min acquisition and blood sampling period. Participants rated fullness and satiety before and after the scan.

Summary of Results: CBF in the hypothalamus, thalamus, insula and striatum was significantly reduced after glucose ingestion (p=0.05, FWE whole brain corrected). In contrast, fructose ingestion reduced CBF in the thalamus, hippocampus and visual cortex (p<0.05). Glucose ingestion increased FC between the hypothalamus (the seed region) and the thalamus, nucleus accumbens and striatum, whereas fructose ingestion increased FC between the hypothalamus and thalamus (p<0.05). Fructose ingestion caused a smaller rise in plasma glucose, insulin and GLP-1 (p<0.01) than glucose. Ratings of fullness (p=0.001) and satiety (p<0.02) were increased only after glucose ingestion.

Conclusions: Our results demonstrate that glucose but not fructose ingestion reduces the activation of the hypothalamus and striatum, brain regions that regulate appetite and reward processing. Moreover, glucose but not fructose ingestion increased functional connections between the hypothalamo-striatal network and increased satiety. These disparate responses to fructose ingestion were associated with reduced levels of insulin and GLP-1 and might play a role in promoting feeding behavior.

Adolescent and Pediatrics
Concurrent Session
1:30 PM
Thursday, January 26, 2012

**5 HEALTH SCREENS - EVALUATING HEALTH CARE INTERVENTIONS IN NORTHERN INDIAN SCHOOLCHILDREN**


Purpose of Study: To evaluate the impact of an integrated approach to anemia reduction in a remote Himalayan valley school in Northern India.

Methods Used: In order to assess more than 400 students, five stations were set up in the school’s health clinic. Height and weight were recorded. Basic cardiovascular, respiratory, dermatology, and head and neck exams were performed. A HemoCue monitor was used to sample hemoglobin levels to determine whether or not the children qualified as anemic. Values used to define anemia were taken from the WHO minimal Hb levels, and calibrated for altitude.

Summary of Results: Preliminary data from 2011 suggests that anemia levels have decreased by 5%, from 89.5% to 84% over one year. The Hb levels ranged from 17.7 to 6.9 g/dL. The average Hb level was 13.35 g/dL, compared to 12.89 g/dL in 2010. Other prevalent medical issues discovered included head lice (76%), dental carries (73%) and worms (12%).

Conclusions: High levels of anemia were discovered in the children when our project began in 2007. Through iron supplementation, water sanitation, health education and nutritional support, the goal of our project was to implement a sustainable system to decrease the prevalence of anemia at Munsel-ling school. Each year we have seen a decline in children diagnosed with anemia. From 2007 to 2009 anemia levels decreased by 17% (88.4 to 71.3%). However, in 2009, iron was not distributed due to a conflicting schedule, and the following year the anemia prevalence increased to its original level (close to 90%). In 2010 iron tablets were again distributed to the children and in 2011 the anemia prevalence decreased 5%. Anemia, however, still remains widespread in this population and more work needs to be done to address the issue.

**6 THE EFFECTIVENESS OF STUDENT HEALTH EDUCATION IN REMOTE NORTHERN INDIA**


Purpose of Study: Since 2007 teams of University of British Columbia students (primarily from the Faculty of Medicine) have been traveling to the Spiti Valley, a remote and isolated region in the Indian Himalayas, to work with the community to improve health conditions of students at the Munseling boarding school. During earlier community needs assessments, a lack of education regarding personal health and hygiene was identified. In collaboration with local teachers and health workers, health education modules covering personal hygiene, handwashing, toothbrushing, water and sanitation, smoking, and diarrheal disease have been delivered to all 446 Munseling students.

To determine the impact of this aspect of our initiative, the effectiveness of our pilot health education curriculum was evaluated during the summer of 2011.

Methods Used: Before engaging in health education in 2011, baseline knowledge quizzes were distributed to three grades (4, 6 and 9) representing 20% of the students; the same quizzes were subsequently repeated post module delivery. Four modules were delivered and evaluated: (1) oral health & tobacco, (2) personal hygiene and skin disease, (3) water safety & toileting and (4) GI, diarrhea & worms.

Summary of Results: Grade 4 students scored an average of 33.7% on the pre-module baseline quiz, while grade 6 students scored 56.9% and grade 9 students scored 75.2%. Test scores improved significantly for both grade 4 and grade 6 with class averages being 49.7% and 69.1%, respectively. The grade 9 average increased to 80.1%, however this was not found to be a significant increase.

Conclusions: From our analysis, the students’ understanding of the topics covered in the health modules has increased considerably in 2011 demonstrating that our curriculum is indeed effective in transferring essential health knowledge. Interestingly, the smallest increase was found with the grade 9 class - this could be due to focusing on higher concepts rather than core principles (which made up the quiz) during module delivery, suggesting that a more basic approach should be taken during subsequent deliveries. Future directions include the continued transfer of health education teaching to the School Health Council (consisting of senior students) in order to promote sustainability.

**7 THE MEDICAL SCHOLARS TEACHING AREA RURAL STUDENTS PROGRAM EFFECTIVELY INCREASES RURAL YOUTH INTENTION TO GRADUATE HIGH SCHOOL**

Brown M, Hunt J University of New Mexico School of Medicine, Albuquerque, NM.

Purpose of Study: To evaluate if the Medical Scholars Teaching Area Rural Students (Medical STARS) program was effective in influencing rural youth to graduate high school.
Methods Used: The sample population for this study consisted of 138 high school students throughout the state of New Mexico who participated in the Medical STARS program. Each student completed an anonymous post-intervention survey the summer of 2008. The 28-point survey had a response scale from 1–4, where 4 was high likelihood and 1 was no likelihood. No demographic or identifying data were collected. The Likert item responses were entered into a spreadsheet. Sample sizes, means, standard deviations, and 95% confidence intervals (CI) were calculated.

Summary of Results: The highest score was on intention to graduate with a mean of 3.84 (CI 3.75–3.93), with likelihood of attending college the second highest at 3.71 (CI 3.59–3.83). There was only one item that scored below the “slight likelihood” response: likelihood of becoming a healthcare worker in the students’ own hometown at 2.0 (CI 1.84–2.16).

Conclusions: Currently, little is published about intervention programs by which medical students help foster rural youth intention to graduate high school. Medical STARS is a novel program created in 2006 by fourth year medical students at the University of New Mexico School of Medicine (UNM SOM) to improve health outcomes by increasing student intent to graduate high school. Studies have shown that students who graduate from high school have better health outcomes than peers who did not.

This study shows that the Medical STARS program effectively increases student intention to graduate high school and attend college. It is a sustainable and successful program through which over 1,200 students around the State of New Mexico have been reached since 2008. The program has also been expanded to include elementary, middle school, and urban students and a pre-intervention survey. We recommend that this program be utilized by other medical schools around the country to increase youth intent to graduate high school and, ultimately, to improve community health outcomes.

8 PROMOTING THE INTEREST OF UNDER-REPRESENTED YOUTH IN HEALTH CARE THROUGH SMALL CLASS SIZE AND EXPERIMENT-DRIVEN INTERACTIVE LEARNING

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Purpose of Study: The under-representation of minority groups in health care fields remains a major issue. A lack of early educational environments designed to encourage interest in health care fields has contributed to this. The objective of this study was to evaluate the effect of small class size and experiment-driven interactive learning in promoting interest in health care fields among underserved elementary school students.

Methods Used: Through a partnership between the Center for Future Health Professionals at UC Irvine and the Boys and Girls Club of Santa Ana, CA, a small class of between ten and fifteen minority fourth and fifth graders were given a biweekly, hour-long course designed to promote healthy lifestyles, scientific achievement and health care careers. The mentors were students pursuing health care careers. Experiments included pulse checking and heart rate determination, the benefits of using fluoride toothpaste and mouthwash by comparing the effects of acid on treated and untreated tooth-like structures (eggshells), and a team-building ball race exercise to study the respiratory system and the principles of bodily organization. At the end of four months a questionnaire was distributed to evaluate the effectiveness of the program.

Summary of Results: Our survey demonstrated that student understanding of health care concepts increased as a result of the class. Many students expressed interest in entering health care fields. The small class size and interactive environment were also met with enthusiasm. Physician was the most popular future career choice among students, but interest in dentistry, nursing and physician assistantships was also expressed. The mentors greatly enjoyed designing the lesson plans and serving as role models in their communities.

Conclusions: Our small class size and experiment-driven interactive learning environment taught the elementary school students about the science behind healthy lifestyles and promoted their interest in entering health care fields. This experience also increased the desire for lifelong civic engagement among the mentors and raised their interest in health care fields. Because of the interest of our community partners, students and teachers, our program is growing to include more class sessions.

9 ADDRESSING CHILDHOOD OBESITY IN TULALIP, WA

Gottlieb GZ. University of Washington School of Medicine, Seattle, WA.

Purpose of Study: The rate of childhood obesity has tripled in the United States in the last three decades, and Native American children have consistently had higher rates of obesity than any other ethnic group. Childhood obesity has been linked with higher rates of type II diabetes, cardiovascular disease, and other chronic diseases, many of which plague the Tulalip reservation.

Methods Used: The Boys and Girls Club is an active part of the community (it serves more than 200 children daily), and therefore was chosen as an ideal place to teach children about healthy eating. A literature review established the most successful means of teaching children about the effects of diet on health, and evaluated the most effective way of communicating with Native American populations about health. Based on this research and advice from the Tulalip clinic’s nutritionist and physicians, worksheets/pamphlets were developed for both the children in the class and their parents. The children’s worksheets were designed to help children 1) critically read nutrition labels, 2) learn about the USDA’s ‘My Plate’ and a balanced diet, and 3) find fruits and vegetables that they enjoyed eating. The pamphlets for parents provided tips on meal planning meals, and tips on serving anti-smoking messages. All this information about healthy lifestyle choices is important, demonstrated how to introduce new foods to picky eaters, and included a flyer for the Hibulip community garden. The garden’s generous donations helped the class immediately experience fresh vegetables.

Summary of Results: Eight children between the ages of nine and twelve attended the class, and all actively participated. Every student left the class able to express at least one new nutrition concept, and a number of the children conveyed a desire to have a healthier diet. Boys and Girls Club teachers who attended the lesson, and the students’ parents, gained awareness about this issue, and learned new ways to make vegetables more palatable to children.

Conclusions: This class taught practical nutrition tips and why healthy eating is important. It also brought awareness to teachers, parents, and health care providers that this should be a topic of further discussion. Curbing the rate of childhood obesity will require long-term interventions, but based on recent publications nutrition education can be successful if it is culturally relevant and backed by support from the entire community.

10 SMOKELESS TOBACCO EDUCATION ON TEEN ATHLETES IN CODY, WYOMING

Higuera D University of Washington Medical School, Seattle, WA.

Purpose of Study: Smokeless tobacco (ST) is most prevalent in small communities, and advertisers target low-income “hard working” households. The social image associated with ST reflects the rugged athletic image used in its promotion. Young athletes are susceptible to these messages and are at risk to use tobacco in the future. 1 in 4 of Wyoming high school students already use ST. Billings Clinic (BC) is a rural clinic that houses the majority of Family Practice doctors who perform sports physicals for young teens. The purpose of this project was to educate both sports athletes and their doctors about the dangers of using ST in an attempt to reduce future use.

Methods Used: Informal discussions with doctors, medical staff, anti-drug campaign leaders, and community members helped identify ST and teenagers as the focus of this project. A multi-target approach was used to address this concern. To develop ST prevention awareness a partnership was made with the Park County Anti-Tobacco Campaign “Through With Chew” providing anti-smoking education to students. ST products to give to teens. A literature review was performed to examine the correlations between education, social pressures in youth, and health concerning ST. Media used included various printed materials including stickers, posters, brochures, playing cards, and imitation/non-narcotic “ST”.

Summary of Results: Sports physicals were administered with ST education and leadership responsibility/accountability talks being held at the end of the physical. An anti-ST newsletter was addressed to the Yellowstone Quake Hockey team for the month of July. Education on physician impacts on teenagers was also conducted with the leadership of the BC, focusing on the power that their medical opinion has on reducing teenager ST use. Agreements were made with the local high school, middle school and BC to donate money spent on physicals towards school athletics with part of the proceeds going toward tobacco awareness.

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Conclusions: The people of Cody, Wyoming recognize that ST manufacturers are targeting them through advertisement and social pressures. Education through peer mediation and physicians is one of the most effective ways to prevent teenagers from using ST. An effort to enlighten both teen/athlete sports participants and doctors about materials and counseling against ST is a first step in a promising campaign at improving adolescent and teen health.

11 PROVIDING TEENS A ROADMAP TO HEALTHY LIVING TO PREVENT OBESITY IN CENTRALIA, WASHINGTON

Mar EY University of Washington, Seattle, WA.

Purpose of Study: Centralia, Washington is a town of 15000 individuals located about 25 miles south of Olympia. Like many other parts of the country, Centralia and its twin city, Chehalis, have seen an epidemic increase in obesity. This issue of unhealthy living is magnified by a poverty rate that is more than 50% below the state average. The purpose of this project was to raise awareness amongst teens and their families about healthy lifestyle choices.

Methods Used: Local leaders and health care providers helped identify teen obesity as an issue of major concern in the community. This lecture was developed as the conclusion of a five week, teen-focused weekly seminar series that included lectures on nutrition, exercise, and grocery shopping. A literature review was conducted for guidance of effective teaching methods for teens. Using these teaching methods, an interactive, discussion-based seminar was delivered at the Chehalis library on June 29, 2011. An article in the local newspaper, The Chronicle, was placed as advertisement for the seminar series.

Summary of Results: Although it was unfortunate that no teens were able to attend the lecture, there were eight community members in attendance. The interactive lecture involved lively discussions that stemmed around the growing understanding that obesity is a societal problem where even little steps can make a big difference in one's health. The participants engaged in active discussions that increased everyone's understanding of the "why's" and "how's" of staying healthy based off of videos, activities, and health statistics trivia.

Conclusions: Providing the families of Centralia and Chehalis an understanding of simple ways to fight obesity and live healthily is a powerful tool towards combatting the epidemic problems that the town faces. Moreover, the discussion based forum provided an opportunity to empower healthy choices rather than demean unhealthy ones. This program hopefully has provided roots for a more long term project. It was unfortunate that promotion for the project was limited by the timing of the seminars coinciding with the beginning of summer vacation for the teens. Local leaders aim to repeat the 5 week series in autumn of 2011 with the experiences learned from this project and aim to advertise through the Centralia and Chehalis school system.

12 ADOLESCENT DEPRESSION AND SUICIDE AWARENESS: TRAINING STUDENT LEADERS IN MOSES LAKE, WASHINGTON

Paul D University of Washington School of Medicine, Seattle, WA.

Purpose of Study: The 2008 Grant County Healthy Youth Survey indicates that 29% of local 8th graders have experienced symptoms consistent with clinical depression. Further, 7% report attempting suicide and 20% would be "very unlikely" to seek help for a suicidal or depressed friend. This reduced help-seeking is significantly higher in Grant County than the rest of Washington State and seems consistent with the finding that this county's 8th graders are less likely to learn about suicide prevention at school. In an attempt to reduce adolescent depression rates and minimize suicide risk, a community-specific depression and suicide awareness program was developed for Moses Lake, WA, the largest city in Grant County.

Methods Used: Fifty-eight Moses Lake sixth, seventh, and eighth graders were nominated by teachers as "leaders capable of supporting classmates". These students were trained in depression and suicide recognition, intervention strategies, and use of community resources. Emphasis was placed on the opportunity these leaders have to educate, support, and refer their at-risk peers. A pamphlet was also developed for student leaders to use as a personal resource and as a tool to reach out to peers. Once at-risk students are recognized, the program encourages reporting to a suicide hotline, school counselor, or physician, with the ultimate goal being referral to Grant Mental Health.

Summary of Results: While the results of this program have not been assessed, initial signs are encouraging. The observed attendance, active participation, and positive feedback all indicate that the program was well received. Students also successfully recognized symptoms of depression, and warning-signs of suicide, in mock case studies. All presentation materials were made available to school counselors for the training of future cohorts.

Conclusions: Adolescent depression and suicide require significant attention in Moses Lake and Grant County. Fortunately, this community displayed a willingness to address these issues by providing support and feedback during the development of this project. By implementing an evidence based program, it seems realistic to expect improved awareness, peer reporting, and use of community resources. In the future, additional research will be needed to determine if improvements in responsiveness to adolescent depression and suicide have been achieved.

13 PARTNERSHIP WITH THE DISCOVERY SCIENCE CENTER: TOWARDS INCREASING DIVERSITY IN HEALTH CARE AND BIOMEDICAL FIELDS

Tran J, Gaffar S, Koussa M, Patel U, Yamaguchi F, Afghani B / UC Irvine School of Medicine, Orange, CA and 2 Discovery Science Center, Santa Ana, CA.

Purpose of Study: Data suggests that there is an under-representation of minority youth in healthcare and science fields. The objective of our project was to increase the interest of a diversified population of youth in healthcare and biomedical careers.

Methods Used: Through partnership of the Center for Future Health Professionals at UC Irvine School of Medicine and the Discovery Science Center in Santa Ana, we established an interactive exhibit for the visitors to learn about the anatomy and functions of the respiratory tract. Using a human simulator model, undergraduate and postgraduate volunteers interested in healthcare careers introduced the young visitors to the anatomy of respiratory system. The visitors had the opportunity to give oxygen using a bag-mask and intubate the simulator. After the hands-on activity, the visitors completed a survey to evaluate the effectiveness of our exhibit.

Summary of Results: Of 253 respondents, one-third were Hispanic, one-third were Caucasian and the others belonged to other ethnicities. More than 80% of the visitors said that they were more interested in a healthcare career as a result of this exhibit and more than 90% thought this activity should be included in their school's science program. Of 205 comments, 98% were positive. Among these were: 1) "This is the most amazing tabletop demonstration I have ever seen," and 2) "fun learning experience. I can't wait to tell my teacher about it." All of the undergraduate and postgraduate students who served as mentors said that this activity enhanced their leadership skills and their commitment to civic engagement.

Conclusions: In summary, our partnership with the Discovery Science Center has been very effective in promoting the interest of a diverse population of youth towards healthcare fields. To promote diversity in health and science careers, community partnerships that use innovative and interactive approaches should be encouraged.

14 NOVEL PHYSICAL ACTIVITIES TO FOSTER LEARNING AND ENGAGEMENT IN YOUTH


Purpose of Study: The rural and remote aboriginal community of Hartley Bay (HB) has developed a partnership with the "Brighter Smiles Program". Our study seeks to extend novel physical activities can engage youth to explore issues of concern to the community such as bullying in elementary school and diabetes prevention.

Methods Used: Medical students delivered 3 sessions of martial arts and group fitness classes to youth in HB. In Session 1, kindergarten/elementary and high school students participated in a single class. It was emphasized that martial arts was to not be used against others but as a tool to increase confidence and self-control. Elementary students were told that there would be
a role-play related to bullying and to think about harms of bullying and how to prevent it. For high school students, Session 2 included a discussion on prevention of Type 2 diabetes and how to stay fit and healthy in their own community.

Summary of Results: Session 1 involved all students and 40(87%) participated. All students reported that they had a “great time” and were “looking forward to the next session”. In Session 2-elementary students 26/28 (93%) participated and all were satisfied. After role play and discussion on bullying, children offered their thoughts and ideas and shared their insight as to how bullying “makes you lose friends”, that “if I was being bullied it wouldn’t feel good” and that “it’s not how a community should get along”. In Session 3-high school students 16/18 (89%) participated. Students enjoyed the class and a general consensus was “that the class was more fun than regular physical exercise classes”. 100% of students were satisfied. Students were informed about Type 2 diabetes and how to help prevent it with dietary factors. The benefit of regular physical exercise to help prevent type 2 diabetes was discussed; what activities they liked and were available in their community and concluded by reinforcing and bridging the importance of remaining active to reduce the risk of diabetes. The school was interested in adopting these exercises.

Conclusions: All students reported they enjoyed the physical activity sessions. Ideally the program would include 3 components 1) Use of a novel and innovative physical activity 2) Be cost effective and 3) Use the activity as a vehicle to address main community health and social concerns while educating youth.

15 PRESTERNAL DERMOID CYST MIMICKING LYMPHATIC MALFORMATION

Berry T, Smitd A University of New Mexico Hospital, Albuquerque, NM.

Case Report: We describe an 11 mo. male with an unusually large prestenral mass present since birth. The large size, fluctuant properties, translumination, compressibility, and imaging of this lesion were very characteristic of a lymphatic malformation. Four treatments with sclerotherapy markedly reduced its size, it was not until definitive treatment with surgical excision and final pathology report that we arrived at the ultimate diagnosis of dermoid cyst.

Dermoid cysts, although appearing along embryologic lines of closure, are rarely prestenral. Additionally, they are relatively small in size, thick walled, and filled with keratinic fluid, typically allowing for clinical diagnosis, with characteristic features on MRI and ultrasound. This case illustrates, however, dermoid cysts can appear in somewhat atypical locations and imaging is not always diagnostic. Thus, dermoid cyst should remain a part of the differential diagnosis in any lesion presenting mid sternally regardless of size and imaging characteristics.

16 PROTECTING YOUR MELON: HELMET SAFETY FOR THE YOUTH OF BUTTE

Irvin LD University of Washington, Seattle, WA.

Purpose of Study: To increase helmet use among youth in Butte, Montana. Without formal safety programs in Butte, encouraging helmets is left up to individual families and physicians. Just after I arrived in Butte, a seven-year-old child was killed in an ATV accident while not wearing a helmet. After this tragedy, my discussions with The Butte Center for Public Health, community physicians and the Trauma Coordinator at St. James Hospital, motivated me to create a helmet education program for local children. Research shows that the important factors in helmet safety are parental education and enforcement, child understanding, helmet ownership, helmet safety laws and peer helmet use. There are no helmet education programs in Butte and almost no helmet laws. As a result, head trauma related to poor helmet safety is a huge issue.

Methods Used: I created an event for children and parents to address helmet safety. Studies show that a multifaceted, interactive approach is best. Activities included a watermelon drop to help the children learn the effectiveness of wearing helmets, learning when helmets are appropriate, helmet sizing and distribution. Parents were provided information about helmet safety and encouraged to help their children follow proper helmet safety rules at home.

Summary of Results: The event addressed helmet education for 19 children, ages 5–12 years old and their parents. It created enthusiasm about helmet safety and the educational material was interactive, focused, and easily understandable. Donated helmets were distributed to children in need and the posters the kids created, as well as a ‘Helmets in the Local News’ collage, are on permanent display in the main foyer of the YMCA.

Conclusions: Helmets are an innovation essential for safe participation in many activities, yet because of a lack in education, most Butte families do not practice helmet safety. It is evident that helmet safety cannot be left to primary care physicians alone. Interactive and focused educational events like this one can significantly increase helmet use and should be a standard part of the curriculum for young children. Research shows that children who wear helmets tend to become adults who use helmets. Furthermore, changes in helmet laws and the establishment education and distribution programs will be essential in tackling the helmet safety issues in Butte, Montana.

17 PEDIATRIC FLEXOR TENDON INJURIES: A 10 YEAR ANALYSIS AT BC CHILDREN’S HOSPITAL

Lai MA1, Sikora S2, Arneja J2 1University of British Columbia, Vancouver, BC, Canada and 2British Columbia Children’s Hospital, Vancouver, BC, Canada.

Purpose of Study: To determine the prevalence and outcomes of pediatric flexor tendon injuries involving zones I, II and III in the past 10 years and to identify treatment paradigms that improve therapeutic outcome.

Methods Used: A retrospective chart review of flexor tendon injuries involving zones I, II and III between April 2001 and December 2010 was performed. Demographics, injury mechanism, repair technique, outcomes, and complications were reviewed.

Summary of Results: A total of 49 patients with a median age of 7.9 years (range 0.03–16) had 106 tendon injuries. Repairs were done at median day 0 (range 0–31 days). The most common cause of injury was glass (23 patients) and the small finger was involved in the highest number of cases (36 tendons). 48 tendons injured were FDS, 47 FDP, 10 FPL and 1 APL. Zone III had the most injuries (47). 92 tendons were repaired with polyester; 4-0 was the most common suture size and Modified Kessler was the predominante repair technique (68). Only 22 tendons had epitenon repair. Splt immobili- zation was used in 32 patients and a full cast in 17. The median immobilization duration was 4 weeks. 42 patients underwent post-operative hand
therapy. Using the ASSH Total Active Motion (TAM) score, 42 patients had complete recovery. 2 patients had a score of less than 100%, not requiring further surgery. A second operation was required for 5 patients with a median age of 12.8 years (range 3–14.9). A mean of 2.20 +/- 0.45 tendons were involved per patient. 3 out of 5 injuries were located in zone II. One patient required a re-repair due to rupture, 2 required tenolysis and 2 required a two-stage tendon reconstruction. All patients in this group received 100% TAM at 1 year.

**Conclusions:** Pediatric flexor tendon injuries are rare and usually involve the predominant hand. An excellent outcome was found in 95.9% of patients using TAM scores. Repair technique chosen was related to the size of tendon involved. Patients not treated with hand therapy and not immobilized are often too young to participate in rehabilitation. Based on our results, immobilization of young children for 4 weeks does not worsen functional outcomes. Of patients requiring a second procedure, no link was found among outcome, cause, location, repair or rehabilitation protocol.

**Behavior and Development**

Concurrent Session

1:30 PM

Thursday, January 26, 2012

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**18 TRISOMY X: EXPANDING THE PHENOTYPE**

D’Epagnier C, Ayari N, Boada R, Tartaglia N

**University of Colorado School of Medicine, Aurora, CO.**

**Purpose of Study:** Trisomy X (47,XXX) occurs in approximately 1:1000 female births and presents with a variable phenotype resulting in only 10% of cases being diagnosed. This study aimed to describe the diagnosis, physical features, medical and developmental problems in a large cohort of females with trisomy X to further characterize the phenotype. We also compared developmental features in those with a prenatal vs. postnatal diagnosis.

**Methods Used:** 41 females age 1–24 (mean 8.33 yrs) with trisomy X were recruited from national support groups and a multidisciplinary clinic for SCAs. Patients were assessed by structured interview and examination. ADHD symptoms were evaluated by DSM-IV criteria. We compared rates of speech and motor delays, ADHD, and special education (SPED) supports in those with a prenatal vs. postnatal diagnosis using Fisher’s exact test.

**Summary of Results:** Most patients were diagnosed prenatally (63%). Mean age of postnatal diagnosis was 5.6 years, and neurodevelopmental features (developmental delays, learning or behavioral problems) were the most common postnatal indications for genetic testing (67%). Physical features including hypertelorism, epicanthal folds, clinodactyly, flat feet, and hypotonia were common across all ages. Tall stature was present in adolescents and adults, with mean adult height of 171.7cm (SD 10.5). Common medical problems include kidney abnormalities, constipation, poor coordination, seizures, strabismus, and tremor. Of the entire cohort, 72% had speech delays and 51% had motor delays. Of the 24 school aged girls, 66% received SPED for learning or speech language disorders, 46% met criteria for ADHD, and 40% had an emotional disorder (including anxiety or depression). The prenatally diagnosed subgroup had lower rates of speech delays (60% vs. 93%), motor delays (59% vs. 75%), and SPED services (64% vs. 100%), however these did not reach statistical significance (Fisher’s p=0.06, 0.08, 0.11, respectively). There were no differences in the rate of ADHD between those with a prenatal vs. postnatal diagnosis (46% vs. 45%, p=1.00).

**Conclusions:** These findings expand upon the phenotypic characteristics of trisomy X. Those with a prenatal diagnosis have lower rates of neurodevelopmental problems, however many still have developmental delays and ADHD. Increased awareness of trisomy X is needed to increase rates of diagnosis and treatment.

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**19 SLEEP PROBLEMS IN SEX CHROMOSOME ANEUPLOIDY AND RELATIONSHIP WITH ASMT EXPRESSION**

Pate l V, Katz T, Tassone F, Tartaglia N

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**Purpose of Study:** The phenotype of sex chromosome aneuploidy (SCA) conditions is hypothesized to result from overexpression of genes in the pseudautosomal region such as acetylseryotonin O-methyltransferase (ASMT), which catalyzes the final step of melatonin synthesis. Melatonin is critical in sleep regulation, and individuals with SCA often report sleep problems. Here we describe sleep behavior in children with SCA, and we evaluate ASMT mRNA expression. We hypothesized that ASMT expression would be higher in SCA compared to controls, and that SCA patients with sleep problems would have higher levels than those without.

**Methods Used:** 69 participants age 1-23 years with SCA (29 XXY, 21 XYY, and 19 XXX) were interviewed in a semi-standardized format about sleep domains. In a subset of 31 males with XXY and XYY, ASMT mRNA expression levels were measured and compared to 24 XY controls by t-test. Further, ASMT expression of SCA males with and without sleep problems were compared.

**Summary of Results:** Of the entire sample, 65.2% (45/69) were identified as problem sleepers. There were no differences in overall sleep problems between XXY, XYY, and XXX. Rates and subtypes of sleep problems are shown in the table. ASMT expression was significantly higher in the SCA group compared to controls (SCA 38.5 +/- 37.13 vs. XY 21.24 +/- 19.15, p<0.043). There were no significant differences in ASMT expression between the SCA subgroups with or without sleep problems (Normal 28.01 +/- 13.8 vs. Sleep problems 43.03 +/- 43.0, p=0.32).

**Conclusions:** There are high rates of sleep problems in children with SCA. Higher ASMT expression was found in males with SCA compared to controls, however the role of ASMT expression on within-group variability in sleep or other neurodevelopmental features is needed. Important next steps include further study of the interplay between melatonin levels, ASMT expression, and clinical features of sleep in individuals with SCA.
subgroup analyses, myeloproliferative/neoplasm was the 5th most common reason for admission among 1–4 year olds, and MSK/CT was the 3rd leading cause of admission among the 10–14 and 15–18 age groups. In the comparison group, the top 5 reasons for admission were respiratory, digestive, mental health, MSK/CT, and nervous system. In subgroup analysis E/MN was the 5th leading cause for admission among 1–4 year olds.

Conclusions: Novel findings in this analysis were the rates of mental health admission among adolescents with CP and the age-specific reasons for hospital admission among children with DS. Training of physicians to care for children with CP and DS should include education about the differing reasons for hospitalization across age groups.

Summary of Results: Infants <501 g BW were significantly more frequently small for gestational age (81%, mean BW of 461±37 g; GA of 26.3±1.8 wk) than infants 601-800 g BW (6%, 709±52 g and 25.4±1.4 wk), but there were no group differences in GA, social status, race, or multiple gestations. Maternal hypertensin and cesarean section delivery were more frequent for <501 g pregnancies, often complicated by oligohydramnios (44%). Infants <501 g BW had longer hospitalizations (131±54 vs 102±21 days), greater duration of intubation (52 ±3 vs 30±13 days, P=0.01), and oxygen exposure (116±6 vs 81±24, P=0.009). Height percentiles were significantly lower for the <501 g children at mean follow up of 73 months, although both groups averaged <10th percentile. <501 g BW children more frequently had cerebral palsy (50% vs 16%), strabismus, refractive errors, noncorrectable visual impairments (31% vs 6%, P=0.02), and had lower mean IQ (76±16 vs 86±14, P=0.02). 2/16 (13%) were considered nonimpaired compared to 17/32 (53%) of the heavier ELBW (P=0.02).

Conclusions: Surviving infants <501 g BW from the past decade appear to be a select group of ELBW frequently born following pregnancy complications associated with growth retardation. They have more neonatal complications and long-term neurodevelopmental sequelae, including greater visual, motor, and cognitive disabilities at school age than heavier ELBW infants.

21 A DOUBLE BLIND, PLACEBO CONTROLLED, CROSSOVER TRIAL OF MINOCYCLINE IN CHILDREN WITH FRAGILE X SYNDROME

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Purpose of Study: The purpose of this study was to determine the efficacy and tolerability of minocycline as a targeted treatment for children with fragile X syndrome (FXS). Minocycline decreases matrix metalloproteinase 9 levels and rescues dendritic spine abnormalities in the fragile X knock out mouse. Prior open label human studies suggest benefits.

Methods Used: Children with FXS ages 3.5–16 years of age were randomized to receive minocycline or placebo. After three months, participants were crossed over to minocycline or placebo as appropriate for the following three months. Investigators and participants were blinded to the randomization. Outcome measures including the Global Impressions-Improvement (CGI-I) Scale, Visual Analog Scale (VAS) for behaviors, and the Aberrant Behavior Checklist (ABC) were administered at baseline, 3 months and 6 months.

Summary of Results: This preliminary analysis focuses on 40 individuals, mean age 8.64 ± 3.46 years. There was a significantly greater improvement in CGI-I scores with minocycline treatment compared to placebo (p=0.0274).

The VAS showed a trend for greater improvement on minocycline when compared to placebo for the three behaviors identified by caregivers (p=0.2875, p=0.1296, 0.0551). The ABC Composite score also showed a trend towards greater improvement on minocycline (p=0.0628) when compared to placebo. No serious adverse events occurred and there was no significant difference in side effects during the minocycline period when compared to the placebo period.

Conclusions: Preliminary analysis supports the potential efficacy of minocycline treatment for FXS, however, there also seems to be a significant placebo effect. Treatment with minocycline for 3 months has been well tolerated. The study will contribute new information to the process of minocycline maturation.

22 COMPARISON OF PERINATAL COMPLICATIONS AND LONG-TERM OUTCOME FOR INFANTS LESS THAN 501 GRAMS COMPARED TO 601-8000 GRAMS BIRTH WEIGHT

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Purpose of Study: To assess perinatal complications and childhood outcomes for surviving ELBW infants <500 g compared with those 601-800 g BW.

Methods Used: Surviving infants <501 g BW cared for in two referral perinatal centers between 1994 to 2003 were identified from record review. 16 were evaluated at a mean of 7 years, including medical history, growth, and developmental testing; disabilities were categorized as none, mild, moderate, or severe. Infants 601–800 g BW born in 1993–95, evaluated at 3 or 6 years of age, were matched 2:1 by gestational age and gender, from a research database. Perinatal and neonatal complications and long-term outcomes were statistically compared between groups.

Summary of Results: Infants <501 g BW were significantly more frequently small for gestational age (81%, mean BW of 461±37 g; GA of 26.3±1.8 wk) than infants 601-800 g BW (6%, 709±52 g and 25.4±1.4 wk), but there were no group differences in GA, social status, race, or multiple gestations. Maternal hypertensin and cesarean section delivery were more frequent for <501 g pregnancies, often complicated by oligohydramnios (44%). Infants <501 g BW had longer hospitalizations (131±54 vs 102±21 days), greater duration of intubation (52 ±3 vs 30±13 days, P=0.01), and oxygen exposure (116±6 vs 81±24, P=0.009). Height percentiles were significantly lower for the <501 g children at mean follow up of 73 months, although both groups averaged <10th percentile. <501 g BW children more frequently had cerebral palsy (50% vs 16%), strabismus, refractive errors, noncorrectable visual impairments (31% vs 6%, P=0.02), and had lower mean IQ (76±16 vs 86±14, P=0.02). 2/16 (13%) were considered nonimpaired compared to 17/32 (53%) of the heavier ELBW (P=0.02).

Conclusions: Surviving infants <501 g BW from the past decade appear to be a select group of ELBW frequently born following pregnancy complications associated with growth retardation. They have more neonatal complications and long-term neurodevelopmental sequelae, including greater visual, motor, and cognitive disabilities at school age than heavier ELBW infants.

23 Withdrawn

24 AUDITORY SENSORY GATING IN CHILDHOOD ONSET SCHIZOPHRENIA PATIENTS DURING REM SLEEP

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Purpose of Study: By early childhood, children who later develop a primary psychotic disorder such as schizophrenia already demonstrate many of the deficits that are associated with the disease in the adult. Children who suffer from Childhood Onset Schizophrenia (COS) also demonstrate more severe psychopathology and have worse prognoses than their adult counterparts. Psychosis-associated deficits in cognition have been shown to be related to a physiological measure of inhibitory functioning, auditory sensory gating. This endophenotype is an information processing deficit, manifesting in an abnormally increased responsivity to repetitive stimuli, as demonstrated by a paired auditory stimulus test. Typically, the brain responds to the first stimulus but shows a significantly diminished response to the second. However, adults with schizophrenia fail to show the decreased response to the second stimulus, suggesting an inability to filter repetitive stimuli due to poor cerebral inhibition. This study seeks to investigate the impaired auditory gating effect in COS patients using a P50 waveform ratio on EEG.

Methods Used: 15 diagnosed COS patients and age-matched controls ages 4–15 will be admitted to a local children’s hospital research facility. EEG will be recorded during sleep while paired auditory stimuli are presented through speakers near the head. Overnight recordings will be analyzed for REM sleep using software analysis and cross-referenced with manual inspection of characteristic eye movements and EEG data.

Summary of Results: The state-dependent P50 measure has historically been difficult to obtain in COS children due to their already heightened anxiety levels. By employing an alternative method of collecting the P50 evoked responses during rapid-eye movement (REM) sleep (previous studies have shown that P50 measurements between wakefulness and REM are comparable), such an obstacle can likely be avoided. This experiment has been successfully performed with adults. We expect that COS patients will demonstrate defective auditory gating, similar to their adult counterparts.

Conclusions: The study will contribute new information to the process of COS, particularly the physiological measure of auditory gating as a reflection of impaired cerebral inhibition capabilities, as well as demonstrate parallels between COS and adult-onset schizophrenia.

25 INFANT BIOMARKERS OF VULNERABILITY TO SCHIZOPHRENIA: SACCADE INTRUSIONS INTO SMOOTH PURSUIT EYE MOVEMENTS IN GENETICALLY VULNERABLE FOUR- AND SIX-MONTH-OLDS

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AFTERDEPOLARIZATIONS CAUSED BY OXIDATIVE STRESS

REVEAL THE EXCHANGER'S ROLE IN EARLY SODIUM-CALCIUM EXCHANGE KNOCKOUT MICE

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Purpose of Study: The sodium-calcium exchanger (NCX) is an electrogenic transporter that is the primary calcium efflux mechanism for cardiomyocytes. There is some evidence suggesting that NCX may be responsible for the depolarizing current leading to early afterdepolarizations (EADs), which can lead to fatal cardiac arrhythmias. The oxidant H2O2 has been shown to induce EADs in rat cardiomyocytes. We used a cardiac-specific NCX knockout mouse to investigate the role of NCX in EAD formation during H2O2 perfusion. We hypothesized that NCX knockout mice, in contrast to wild type mice, would not exhibit EADs in the presence of H2O2.

Methods Used: Action potentials from cardiomyocytes were recorded with the patch clamp technique using whole cell current clamp mode on an Axoclamp 900A system. An H2O2 concentration of 200 μM was used, and action potentials were recorded at a pacing cycle length of 6 seconds until the cells either died or became inexcitable. Because NCX knockout mice still show NCX expression in a minority of cells, the cells were phenotyped prior to acquiring patch data. Phenotyping of knockout cells was based on a reduced action potential duration (APD) compared to wild type. Summary of Results: EADs were elicited from all wild type cells (n=2) in the presence of H2O2. In cells from the NCX knockout that were suspected of having the wild type phenotype (expressing NCX), all cells (n=5) displayed EADs in the presence of H2O2. Two of four cells that we suspected were true knockouts (not expressing NCX) showed EADs.

Conclusions: EAD formation in NCX knockout mice was reduced compared to wild type. This suggests a direct role of NCX in the generation of EADs. Because phenotyping was based on relatively subjective criteria, it is essential to use a more reliable phenotyping procedure in future experiments.

27 TIME COURSE OF DEVELOPMENT OF A MURINE MODEL OF DIET-INDUCED INSULIN RESISTANCE AND CARDIOMYOPATHY

Sta Teresa A 1, Kim J 1, Wietecha T 2, Hudkins K 2, Alpers C 2, O’Brien KD 1 1University of Washington, Seattle, WA and 2University of Washington, Seattle, WA.

Purpose of Study: Diabetes is associated with a 2- to 3-fold ↑ in risk for congestive heart failure (CHF), due primarily to cardiac hypertrophy and fibrosis. We recently have shown that leptin-deficient, female BTBR mice (BTBRob/ob) develop cardiomyopathy, with a 24-25% ↑ in heart weight and a 5-10% ↑ in fibrosis. We investigated whether the cardiomyopathy phenotype might be replicated with diet-induced obesity in wild-type, BTBR mice.

Methods Used: At 4 weeks of age, female BTBR mice were placed on either standard rodent chow (“Chow”) or a “diabetogenic” diet with 50% of calories from fat and 26% of calories from carbohydrates (“DD”). Oral glucose tolerance tests were performed at 8 and 16 weeks on diets. Mice were sacrificed after 16 and 30 weeks on diets for determination of heart weights and fibrosis. Final group sizes were 7-8 mice/diet group for each timepoint.

Summary of Results: By 8 weeks on DD, female BTBR mice had normal fasting glucose, but glucose tolerance (as judged by area under the glucose excursion curve) was significantly impaired vs. Chow-fed controls. At 16 weeks on diets, blood pressures did not differ significantly, but fasting glucose was increased by 22% (P=0.0125), AUC by 23% (P=0.003), heart weights 18% (P=0.001), and LV cross-sectional area by 13% (P=0.020) in DD as compared to Chow mice. At 30 weeks on diets, mean fasting glucose was increased by 21% (P=0.0034), AUC was increased by 27% (P=0.023), heart weights increased by 20% (P=0.001), and LV cross-sectional area increased by 18% (P=0.0049) in DD as compared to Chow mice. Though fibrosis, as measured by picrosirius stain, was increased by 26% at 16 weeks and by 23% at 30 weeks in DD vs. Chow, these differences did not reach statistical significance.

Conclusions: Thus, 16 weeks feeding of a “diabetogenic” diet to wild-type, female BTBR mice results in significant dysglycemia and myocardial hypertrophy. Increasing the length of diet treatment to 30 weeks does not further worsen dysglycemia or the cardiomyopathy phenotype. These findings suggest that feeding a diabetogenic diet to wild-type BTBR mice for 16 weeks is sufficient for studying the pathogenic mechanisms underlying cardiomyopathy in insulin resistance and diabetes.

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Metformin on heart weight, LV cross-sectional area, fibrosis or low-grade myocardial inflammation.

Conclusions: Thus, despite significant improvements in both obesity and fasting hyperglycemia, 10 weeks of metformin treatment had no measurable effect on established cardiac hypertrophy or fibrosis in this murine model of diet-induced cardiomyopathy. This study did not address whether earlier institution of Metformin might prevent or delay the development of cardiomyopathy in this model, a possibility that warrants further study.

29 DIETARY REGRESSION REDUCES BODY WEIGHT BUT NOT DYSGLYCEMIA OR ESTABLISHED CARDIAC HYPERTROPHY AND FIBROSION IN A MURINE MODEL OF DIET-INDUCED INSULIN RESISTANCE AND CARDIOMYOPATHY

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1University of Washington, Seattle, WA and 2University of Washington, Seattle, WA.

Purpose of Study: Diabetes is associated with a 2- to 3-fold increase in risk for congestive heart failure (CHF), due primarily to cardiac hypertrophy and fibrosis. We recently have shown that feeding of a diabetogenic diet high in fat and sucrose (DD) to wild-type BTBR mice for 16 weeks induces significant dysglycemia and cardiac hypertrophy. Here, we investigated whether switching to a Chow diet might favorably affect body weight, dysglycemia and cardiomyopathy in this model.

Methods Used: At 4 weeks of age, female BTBR mice were placed on a “diabetogenic” diet, with 59% of calories from fat and 26% of calories from carbohydrates (“DD”). At 20 weeks on DD, half of the mice were placed on standard rodent chow diet and half were continued on DD for an additional 10 weeks until sacrifice at 30 weeks on diets. Final group sizes were 7 mice/group.

Summary of Results: As compared to 30 weeks of DD, switching to Chow diet for 10 weeks following an initial 20 weeks of DD resulted in a significant reduction in body weight (53.9±2.1 vs. 38.5±3.0 gm, P=0.0013), but had no significant effects on fasting glucose levels (P=0.24), oral glucose tolerance (P=0.15), heart weight (P=0.69), LV cross-sectional area (P=0.75), low-grade myocardial inflammation (P=0.79) or myocardial fibrosis (P=0.45).

Conclusions: Despite a significant improvement in body weight, changing to a Chow diet might favorably affect body weight, dysglycemia and cardiomyopathy in this model.

30 CONTRACTILE RECOVERY FROM ISCHEMIA IS IMPAIRED IN A PORCINE MODEL OF METABOLIC SYNDROME, BUT AMELIORATED BY RESTRICTING FATTY ACID AVAILABILITY

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Purpose of Study: We tested the hypothesis that myocardial contractile and metabolic recovery after regional ischemia is impaired in a porcine model of Met Syn and investigated underlying mechanisms for such a response.

Methods Used: Micropigs (n=28) were assigned to control (low-fat, no added sugars) or Met Syn diet (25% coconut oil and 20% high-fructose corn syrup w/w) for seven months. Met Syn diet caused obesity, hypertension, dyslipidemia, insulin resistance without diabetes, and elevated plasma free fatty acids (FFA). Anesthetized pigs were subjected to 45 min low-flow regional ischemia followed by 120 min reperfusion. In 16 pigs, ischemia was imposed with ambient levels of FFA (arterial plasma concentration 0.2 mmol/L, 0.5 mmol/L Met Syn). In 12 pigs, 90 min of euglycemic hyperinsulinemia, ending 90 min prior to ischemia.

Summary of Results: Contractile function (regional work) was similar in both groups at baseline and declined to a similar extent in both groups during ischemia. Myocardial FFA utilization was greater in Met Syn than in control. Recovery of contractile function at 120 min reperfusion was significantly lower in Met Syn (21±12% of baseline) compared to controls (61±13% of baseline, p=0.01). We investigated whether Met Syn altered the activation of stress kinases by ischemia. ERK was activated by ischemia/reperfusion to a similar degree in both groups. Akt was activated by ischemia in controls; however, in Met Syn Akt phosphorylation was higher in non-ischemic myocardium compared with controls, and no activation occurred with ischemia/reperfusion. The experiments with the additional pigs allowed plasma insulin levels and Akt activity to normalize before ischemia, but plasma FFA concentration and myocardial FFA utilization remained persistently low throughout ischemia and reperfusion.

Conclusions: Pigs with characteristics of Met Syn exhibit poor contractile recovery after myocardial ischemia. Tonic activation of Akt and a shift in substrate preference for FFA may be contributing factors. Pre-ischemic exposure to insulin, resulting in restricted FFA availability, improves contractile recovery of Met Syn hearts.

31 CHARACTERIZATION AND THERAPEUTIC POTENTIAL OF INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOVASCULAR PROGENITOR CELLS


Purpose of Study: Cardiovascular progenitor cells (CPCs) have been identified within the developing mouse heart by expression of the transcription factors Nkx2.5 and Isil. Detailed study of endogenous CPCs has been limited due to the lack of specific cell-surface markers needed to isolate them and the absence of suitable conditions to expand them in vitro. We sought to identify specific cell-surface markers to label endogenous embryonic Isil+ CPCs and functionally validate these CPC markers in induced pluripotent stem cell (iPSC)-derived Isil+ progenitors. Furthermore, we developed conditions that would allow for the propagation and characterization of these CPCs and protocols for their clonal expansion in vitro and transplantation in vivo.

Methods Used: Total RNA from CPCs was isolated (Qiagen RNeasy), amplified (Illumina RNA Amplification kit) and gene expression quantified using Illumina microarrays. Fluorescence Activated Cell Sorter at the UCLA Core Flow Cytometry Laboratory was used to quantify Flt1+/Flt4+ cells. Differentiation was assessed by PCR and immunostaining for a panel of cardiovascular markers.

Summary of Results: To identify cell surface markers for the isolation of CPCs from iPSCs, we analyzed the transcriptome of Isil+ CPCs. This analysis of Isil+/Flt1+ mouse CPCs identified a panel of surface markers expressed on Isil+ CPCs. Comparison of these markers revealed that the combination of Flt1+/Flt4+ best identified and facilitated the purification of Isil+ CPCs from embryonic hearts as well as differentiating iPSCs. To investigate their in vivo potential to differentiate into cardiomyocytes (CM), Flt1+/Flt4+ cells were isolated from GEP+ cardiac iPSCs, maintained in prosurvival media and transplanted into strain-matched hearts. Three-weeks post-CPC transplantation, hearts were harvested and immunofluorescence imaging demonstrated robust engraftment and differentiation into mature adult CMs in vivo.

Conclusions: We have demonstrated that the combination of cell surface markers Flt1 and Flt4 specifically identify an Isil+ CPC with trilineage cardiovascular potential in vitro and robust ability for engraftment and differentiation into CMs in vivo post transplantation.

32 INTRAPARTUM GROWTH RESTRICTION ALTERS PPAR GAMMA EXPRESSION IN THE RAT HEART IN A GENDER AND MODEL SPECIFIC MANNER


Purpose of Study: Intrapartum growth restriction (IUGR) impairs postnatal cardiovascular health. Cardiac hypertrophy occurs in multiple animal
CAVEOLIN-1, A STRUCTURAL PROTEIN COMPONENT OF CAVEOLAE, REGULATES MEMBRANE OXYGEN

Levy K², Agrawal S¹, Finley J¹, Fridolfsson HN¹, Ali SS¹, Patel HH¹,¹ Vitamin San Diego Healthcare System, La Jolla, CA and ²University of California San Diego, La Jolla, CA.

Purpose of Study: Caveolae are key to protection of cardiac myocytes from ischemic damage (Patel 2006). Based on preliminary data, we hypothesize that caveolins, structural proteins critical for caveolae formation, enhance the oxygen-storage capacity of caveolae/plasma membrane. This study evaluates whether Cav-1 facilitates the storage of oxygen in the plasma membrane.

Methods Used: HT29 human colon cancer cells do not express caveolin and thus serve as an ideal tool to determine the impact of caveolin re-expression on membrane oxygen. Three specific HT29-Cav-1 stable lines were generated: Cav-1 targeted to the plasma membrane, Cav-1 targeted to the mitochondria, and Cav-1 expressed globally. HT29 cells with an empty vector served as control.

Western blots were used to quantify Cav-1 protein and five mitochondrial respiratory complexes in these cells. Live cells were also placed in an Oxigraph system to measure ambient free oxygen concentrations in the presence and absence of various detergents.

Cells from each line were also exposed to anoxic conditions using mineral oil layering for 16, 16 and 24 hours respectively, followed by assessment of hypoxia inducible factor (HIF-1-alpha) and caspase 3 expression.

Summary of Results: All cells expressing caveolin had a robust expression of Cav-1, and immunohistochemical staining confirmed sub-cellular localization. Cells expressing caveolin showed elevated mitochondrial respiratory components, with the largest effect observed in the mitochondrial targeted Cav-1. Oxigraph showed a 3-fold increase in oxygen release from Cav-1 expressing HT29 cells upon membrane solubilization with digitonin compared to the empty vector control indicative of enhanced membrane storage of oxygen.

We were unable to stress the cells with anoxia enough to produce a HIF-1-alpha response; however, there was a qualitative reduction in cleaved caspase 3 in the membrane-targeted Cav-1 expressing cells compared to the controls suggestive of stress adaptation.

Conclusions: Our data suggest that Cav-1 may facilitate oxygen storage in the cell and attenuate the negative effects from hypoxia-induced damage, including a decreased expression of apoptotic factors compared to the controls thus providing a novel control point for stress adaptation.

A NOVEL ANIMAL MODEL OF PEDIATRIC HEART FAILURE

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Purpose of Study: Treatment of heart failure (HF) with β-adrenergic receptor (β-AR) antagonists or beta-blockers (BB) is beneficial in adults, but not in children. In both populations HF is driven by excessive catecholamine stimulation. The mechanisms underlying the age related differences in clinical response are unknown. It is known that the β-AR profile is different in children and adults with HF. The current pharmacological paradigm for treatment of HF doesn’t consider phenotypic differences between adults and children with HF. Moreover, doing mechanistic studies in children is difficult. We developed a mouse model of pediatric HF and determined the effect of selective and non-selective BB. We hypothesized that isoproterenol (ISO) treatment of young mice is an appropriate model as β-AR selective but not nonselective BB would be effective in young mice.

Methods Used: Young (4 week) and old (4 month) FVB mice were treated (all in mg/kg/day) for 1 week with ISO (30), or vehicle with or without BB (metoprolol (300), carvedilol (30)). Young mice were also studied with or without nebivolol (10) or bisoprolol (2.5). At the time of sacrifice morphological data was collected and phospholamban (PLB) phosphorylation was determined by Western blot.

Summary of Results: ISO produced cardiac hypertrophy in young (~17%, p<0.05) and old mice (~21%, p<0.05). PLB phosphorylation (Theonine 17; Vehicle vs. ISO) was decreased with ISO in old (0.82±0.13 vs. 0.28±0.079 P<0.05) but unchanged with ISO in young mice (0.94±0.11 vs. 0.76±0.16 P<0.05). Hypertrophy (HW/BW ratio; ISO vs. ISO+BB) was blunted in the old mice to both selective (metoprolol, 4.95±0.16 vs. 4.55±0.14) and nonselective (carvedilol, 4.41±0.15 vs. 4.75±0.18) BB.
nonselective BB (carvedilol, 4.8±0.16 vs. 4.2±0.08) (both P<0.05). In contrast, hyper trophy was blunted by selective BB in the young (metoprolol, 5.6±0.07 vs. 5.6±0.12; nebivolol, 6.1±0.12 vs. 5.7±0.07; bisoprolol, 6.3±0.18 vs. 5.6±0.15; all P>0.05) but not non-selective BB (carvedilol, 5.73±0.18 vs. 5.55±0.14).

Conclusions: ISO treatment in young and old mice produces a similar PLB profile to that in children and adults with HF. Similar to human pediatric HF, nonselective BB is ineffective at blunting ISO mediated cardiac pathology. In contrast, selective BB therapy is effective at blunting cardiace pathology in young mice. These data suggest that selective BB therapy may be efficacious in children with HF.

36 EFFECT OF ANTI-INFLAMMATORY PEPTIDE J ON CIRCULATING MARKERS OF INFLAMMATION IN A MOUSE MODEL OF ATHEROSCLEROSIS

Okhovat J, Vakili L, Shahibehzadi M, Safarpour S, Haghnejad M, Vazirian S, Habibagahi S. David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: In populations there is a strong inverse relation between HDL levels and coronary heart disease (CHD). Over the past three decades, the use of statins has significantly reduced the incidence of CHD. A large percentage of patients however, still present with CHD and need treatments reducing the coronary artery disease risk in them. Several peptides have been designed that sequester inflammatory molecules and reduce vascular complications in preclinical studies. Anti-inflammatory peptide J (AIPJ) is one example. We have previously demonstrated that in animal models of CHD the AIPJ can reduce atherosclerotic lesions. In the current investigation we sought to study the effect of the AIPJ on serum amyloid A, a well-accepted inflammatory marker in plasma.

Methods Used: Female LDL receptor deficient mice, groups of ten each were maintained on high fat, high cholesterol diet (Western Diet) for 8 weeks. Group 1 received normal chow diet; Group 2, Western diet alone; Group 3, Western diet supplemented with AIPJ. After 8 weeks, fasting blood was removed, plasma separated and serum amyloid A was determined using a commercially available kit.

Summary of Results: Administration of the AIPJ reduced the circulating serum amyloid A levels (p<0.01) as compared with the administration of the Western diet without the added peptide.

Conclusions: In animals that received the anti-inflammatory peptide J, the removal of oxidized lipid by the peptide likely affected several oxidative reaction cascades and covered pathways that are involved in the induction of inflammatory molecules such as serum amyloid A. It would be useful to determine if the effect is on the liver, via the macrophages or on other tissues and cell types. The current observation might have therapeutic implications and be useful in reducing vascular inflammation in hyperlipemia.

Endocrinology and Metabolism 1
Concurrent Session
1:15 PM
Thursday, January 26, 2012

37 A CASE OF STERNOCOSTOCLAVICULAR HYPEROSTOSIS INITIALLY DIAGNOSED AS PAGET’S DISEASE OF BONE

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Case Report: A 59 year old woman with Graves’ disease and microscopic polyangiitis with optic neuritis was incidentally found to have abnormal clavicles on chest x-ray. The clavicles were noted to be expandable with thickening of trabeculae and an area of lytic change in the medial aspect. A whole-body bone scan showed increased activity diffusely in the clavicles, sternum, and skull. Biochemical data revealed elevated alkaline phosphatase levels with normal calcium and PTH. Paget’s disease was suspected, however, bisphosphonate therapy was not administered due to significant dental disease. Additionally, given the atypical bone involvement further imaging and biochemical testing was performed. CT scan of the head showed diffuse thickening of the calvarium but no lytic lesions. CT scan of the chest revealed symmetric hyperostotic changes of the clavicles, sternum, and first ribs. In addition, fusion of the clavicle to the sternum and acromion was seen bilaterally. MRI of the lumbar spine revealed flowing bridging anterior marginal osteophytes extending from L2-S2 which was suggestive of diffuse idiopathic skeletal hyperostosis. SSEP was negative for M-component and a bone specific alkaline phosphatase was normal. A diagnosis of sternocostoclavicular hyperostosis with spinal involvement was made given the constellation of radiographic findings.

Sternocostoclavicular hyperostosis is a clinical entity characterized by endosteal and periosteal bone formation and proliferation of fibrous tissue that is partially destructive with subsequent ossification occurring in the clavicles and sternum. Case studies have revealed extrasternal sites in some patients, involving the acromioclavicular joint, vertebral column, and pelvis. Alkaline phosphatase levels are typically normal or minimally increased. This clinical entity has also been associated with skin manifestations, particularly gustation of the palms and soles. Conversely, Paget’s disease of bone is a focal disorder of bone remodeling that leads to accelerated rates of bone turnover and, thus elevated alkaline phosphatase levels. It typically involves just one bone or a few bones, primarily the sacrum, spine, femur, skull and/or pelvis.

The clinical manifestations and treatment of Paget’s disease and sternocostoclavicular hyperostosis will be reviewed.

38 TERTIARY HYPERPARATHYROIDISM IN A PATIENT WITH X-LINKED HYPOPHOSPHATEMIC RICKETS

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Case Report: The most common form of hereditary hypophosphatemic rickets is X-linked hypophosphatemic rickets (XLH), caused by a genetic mutation in the phosphate regulating endopeptidase on the X chromosome (PHEX) gene. The mutation results in renal phosphate wasting, likely mediated by increased circulating levels of FGF23, and impaired bone mineralization. Treatment consists of phosphorus supplementation and calcitriol. These treatments are associated with development secondary hyperparathyroidism (HPT) and nephrocalcinosis due to hypercalcemia. Tertiary HPT rarely develops in patients with longstanding uncontrolled secondary HPT.

We present a case of XLH with recurrent tertiary HPT. A 22-year-old female with XLH, history of brown tumors and chronic renal insufficiency was referred for hypercalcemia. She was diagnosed early in life with XLH and had two parathyroidectomies at an outside facility. In 2009, she was evaluated at UNM for brown tumors and was found to have significantly elevated PTH levels. She underwent bilateral inferior parathyroid gland removal and auto-transplantation into the right forearm. Post op course was complicated by acute renal injury presumed due to intraoperative hypotension, hyperkalemia and hypercalcemia felt to be secondary to hungry bone syndrome. She was stabilized on calcitriol 1mcg BID and 4 gm elemental calcium. At follow up in the spring of 2010, PTH was 63 pg/ml and calcium 9.1 mg/dl. In early 2011 she developed hypercalcemia with a calcium level of 14 mg/dl requiring discontinuation of both calcium and calcitriol supplements. At return visit, calcium was 10.8 mg/dl, PTH 116 pg/ml with normal albumin. Following five minutes of occlusion of right arm venous return using a blood pressure cuff, calcium level was 10.0 mg/dl and PTH was 22 pg/ml localizing source of PTH to the implant. Tc-99m Sestamibi showed no enlarged or hyperfunctioning parathyroid gland in the neck, mediastinum or right forearm, but did note diffuse physiologic muscaric activity in the forearm. This case demonstrates the rare complication of tertiary HPT in a patient with XLH. We will review mechanisms and literature relevant to the diagnosis, complications and management of tertiary HPT in XLH.

39 UNDETECTABLE URINARY CALCIUM IN TWO PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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Case Report: Primary hyperparathyroidism (PHPT) is characterized by autonomous production of parathyroid hormone (PTH) and hypercalcemia or high normal serum calcium levels in the presence of elevated or inappropriately normal serum PTH concentrations. Diagnosis of PHPT is made with biochemical testing, including serum PTH, calcium, phosphate, and 25-hydroxyvitamin D (25-OH-D) levels, as well as a 24 hour urine calcium and creatinine. A low 24 hour urine calcium helps distinguish the diagnosis of PHPT from Familial Hypocalciuric Hypercalcemia (FHH). This distinction is important as a parathyroidectomist is not indicated in FHH.

We present two unique cases of PHPT in which urinary calcium was undetectable. The first case is a 58 year-old female with calcium levels of 9.3–10.6 mg/dL, elevated PTH levels (most recent 115 pg/dL) and normal 25-OH-D levels. A TC-99m sestamibi parathyroid scan showed a left parathyroid adenoma. Fine needle aspiration of the suspected left parathyroid adenoma was done at the time of evaluation of a thyroid nodule. PTH level in the aspirate was 12,500 pg/mL. A 24 hour urine calcium was 225 mg with a creatinine of 700mg. Fractional excretion of calcium was 0.029, consistent with PHPT. A more recent 24 hour urine showed undetectable levels of urinary calcium with a creatinine of 1200 mg.

The second case is a 72 year-old female with a history of hypercalcemia, PHPT, and sarcoidosis, not felt to be the cause of her hypercalcemia (normal 1.25-(OH)2-D level). Calcium has ranged from 10.2–11.4 mg/dL. PTH has ranged from 101-204 pg/dL. A TC-99m sestamibi parathyroid scan showed a right posterior parathyroid adenoma. In 2008, a 24 hour urinary calcium was 140mg. A collection in July 2011 showed undetectable levels. In August 2011, the 24 hour urinary calcium was 94 mg. Fractional excretion of calcium was 0.009, which is suspicious for FHH in a patient with a parathyroid adenoma.

These two cases demonstrate undetectable urinary calcium excretion in patients with primary hyperparathyroidism. We review the diagnosis of PHPT, strategies to differentiate it from FHH and the etiologies and mechanisms of low or undetectable urinary calcium.

40 IS WRIST CIRCUMFERENCE A PREDICTOR OF METABOLIC SYNDROME?
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Purpose of Study: Metabolic syndrome (MetS) is characterized by elevated triglycerides and fasting glucose levels, increased waist circumference, high blood pressure, and low HDL levels. MetS criteria are associated with insulin resistance and cardiovascular disease. Wrist circumference has been shown to be positively correlated with insulin resistance. In contrast, brown adipose tissue (BAT) is associated with decreased insulin resistance and improved cardiovascular health. Our objective is to determine: 1) if larger wrist circumference is predictive of MetS; and 2) if a smaller wrist circumference is associated with the presence of BAT.

Methods Used: We measured wrist and waist circumferences, weight, height, blood pressure, fasting serum glucose, triglycerides, and HDL, in males and females, aged 27–79 years who were undergoing clinical FDG-PET/CT. Wrist circumference was measured at Lister’s tubercle (posterior distal radius) in both wrists using a fiberglass tape measure. The maximum wrist size per participant was used in analysis. FDG-PET/CT scans were used to determine the presence of BAT. Independent t-tests were used to assess the relationship between wrist circumference and MetS and wrist circumference and the presence of BAT.

Summary of Results: Of 36 participants (21 male and 15 female) 14 had MetS (11 male and 3 female). The mean age of the MetS group (61.5±9.8 years) did not differ from the non-MetS group (56.3±12.4 years). Wrist circumference for males with MetS was larger than those without MetS (18.6±1.22 vs. 17.64±0.90cm, p<0.05). Wrist circumference for females with MetS was not different from those without MetS (15.77±0.42 vs. 15.83±1.42 cm). Only 1 participant had metabolically active BAT. Data collection is ongoing.

Conclusions: Wrist circumference is predictive of MetS in adult males. Failure to detect a difference in wrist circumference in females may be due to the small numbers with (n=3) and without (n=12) MetS. Only 1 participant had BAT, thus we were unable to determine if wrist circumference is associated with BAT.

41 PREVALENCE OF LOW HDL AND ITS ASSOCIATION WITH BMI IN A NON-DIABETIC VA POPULATION
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Purpose of Study: Low HDL value is an independent predictor of cardiovascular disease (CVD). Recent evidence suggests the association between CVD and elevated triglycerides (TG). However, the contribution from low HDL with co-existing high TG is not well studied. We determined the prevalence of isolated low HDL (<40mg/dl; TG<150mg/dl) and low HDL with elevated TG (>150mg/dl) in a VA population, its association with BMI and other lipid components, including total cholesterol (TC) and LDL.

Methods Used: A retrospective review was conducted on 10107 non-diabetic patients at VACHCS. Patients were divided into three groups: 1) normal HDL (40mg/dl) and normal TG (<150mg/dl), 2) isolated low HDL with normal TG, and 3) low HDL with high TG. The mean BMI, lipid components and the TC/HDL and TG/HDL ratios were analyzed by ANOVA. T test of lipid profile was performed between those with/without anti-lipid agents.

Summary of Results: Mean values were: age 54.7 years; BMI 28.9; TC 186.8; LDL 108.2; HLD 42.4; TG 133.5; 98% males and 38% on anti-lipid medications.

BMI, lipid components and the ratios of TC/HDL and TG/HDL among three groups were shown in the table. 892 patients (8.8%) with normal HDL and elevated TG were excluded. Anti-lipid agents did not affect the lipid analysis.

Conclusions: There were more patients with isolated low HDL than those with low HDL and high TG in our non-diabetic population. Increasing BMI was significantly associated with both low HDL groups. This underscores the importance of weight reduction in non-diabetic population. Compared to normal group, the ratios of TC/HDL, a widely used CVD predictor, and TG/HDL, an indicator of dyslipidemia, were significantly higher in patients with low HDL, especially those with both low HDL and high TG. TC values were significantly different in normal HDL and low HDL groups, but did not correspond well to TG values. Therefore, we may add TG values when studying the impact of low HDL on CVD. Prospective studies in a more age and gender diverse population are warranted.

42 HYPERTRIGLYCEREMIA DURING PARENTERAL NUTRITION AND ITS RELATIONSHIP WITH BMI, VISCERAL FAT AND SUBCUTANEOUS FAT
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Purpose of Study: Hypertriglyceridemia is associated with abdominal obesity in free living individuals. In addition, hypertriglyceridemia has been associated with adverse outcomes in hospitalized patients receiving parenteral nutrition. This study was conducted to determine whether triglyceride concentration relates to BMI and body fat deposits in parenterally fed patients.

Methods Used: We measured triglyceride concentrations in very low BMI (VLBMI, ≤16 kg/m², n=44) and normal BMI (NBMI, 18.5–24.9 kg/m², n=74) patients receiving lipid-containing parenteral nutrition in order to determine whether VLBMI patients have lower triglyceride concentrations than NBMI patients. In addition, we performed single-slice CT (L2–L3) analysis for visceral and abdominal subcutaneous fat in a subset of VLBMI subjects who had abdominal CT scans available (n=56) to determine whether the cross-sectional area of these abdominal fat deposits and triglyceride tolerance. Patients receiving concurrent enteral nutrition, oral diet, or intravenous propofol infusion were excluded.

Summary of Results: BMI was 14.7 ± 0.1 in VLBMI and 22.0 ± 0.2 kg/m² in NBMI patients. Hypertriglyceridemia, defined as ≥150 mg/dL, was present in 24% of VLBMI and 35% of NBMI patients, with triglyceride concentrations of 131 ± 15 and 143 ± 9 mg/dL, respectively in the two groups (p = NS). Lipid infusion rates were 1.27 ± 0.08 and 1.17 ± 0.05 g·m³·h⁻¹ in VLBMI and NBMI patients, respectively.

* (P < 0.001 between normal HDL and low HDLs)
43 TESTOSTERONE REPLACEMENT THERAPY IN HYPOGONADAL MEN ALTERS THE HDL PROTEOME EFFLUX CAPACITY
Rubinow K1, Vaisar T1, Tang C1, Matsumoto A2, Heinecke J1, Page S3
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Purpose of Study: The effects of androgens on cardiovascular disease (CVD) risk in men remain unclear. Exogenous testosterone administration can decrease serum concentrations of high density lipoprotein-associated cholesterol (HDL-C), but low circulating androgen levels have been associated with increased CVD risk in men. To better characterize the relationship between androgens and HDL, we investigated the effects of testosterone replacement in hypogonadal men on HDL protein composition and cholesterol efflux capacity.

Methods Used: 27 older, hypogonadal men (baseline testosterone <9.7 nmol/L, ages 51–83) were administered replacement testosterone therapy (1% transdermal gel) to achieve physiologic serum levels (500–1000 ng/dL), with or without the 5α-reductase inhibitor dutasteride. At baseline and after 3 months of testosterone replacement, fasting lipids were measured, the protein cargo of HDL was determined, and HDL cholesterol efflux capacity was assessed.

Summary of Results: Testosterone replacement did not affect HDL-C concentrations but conferred significant changes in the HDL proteome, with an increase in HDL-associated PON1 and a decrease in apoA-IV evident after 3 months (p = 0.035 and p < 0.01, respectively, versus baseline). Exogenous testosterone did not alter the cholesterol efflux capacity of serum HDL. No differences were observed between men who received testosterone alone and those who received testosterone with dutasteride.

Conclusions: Testosterone replacement in older, hypogonadal men alters the proteome composition of HDL but does not significantly change HDL-mediated cholesterol efflux. The observed effects appear independent of testosterone conversion to dihydrotestosterone. Further research is needed to determine how changes in HDL protein content affect HDL function and CVD risk.

44 SIMVASTATIN DECREASES THE PERMEABILITY OF THE BLOOD RETINAL BARRIER BY ALTERATION OF ENDOTHELIAL JUNCTION PROTEIN EXPRESSION
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Purpose of Study: This study evaluates whether statin drugs decrease the permeability of the blood retinal barrier by altering the expression of endothelial junction proteins. The upregulation of occludin, VE-Cadherin and other endothelial junction proteins have been shown to strengthen the blood-retinal barrier.

Methods Used: In preparation for the study, type I diabetes was induced in C57BL6 mice with Streptozotocin. Both human retinal endothelial cells (HRECs) and diabetic mice were treated with simvastatin. The impacts of simvastatin on expression of endothelial junction proteins and vascular permeability were measured.

Summary of Results: We found that HRECs treated with 100nm to 500nm of statin produced a significant increase in occludin, a blood retinal barrier junctional protein (p<0.05). The mice given a dose of 0.025 mg/g of statin daily for two weeks demonstrated a significant decrease in retinal permeability (p<0.05).

Conclusions: These two experiments indicate that statin drugs may help prevent vascular leakage in the retina by increasing inter-endothelial tight junctions and adhesion.

45 INSULIN TIMING–A BENEFICIAL ADDITION TO INTENSIVE INSULIN THERAPY IN TYPE 1 DIABETES

Purpose of Study: The goal of insulin therapy in T1DM is to reduce A1C to < 7.0% with minimal hypoglycemia. This goal is often very difficult to achieve. We investigated the possibility that “insulin timing” would improve A1C without severe hypoglycemia. This approach is based on the concept of closely matching subcutaneous insulin absorption with meal induced glucose absorption to greatly reduce postprandial hyperglycemia.

Methods Used: Forty healthy adult volunteers with type 1 diabetes were randomly assigned for six months to one of two groups, a control group or an insulin timing group. The insulin timing algorithm altered the time when the meal dose of insulin was injected (MDI regimen) or infused (CSII regimen) from 30 minutes before the meal to 15 minutes after the meal depending upon the premeal blood glucose concentration. Fasting blood samples were drawn for A1C and other glucose parameters each month. Five day continuous glucose monitoring was also performed each month in each individual. All subjects were questioned at each monthly visit about the occurrence of serious hypoglycemia.

Summary of Results: As shown in the figure, by 5 months individuals in the insulin timing group decreased their A1C by 0.59% compared to the Control group which had a decrease by 0.05% (p<0.05). No severe hypoglycemia occurred in either group.

Conclusions: Insulin timing is a safe approach to improving A1C in individuals with type 1 diabetes. It is easy to learn, is associated with no additional cost to the individual, and does not increase the incidence of severe hypoglycemia. We recommend its addition to all intensive insulin therapy regimens.
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EFFECTS OF 3 MONTHS OF METFORMIN IN ADOLESCENTS WITH TYPE 1 DIABETES

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Purpose of Study: Cardiovascular disease (CVD) risk remains increased in type 1 diabetes (T1D), despite best efforts at reducing known CVD risk factors (glycemia, blood pressure and lipids). Insulin resistance (IR) is central to type 2 diabetes (T2D), and correlates with CVD in T2D. Using a hyperinsulinemic euglycemic clamp, we found also found significant IR in T1D youth relative to BMI-matched, nondiabetic controls. Improving this IR might decrease CVD risk in T1D.

Methods Used: We performed a 6 month double-blind, placebo controlled trial to assess the effect of the addition of the insulin sensitizer metformin (500 mg bid) in a group of 80 T1D adolescents. The metformin (M) and placebo (P) groups had similar initial baseline values for age: 15.9 vs. 16.0 yrs, T1D duration: 7.1 vs. 6.6 years, HbA1c: 9.6 vs. 9.5%, weight: 66 vs. 68.5 kg, BMI 23.5 vs. 24.8 kg/m2, respectively, all p ns.

Summary of Results: Preliminary data analysis was restricted to subjects who completed at least the screening and 3 month study visit. After 3 months, there were significant differences (p<0.05) between the M and P groups respectively in HbA1c: 8.7 vs. 9.4%, and weight: 64 vs. 70 kg. Insulin dose was unchanged in M females and was decreased by 10% in M males. HDL-C was also significantly higher in the M group (56.2 vs. 45.9 mg/dL).

Conclusions: Initial results from this study show that low dose metformin can improve short term glycemic control, BMI and HDL cholesterol in adolescent T1D youth with relatively poor glycemic control. In addition, the reduction in HbA1c with metformin was achieved with a similar or even lower insulin dose, suggesting that insulin sensitivity was improved. Using a higher metformin dose and including youth with better glucose control (i.e. more compliant subjects) might both lead to more pronounced effects. Further studies evaluating the efficacy of metformin and its effects on short-term markers of CVD in T1D youth and longer-term CVD outcomes are now needed.

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MANAGEMENT OF AN UNUSUAL CASE OF RECURRENT HYPOGLYCEMIA IN A PATIENT WITH TYPE 1 DIABETES MELLITUS

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Case Report: The development of circulating antibodies to exogenous insulin is common in patients with type 1 diabetes mellitus, though the impact on glycemic control remains controversial. While the neutralizing action of these antibodies on exogenous insulin has been demonstrated, clinical data have been conflicting in terms of clinical significance. We describe an unusual case of recurrent severe, unexplained hypoglycemia in a patient with long standing type 1 diabetes mellitus and hypoglycemia unawareness.

The patient, a 43 year-old female with Type 1 DM and depression, had numerous hospital admissions for severe hypoglycemia. Concerns regarding potential intentional overdosing with insulin by the patient prompted transfer to a mental health facility. Hypoglycemic episodes however continued. Historically the patient was treated with insulin glargine and lispro and described significant glycemnic lability with frequent unpredictable episodes of hypoglycemia, particularly worrisome given her lack of physiologic awareness. Laboratory investigation demonstrated normal renal function and adrenal function. A1c was 68.8%. C-peptide was undetectable. Insulin antibody titters were positive at 5.5 U/mL (reference range 0.0-0.4 U/mL). Total insulin levels were elevated at 61 uU/mL (reference range 3-19 uU/mL) though free insulin levels were only 2 uU/mL, indicating that 97% of her circulating insulin was bound by antibody. After persistent difficulties with managing her diabetes with atypical insulin regimens and continued frequent admissions to the hospital, she was subsequently treated with oral steroids and plasmapheresis followed by maintenance therapy with azathioprine. Repeat laboratory studies demonstrate that the majority of her circulating insulin is now unbound. Total insulin levels are 41 (reference range 3-19 uU/mL) with free insulin levels of 35 uU/mL. Remarkably, she is doing well clinically with no further hospitalizations or recurrent episodes of unexplained hypoglycemia. We review the impact of antibodies to exogenous insulin on glycemic control as well as a review of the literature in terms of management of such cases.

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THE EFFECT OF SIX MONTHS OF VITAMIN D SUPPLEMENTATION IN MINORITIES WITH PRE-DIABETES AND HYPOVITAMINOSIS D

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Purpose of Study: Low vitamin D levels, which are particularly common in minorities, are a risk factor for type 2 diabetes. This randomized control trial examined if high doses of vitamin D delayed the development of diabetes in minorities with both pre-diabetes and hypovitaminosis D.

Methods Used: 1551 Latinos and African-Americans over 39 years old with one or more of the following risk factors, central obesity (waist circumference in males ≥40 inches, females ≥35 inches), hypertension, diabetes in 1st degree relatives, were screened with A1C levels. Those with one or more of the following risk factors, central obesity (waist circumference in males ≥40 inches, females ≥35 inches), hypertension, diabetes in 1st degree relatives, were screened with A1C levels. Those with values 5.8-6.9% (study designed before A1C diagnosis of diabetes accepted) were invited for an OGTT. If FPG 110–125 mg/dl or 2-hour glucose 140–199 mg/dl and vitamin D level <30 ng/ml, subjects were randomized to receive weekly oral doses of placebo or vitamin D to achieve a serum level of 65-90 ng/ml. The dose was calculated as (100-baseline vitamin D) x weight x 6.3 = IU/week. When level ≥80 ng/dl, dose decreased by 20%, 50 received placebo and 55 received vitamin D.

Summary of Results: At 6 months, 34% and 49% of subjects receiving placebo and vitamin D, respectively, had reverted to NGT (P=0.12, chi square analysis) and 6% and 9%, respectively, had developed diabetes (P=0.55).

Conclusions: In conclusion, although there is a potential trend that vitamin D increased return of pre-diabetes to normal at 6 months, there is no significant difference between the 2 groups.

Results at 6 Months

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2-way repeated measures ANOVA. *P=0.32; †P=0.48
50 DE NOVO MICRODELETION OF XPI13 TARGETING THE MONOAMINE OXIDASE A AND B GENES IN A MALE INFANT WITH EPISODIC HYPTONIA: A GENOMICS APPROACH TO PERSONALIZED MEDICINE

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Purpose of Study: Monoamine oxidase A and B play key roles in deamining neurotransmitters, biogenic metabolites, and dietary amines. Patients deficient in one or both enzymes have distinct metabolic and neurologic profiles. MAOB deficient patients exhibit normal clinical characteristics and behavior, while MAOA deficient patients have borderline cognitive deficiency and impaired impulse control. Patients who lack both MAOA and MAOB tend to have the most extreme laboratory values (urine serotonin 3-4 times normal; urine dopamine 3-5 times normal; marked elevations in O-methylated amine metabolites and marked decreases in deaminated metabolites) in addition to severe mental deficiency and behavioral problems. Mice lacking monoamine oxidase B show increased proliferation of neural stem cells beginning in late gestation and persisting into adulthood. These mice show significantly increased monoamine levels, particularly serotonin, as well as anxiety-like behaviors as adults, suggesting that brain maturation in late embryonic development is adversely affected by increased serotonin levels.

Methods Used: We report the case of a male infant with a de novo Xp11.3 microdeletion targeting the MAOA and MAOB genes. The concentrations of monoamine substrates were measured in urine, serum, and CSF after dietary manipulation.

Summary of Results: This newly recognized X-linked disorder is characterized by severe cognitive deficiency and unusual episodes of hypotonia, which resemble absence seizures, but have no EEG correlate. A customized low tryamine diet was implemented in an attempt to normalize the monoamine profile of our patient.

Conclusions: Our study represents only the second recognized case of such a deletion and the first to treat this disorder through dietary manipulation. The use of serotonin synthesis inhibitors like p-chlorophenylalanine and p-ethylp-henylalanine could potentially be even more effective in lowering serotonin levels in the absence of monoamine oxidase enzymes.

51 IMPROVEMENT IN JOINT MANIFESTATIONS IN A PATIENT WITH MUCOPOLYSACCHARIDOsis TYPE 1 (MPS I) TREATED WITH ETANERCEPT

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Case Report: The purpose of this abstract is to present a patient recently diagnosed with MPS I who had improvement in her dysostosis multiplex symptoms during treatment with etanercept for a presumed diagnosis of Juvenile Rheumatoid Arthritis (JRA). KG is a 12 year old female who first presented to our genetics clinic at age 9. She had been diagnosed with Noonan syndrome previously, due to her cardiac valve abnormalities, short stature, and facial features. Sequencing of Noonan gene panel identified a variant in the SOS1 gene which was felt to confirm her diagnosis. At 7 years old she had decreased range of motion in her shoulders and stiffness in a number of other joints. This led to a diagnosis of JRA for which she was treated with etanercept. When she presented to our clinic we felt Noonan and JRA did not explain her phenotype. An arthritis survey was not consistent with her diagnoses. We also found that the patient’s unaffected mother carried the same SOS1 variant, now known to be a common Hispanic polymorphism. KG was lost to follow up with genetics for 2 years during which time she developed bilateral knee contractures and worsening claw deformity of her hands. Her mother discontinued etanercept, but when KG began experiencing pain and inflammation in her knees, it was restarted. KG subsequently had significant improvement in these symptoms as well as improved range of motion. When she represented, she’d developed coarsening of her facial features, and hepatomegaly. These new features suggested a storage disorder and MPS type I was confirmed through enzymatic and molecular testing. MPS I is a prototypic lysosomal storage disease with a spectrum of disease severity. Current treatment for MPS I includes enzyme replacement therapy, hematopoietic stem cell transplantation, physical therapy, surgery for contractures and decompression for nerve entrapments. Animal studies suggest that storage of dermatan sulfate, an endotoxin-like molecule, in MPS incites an inflammatory response via the tumor necrosis factor pathway. Etanercept is a competitive inhibitor of TNF-α. To our knowledge, Etanercept has never been reported as being used to treat skeletal manifestations of MPS I. The benefit to our patient with etanercept suggests a new area of treatment for MPS associated dysostosis multiplex.

52 CLONING AND CHARACTERIZATION OF AGXT (ALANINE GLYOXYLATE AMINOTRANSFERASE) GENE PROMOTER

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Purpose of Study: Primary hyperoxaluria type 1 is a rare autosomal-recessive disorder caused by abnormal activity of the liver specific enzyme, peroxisomal alanine glyoxylate aminotransferase (AGT). The AGT enzyme acts as a catalyst in the transamination (detoxification) of glyoxylate to glycine. Without functioning AGT, glyoxylate is converted into oxalate. Oxalate is renally excreted and in high concentrations will form insoluble calcium salts that deposit into the kidneys as well as other tissues. With an AGT deficiency, nephrolithiasis and/or nephrocalcinosis (renal parenchymal calcification) can occur resulting in oxaluria (extra-renal oxalate deposition) and end-stage renal disease (ESRD). When kidneys are compromised, plasma oxalate levels dramatically increase leading to the deposition of oxalate in many body tissues with severe consequences. Dialysis often fails to control the hyperoxalemia and these patients eventually die.

Methods Used: The goal of this study is to understand how the AGT gene promoter is regulated by generating fragmented AGT Promoter-Luciferase plasmid constructs and analyze their relative transcriptional contribution by measuring luciferase activity. This method will be used to identify critical transcription factors and their binding sites within the AGXT promoter which are involved in AGXT regulation.

Summary of Results: Presently there is no corrective therapy available to PH-1 patients. Even in patients that receive renal transplantation, outcomes are poor as the transplanted kidneys are rapidly damaged by the high oxalate load. At present, a combined liver and kidney transplant are needed for these patients, but quality of life as well as survival are poor. Yet, despite the poor outcome, only small progress has been made towards toward effective treatments.

Conclusions: Lastly, by understanding how the AGXT promoter is regulated, these studies may help identify subsets of patients with promoter dysfunction and may lead to future therapeutic strategies.

53 AQUADYNIA - FIRST REPORT OF FAMILIAL OCCURRENCE

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Case Report: Aquadynia is a rare phenomenon characterized by cutaneous pain associated with exposure to water. In contrast to aquagenic pruritus, aquagenic wrinkling and aquagenic urticaria, there are no observable changes to the skin or distinctive findings on skin biopsy. Seven cases of aquadynia currently exist in the literature. Here we report aquadynia in a mother and son. To our knowledge, this family represents the first reported instance of aquadynia in two related individuals.

A 16-year-old male was referred to dysmorphology clinic with the complaint of burning, stinging pain when his skin came into contact with water. The pain develops within minutes of contact with water, and is most severe on the extremities, but involves the entire body including the scalp. These symptoms were first noted around the age of 8 years, and initially occurred almost always after contact with water. The pain is not associated with urticaria or observable skin changes. If he wraps himself in a blanket following bathing, the sensation diminishes slightly. The pain resolves spontaneously in about 30 minutes. As his athletic activities have increased, he has noted that the painful sensation can occur in response to his own perspiration. In the last 1-2 years, the symptoms have abated and are estimated to occur only 25% of the time upon exposure to water. Non-steroidal
anti-inflammatory medications, loratadine and cetirizine failed to relieve symptoms. Follicular papules on the patient’s anterior neck and a nevus on his left lower leg were biopsied and found to be benign unrelated to the aquadynia. Currently, he is not taking any medications.

The patient’s mother also reports pain with skin exposure to water that began in adolescence and periodically occurs, though not as consistently as in the past. The symptoms seem more likely to occur in cold weather, but are not affected by water temperature. The mother’s family is originally from Michoacan, Mexico. To her knowledge, no other family members have these or similar symptoms, including her parents, her three sisters, and the patient’s two siblings, sister age 12 and brother age 3.

Of our 35 cases of arthrogryposis, 1/3 had obvious asymmetry and proximal limb contracture involvement which resolved rapidly, 1/3 had mild asymmetry and lack of rapid resolution, and 1/3 appeared to have not been affected by the uterine structural anomaly.

Conclusions: With a background rate of 2% – 3% uterine anomalies among pregnant women, our data suggest that bicornuate uterus is usually an incidental finding (1.5% of our cases) in the mothers of arthrogryposis cases rather than the cause of arthrogryposis. None of the 35 cases had severe involvement suggesting that maternal uterine anomaly is rarely if ever the primary cause of arthrogryposis.

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A RETROSPECTIVE STUDY OF INFANTS WITH SUSPECTED VERY LONG-CHAIN ACYL-ACOA DEHYDROGENASE DEFICIENCY ON NEWBORN SCREENING
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Purpose of Study: The Western States Regional Genetics Services Collaborative is a federally funded multi-state project that seeks to coordinate and increase access to genetic services. A workgroup was created to study the outcomes of infants who are at risk to be affected with very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) based on retrospective screen positive newborn screen (NBS) results. VLCADD is a fatty acid oxidation disorder presenting with cardiomyopathy, hypoketotic hypoglycemia, or rhabdomyolysis. Following the introduction of NBS to include VLCADD a large number of newborns have been identified with elevations of C14:1-acylcarnitine that were found to be false positive or asymptomatic.

Methods Used: Detection of VLCADD on NBS is performed through detection of elevations of C14:1-acylcarnitine along with elevations of C12-, C14-, C16-acylcarnitines and related analyte ratios. We performed a retrospective analysis of newborns screened in California, Oregon, Washington, and Hawaii from July 2005 through 2009. Data was de-identified following IRB-review and included data from the NBS card and limited diagnostic testing. Cases were defined as true positive (TP), true positive asymptomatic (ATP), heterozygote (Het), false positive (FP), other alternative diagnosis (OTH), or lost to follow-up (LOST) from information reported by clinicians.

Summary of Results: Overall from 2.8 million children screened there were 242 cases screen positive for VLCADD. There were 52 TP cases of which 14 were ATP, 55 Het, 112 FP, 11 LOST, and 12 OTH. There were no observed differences in average age at collection and birth weight. Male infants were more commonly found in the FP or Het groups. Only 79 cases reported DNA testing, 9 reported fatty-acid oxidation probe studies, and 30 reported acylcarnitine profiles. Comparison of C14:1 demonstrated a separation between TP and ATP groups with other groups at 1.0 um.

Conclusions: This study is the largest currently reported follow-up of infants with NBS positive for suspected VLCADD reported to date. This information serves as a foundation for further analysis and development of long-term clinical follow-up studies.

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BICORNUATE UTERUS CAUSES ARTHROGRYPOSIS - AN URBAN LEGEND DISPelled
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Purpose of Study: Determine if uterine abnormalities cause of worsen secondary to uterine malformation leading to fetal constraint. Their presenting case died of pulmonary hypoplasia with severe asymmetric deformations while all the other cases showed restoration toward normal form relatively rapidly postnatally (theoretically when constrain was removed).
Methods Used: We report the phenotypic classification and genetic testing evaluation of a cohort of 20 patients with autism and macrocephaly seen at the UCLA Medical Genetics Clinic over the past 4 years.

Summary of Results: In this cohort, 25% (5) have confirmed mutations of PTEN, 50% associated with extreme macrocephaly (>3SD). We further expand the genetic etiologies for autism cases associated with macrocephaly by describing three novel genetic variations in the PTEN gene. Among the remaining 15 patients that lack PTEN mutations, our analysis identified two subgroups of patients with autism and macrocephaly. One group of patients (30%) presents with somatic overgrowth and the other group (45%) has disproportionate macrocephaly. Chromosomal microarray identified two CNVs in this cohort. These findings have prompted us to propose a diagnostic algorithm for the evaluation of patients who present with autism and macrocephaly.

Conclusions: We have defined two novel subgroups of autism for future study, one with somatic overgrowth and the other with disproportionate macrocephaly. We report a clinical yield of 25% from PTEN mutation analysis and a 6% yield from CMA testing in this cohort, which supports the current testing standards. In total, current testing modalities provide a 30% diagnostic yield in genetic testing within this autism subtype.

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FETUS WITH HYDROCEPHALUS AND MULTIPLE PTERYGIUM
Wilnai Y1, Vogel H2, Pham T3, Lopez G1, Enns G1, Stanford University, Stanford, CA; 2Stanford University, Stanford, CA, and 3Stanford University, Stanford, CA.

Case Report: Purpose of Study: This is one of the few reported cases of Fowler- type hydranencephaly, or prolificative vasculopathy and hydranencephaly-hydrocephaly (PVHH). In 1972 Fowler et al were the first to describe hydranencephalic-hydrocephalic syndrome with glomeruloid vasculopathy of the brain vessels and a fetal akinesia deformation sequence. We present a 15-week fetus showing severe bilateral ventriculomegaly, complete extension of lower extremities and abnormal curvature of the spine. Autosomal X-linked severe hydrocephalus, severe arthrogryposis and pterygia. Neuro pathological autopsy noted a proliferative vasculopathy affecting the CNS. Previous pregnancy was terminated by dilatation and evacuation at 21 weeks due to severe hydrocephalus and arthrogryposis.

Method used: Direct sequencing of the FLVCR2 gene. Review of electronic chart & medical literature.

Summary of Results: Our 15 week fetus showed severe hydranencephaly with fetal akinesia deformation sequence, as well as proliferative vasculopathy of the CNS in neuropathological exam. Molecular testing detected two heterozygous mutations in the FLVCR2 gene, the previously described c.473C>A, p.S158X and a novel mutation (c.1021-1G>GG) that likely causes the loss of the acceptor splice site of intron 4, resulting in non-functional FLVCR2 protein.

Conclusions: Fowler syndrome, is an autosomal-recessive prenatal lethal disorder characterized by hydranencephaly; glomeruloid vasculopathy of the central nervous system and retinal vessels, and a fetal akinesia deformation sequence with muscular neurogenic atrophy. Different germline mutations in the FLVCR2 gene are the molecular basis for Fowler syndrome. FLVCR2 encodes a transmembrane transporter of the major facilitator superfamily hypothesized to be involved in regulation of growth, calcium exchange, and homeostasis. Although the neuropathology is pathognomonic and can readily distinguish Fowler syndrome, the identification of germline mutations in FLVCR2 will enable genetic testing in suspected cases, carrier testing and earlier prenatal diagnosis, as well as provide a basis for determining the frequency and range of the phenotype of Fowler syndrome.

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A PATIENT WITH ATELOSTEOGENESIS TYPE I CAUSED BY A NOVEL MISSENSE MUTATION IN FLNB AND TRACHEAL HYPOPLASIA
Li B, Hogue J, Slavotinek A. UCSF, San Francisco, CA.

Purpose of Study: Atelosteogenesis (AO) type I is a rare disorder characterized by incomplete ossification of the thoracic spine, humeri and femora and caused by mutations in Filamin B (FLNB). AO type I has been described as lethal, with all reported cases being stillborn or unable to survive the neonatal period. Pulmonary hypoplasia, laryngeal stenosis and instability of the cervical spine have been reported as causes of mortality. We report a male infant with AO type I with a novel FLNB mutation and severe tracheal hypoplasia in order to describe postnatal events that can occur with AO type I.

Methods Used: We tabulated the clinical features of this proband and the other children with AO type I reported in the medical literature.

Summary of Results: The child was born by Cesarean section at 27 weeks gestation with a birth weight of 1,030 grams (50th centile) and length of 31 cm (<3rd centile). He had hypoplasia, hypertelorism, downslanting palpebral fissures, cleft palate and retromicrognathia. His skeletal findings comprised rhizomelic shortening, limited extension of the elbows and knees, a pectus excavatum, dislocated hips, bilateral talipes equinovarus, severe brachydactyly for fingers 3-5 and short and broad thumbs. A skeletal survey revealed shortening of the humeri, angulated clavicles, hypoplasia of the pelvis and spine and absent fibulae. Clinical testing for FLNB mutations showed p.Gly181Asp, a novel mutation in FLNB that was located in the CH2 domain and consistent with AO type I. This child had respiratory failure from birth that required mechanical ventilation and increasing ventilatory support and he was deceased at 3 months age from complications of tracheal hypoplasia. Our literature review revealed one other child with AO type I who had significant tracheal hypoplasia and who had support withdrawn on day 3 of life.

Conclusions: The clinical course of this child was influenced by severe tracheal hypoplasia that complicated intubation and prevented separation from ventilator support. Tracheal hypoplasia should therefore be added to the respiratory causes of mortality in AO type I.

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17Q12 DELETION AND RISK FOR MULTIORGAN SYSTEM DISEASE
Krishnamurthi S, Miyamoto J, Slavotinek A, Shieh J University of California San Francisco, San Francisco, CA.

Purpose of Study: Individuals with 17q12 deletion have overlapping features with maturity-onset diabetes of the young (MODY) type 5 given the common involvement of HNF1B, but there is increasing recognition of developmental abnormalities that accompany 17q12 deletion. Here we examine and expand the phenotype of 17q12 deletion by reporting several classic features of this disorder in a patient and parent and by describing skeletal involvement as a previously unreported feature, to our knowledge. We also compare genes typically affected by 17q12 deletion to our results using genome-wide array.

Methods Used: We review all studies on 17q12 deletion to date and compare the index case phenotype. To examine a potential genetic basis for disease in the described family, we performed 102K CGH microarray analysis (ISCA v2 clinical design) and compared this to pooled reference. Regions of copy number variation were compared with annotated copy number variation to determine polymorphic versus potentially unique variation.

Summary of Results: CGH analysis revealed a deletion of 1.426 Mb. These clinical presentation and findings add further emphasis to the developmental disability that can characterize 17q12 deletion and add the unique feature of rib abnormalities. We also describe severe peripheral nervous system and hepatic manifestations that are severe and these should be further investigated.

Conclusions: 17q12 deletion includes a spectrum of features involving multiple systems that can include the pancreas, kidneys, brain and liver. We describe that developmental abnormalities including skeletal abnormalities seen in our patient as associated with this condition, and this may lend additional insight into disease pathophysiology. We also emphasize that cognitive developmental problems may complicate management of progressive disease, and we should strive for early detection and multidisciplinary care.

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C. ELEGANS AS A GENETIC MODEL OF HYPOXIC INJURY
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Purpose of Study: The nematode caenorhabditis elegans represents a powerful animal model for the elucidation of novel gene activities. To date, however, the study of the genetic basis for the hypoxic response in c. elegans
has been limited by the organism's remarkable tolerance for extended periods of anoxia. Recently, we discovered that osmotic stress significantly sensitizes C. elegans to anoxia. Because osmotic stress is tightly linked to clinical hypoxic injury, "anisotonic anoxia" represents the most clinically relevant model of hypoxic injury in C. elegans to date.

Methods Used: For all experiments, osmotic stress ("anisotonicity") was achieved by varying the concentration of NaCl in the nematode culture medium. Survival was scored after 24 h exposure to a 100% nitrogen atmosphere. A genome-wide screen for enhanced survival in hypotonic anoxia was performed on F2 progeny from an EMS-mutagenized population. Additionally, several mutant strains with known alterations in glucose metabolism and osmotic balance were assayed for anoxia survival in hypotonic and hypertonic conditions.

Summary of Results: Out of a cohort of 227 primary screen survivors, 5 mutants screened as possessing increased survival relative to wild type. Genetic mapping of these mutants is ongoing. Strains osn-7, osn-11 and dpy-10, which have constitutively elevated intracellular glycerol levels, are resistant to hypertonic anoxia but sensitive to hypotonic anoxia. Both glucose soaking and starvation rescues wild type animals from hypotonic anoxia death. The daf-2 strain, which lacks a functional insulin/IGF1 receptor and is known to be generally stress-resistant, exhibits partial resistance to hypotonic anoxia. Most interestingly, aquaporin-null strains exhibited varied survival in hypotonic anoxia, ranging from significant resistance (aqp-2 and aqp-4) to sensitivity (aqp-9).

Conclusions: "Anisotonic anoxia" in C. elegans represents a novel and potentially clinically relevant model of hypoxic injury. From the results above, survival in this model is clearly dependent on both bioenergetics and water balance. However, the divergent survival phenotypes observed in the aqp strains suggests that the aquaporins are not functionally redundant as was previously thought.

62 TESTING THE MULTISTAGE MODEL OF CARCINOGENESIS REVEALS EVIDENCE OF ONE MUTATION FOR SYNOVIAL SARCOMA AND TWO MUTATIONS FOR ACUTE PROMYELOCYTIC LEUKEMIA

Purpose of Study: To test the multistage model of carcinogenesis with the incidence data obtained from the Surveillance, Epidemiology, and End Results (SEER) registries (1973–2007), in synovial sarcoma (SS) and acute promyelocytic leukemia (APL), both of which are defined by a single genetic aberration.

Methods: Used: A total of 1772 SS cases and 2439 APL cases were diagnosed in 17 SEER registry regions from 1973 to 2007. A single rate-limiting mutation for SS was assumed to explain the relatively constant incidence rate throughout adulthood for SS. Based on this hypothesis, the expected number of SS cases in each age group of adults was obtained by applying the age-specific and age-adjusted SS incidence rates for adults in the 15 to 79 year old age range to the corresponding Year 2000 U.S. Standard Population for those age groups. A statistical test for heterogeneity was used to determine if there were significant differences between the observed and the expected SS cases. Since a relatively straight line with a positive slope on a normal plot for the APL incidence rate was observed, a two rate-limiting mutation model was suggested and a linear regression line was fit to the data to further evaluate this. Parameters of both slope and intercept were estimated by the least squares approach, and the correlation coefficient (R) and R2 were calculated. Analysis of variance (ANOVA) was utilized to test for the significance of linear regression. This significant linear regression line was then used to calculate the expected incidence rate for each age group. Next, the expected APL cases within each age group were computed by applying the corresponding Year 2000 U.S. Standard Population to the expected incidence rate.

Summary of Results: By analyzing the SEER data, we show that a single rate-limiting mutation can best explain a constant incidence rate for SS (p = 0.29). On the other hand, analyzing the APL incidence rates from the SEER data under the two hits model of carcinogenesis reveals a significant linear regression line (p = 0). 95% of the variation in APL incidence can be explained by age.

Conclusions: By applying the multistage model of carcinogenesis to the incidence data obtained from the SEER registries, we find strong evidence of one rate-limiting mutation for SS and two rate-limiting mutations for APL.

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Thursday, January 26, 2012

63 PATIENT PERCEPTION OF MEDICAL PROFESSIONALISM: A COMPARISON IN DIFFERENT CLINICAL SETTINGS
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Purpose of Study: Medical professionalism is one of six core competency requirements of the ACGME, yet defining, and therefore teaching its principles remains a challenge. The "social contract" between physician and community is clearly central to professionalism; therefore determining the patient’s understanding of the physician's role in the patient-doctor relationship is important. The objective of this study is to determine if patients have different conceptions of professionalism when considering physicians in different clinical environments.

Methods Used: Patients and those accompanying them were surveyed in the waiting room of an emergency and an outpatient internal medicine clinic and a pre-operative/anesthesia clinic. The survey contained 18 professional attributes, drawn from the American Board of Internal Medicine's 8 characteristics of professionalism. Participants were asked to rate, on a 10-point scale, the importance that a physician possess each attribute. ANOVA analysis was used to compare the sites for each question.

Summary of Results: Of 604 who took the survey, 200 were in the emergency department, 202 were in the medicine clinic, and 202 were in the pre-operative clinic. Patients comprised 61% of the group (39% were accompanying friends and family) and 56% were female. The average age was 49 with a range from 18 to 94. There was a significant difference on the attribute of "providing a portion of work for those who cannot pay;" this was rated higher in the emergency department (p = 0.03). There was near-significance (p = .05) on the attribute of “being able to make difficult decisions under pressure,” which was rated higher in the pre-op clinic. There was no difference for any of the other questions. The top four professional attributes at each clinical site were the same - “honesty,” “excellence in communication and listening,” “taking full responsibility for mistakes,” and “technical competence/skill;” the bottom two were “being an active leader in the community” and “patient concerns should come before a doctor's family commitments.”

Conclusions: Very few differences between clinical sites were found when surveying patient perception of the important elements of medical professionalism. This may suggest a core set of values desired by patients for physicians across specialties.

64 A TEN-YEAR REVIEW OF CLINICAL ETHICS CONSULTATIONS AND THEIR LONG-TERM FOLLOW-UP
McDearmon S, Orr R. Loma Linda University School of Medicine, Loma Linda, CA.

Purpose of Study: Clinical ethics is a growing field, and it has become an integral part of the curriculum at many medical schools. There is, however, a need to understand what the major issues are that students will face - to help ensure ethics education prepares student doctors to the greatest extent possible. Previous studies have attempted to accomplish this by examining all the cases in a specific time period, often one or two years. This approach has limited the applicability of the results because of small sample sizes and a short time span.

Methods Used: In this study clinical ethics consults requested and performed at the Loma Linda University Medical Center in Loma Linda, CA, between the years of 1990 and 2000 were assessed on an individual basis. Each of the over 900 consults was categorized based on the underlying topic being addressed. In addition, demographic data was collected regarding patient age, patient gender, patient ethnicity, requesting service, and requesting party to help determine possible trends in these areas. Finally, consults without complete follow-up (as to the outcome of the case and further complications) were tagged for medical record review. All of this data was organized into pie and bar graphs to help with visualization and analysis of the most commonly requested topics.
Summary of Results: It was determined that these topics included suffering/quality of life (21% of consults), uncertainty (19%), and conflicts of opinion (15%).

Conclusions: While it is important for medical students to understand the basic ethical principles behind a wide variety of issues, this information will make it possible to guide future medical student education - focusing on ensuring students have a strong foundation in the issues they are most likely to face on a day-to-day basis.

65 EVALUATION OF CAPACITY FOR INTERNATIONAL PATIENT CARE AT BC CHILDREN'S HOSPITAL
Rasmussen D1,2, Duffy D3,4, O'Hara N2,3, Chen S2, Masterson J3,1, Gandhi S2,3,1, University of British Columbia, Vancouver, BC, Canada; and BC Children's Hospital, Vancouver, BC, Canada.

Purpose of Study: While low-and-middle-income-countries develop medical infrastructure and human resources (HR), international patient programs (IPPs) in high-resource countries can provide children battling complex conditions with life-saving surgical procedures not offered in their home countries. BC Children's Hospital (BCCH) routinely receives requests to deliver care to patients from low-income families overseas. Yet, little has been done to assess our capacity to do so. We are consulting with the BCCH community and BC patient families, analyzing infrastructure data and interviewing leadership staff and provincial health authorities in a multi-phase project to provide a comprehensive assessment of capacity for an IPP at BCCH. A BCCH online survey has generated early results.

Methods Used: We designed an online survey to record respondents' demographics, identify HR support, and collect perspectives on global health commitment and capacity for an IPP at BCCH. The survey included Likert-based agree/disagree, ranking and essay-style questions. An online survey email invitation was distributed to clinical staff (n = 2039) with 2 weekly reminders. Quantitative responses were analyzed by employment demographics. Responses to essay-style questions were reported as part of a narrative.

Summary of Results: There were 226 respondents (74 physicians, 59 nurses, 53 allied health, 14 administration and 26 other). In total, 80% of all respondents agree that BCCH should play a role in the care of international patients (6% disagree, 14% neutral) and 47% of all respondents agree that BCCH currently has the capacity for an IPP (29% disagree, 24% neutral). To provide care for international patients, respondents indicate that BCCH must increase social support (80%), language services (78%), cross-cultural care (69%), operating room time (67%) and HR (62%). Compromising care to BC residents is the issue of greatest concern, followed by workload- and medicolegal-insurance- issues.

Conclusions: Early results suggest that staff would support an IPP at BCCH with specific provisions: Capacity for an IPP must be improved in the identified areas and the care provided to BC residents must not be compromised; an IPP must not place excessive demands on staff or generate medicolegal/insurance issues.

66 A LONGITUDINAL STUDY OF MEDICAL STUDENTS' MALPRACTICE FEAR AND DEFENSIVE MEDICINE: A "HIDDEN CURRICULUM"?
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Purpose of Study: To characterize medical students' exposure to defensive medicine (DM) and development of malpractice concern (MC) during third and fourth year clinical rotations.

Methods Used: Using a questionnaire consisting of 31 Likert-type scale questions, we performed a prospective, longitudinal (June 2008 to May 2010) study of third and fourth year medical students. Additionally, students logged DM comments and practices that they observed during their clinical rotations.

Summary of Results: At the beginning of their third year 102 students (MS3s) and at the end of their fourth year 59 graduating students (MS4s) were evaluated. Most MS3s and MS4s stated that they rarely worried about being sued as students: 85.3% (95% CI = 77.1% to 90.9%) and 81.4% (95% CI = 69.6% to 89.3%), respectively. Few students worried about practicing and learning procedures because of MC: 16.7% (95% CI = 10.7% to 22.1%) and 16.9% (95% CI = 9.5% to 28.5%), respectively. However, most students believed that their satisfaction as physicians would be decreased by concerns about malpractice and lawsuits: 51.0% (95% CI = 41.4% to 60.5%) and 55.9% (95% CI = 43.3% to 67.8%). Most students felt that faculty they had worked with were concerned about malpractice: 55.9% (95% CI = 46.2% to 65.1%) and 55.9% (95% CI = 43.3% to 67.8%), respectively; 32.4% (95% CI = 24.1% to 41.9%) of MS3s and 44.1% (95% CI = 32.2% to 56.7%) of MS4s felt that faculty taught defensive medicine, especially in emergency medicine (25.5%), obstetrics/gynecology (21.8%), and surgery (21.5%). Fifty-six students logged episodes of DM during their clinical rotations, of which 70.7% were of the attending physician, 24.4% were of resident physicians, and 4.9% were of nurses.

Conclusions: Although third and fourth year medical students have little concern about being sued, they are exposed to and taught a considerable amount of MC and DM from faculty during clinical rotations, especially in obstetrics/gynecology, emergency medicine and surgery. Students worry more when they have patients who have sued physicians, and most students believe that fear of lawsuits will decrease their future enjoyment of the practice of medicine.

67 NURSING EMPLOYMENT STRUCTURE IN UGANDA
Zomorodian L1, Luboga S2, Herrera SJ1, Kamwita KA2, Hagopian A1, University of Washington, Seattle, WA; and 1Makerere University, Kampala, Uganda.

Purpose of Study: The shortage of healthcare professionals, particularly nurses, in Uganda is an obstacle to achieving the Millennium Development Goals, especially since nurses make up the majority of the workforce. In the past decade, this deficit has been addressed by changes to nursing curriculum and a general increase in the number of nursing schools. With these changes, there exists an unclear structuring of employment levels of nurses, given the additional levels of education. Our purpose was to examine current employment structure among various nursing cadres, and to identify areas where employment suffered most.

Methods Used: Six graduate students from Makerere University and the University of Washington performed a cross sectional mixed methods study in June-July 2011, consisting of 34 in-depth interviews and 5 student focus groups. The in-depth interviews asked 9 administrators and 25 professors about curriculum changes, teaching methods and their students' leadership preparation, prospective job opportunities, and reasons for going into nursing. We also conducted 5 focus groups of 6 to 10 nursing students to evaluate general student experiences, challenges, and potential career paths. We analyzed verbatim transcripts to identify major themes, and compared themes of in-depth interviews with those of focus groups.

Summary of Results: We identified 3 themes related to employment in the Ugandan nursing workforce. First, an increase in education (eg. an upgrade from certificate to diploma), is not necessarily associated with an increase in salary scale. Second, the job prospects after completion of certain programs—particularly a Bachelors in Nursing Science and a certificate in Enrolled Comprehensive Nursing (ECN)—seem poor to students, who observe a lack of any apparent employment schemes for either of those qualifications. Third, administrators and faculty report sentiments that students from ECN programs are underprepared or incapable of providing adequate care to patients.

Conclusions: Changes in nursing education in Uganda in the past decade have not been met with proportional changes to the employment structure. Both students and educators feel that program graduates will struggle to find employment after graduation, even though there remains a clear need for additional nurses in Uganda.

68 SPECIALTY, GEOGRAPHIC, AND PRACTICE DISTRIBUTION OF BUPRENORPHINE PROVIDERS IN WASHINGTON STATE
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Purpose of Study: The amount of opioids prescribed for chronic pain has increased rapidly over the last two decades, a trend accompanied by opioid misuse, abuse, and addiction. Buprenorphine Management Therapy (BMT) has demonstrated effectiveness as a treatment modality for opioid addiction, and is especially useful in rural areas where Methadone Maintenance Therapy (MMT) is rarely available. The goal of this study is to determine the specialty,
VIRTUAL PROBLEM-BASED LEARNING ASSESSMENT EXAMINING TRADITIONAL VERSUS PROBLEM-BASED LEARNING (PBL) AND THE INTEREST IN VIRTUAL LEARNING AS PART OF THE PBL EXPERIENCE.

Purpose of Study: The University of British Columbia has an increased need for flexibility in undergraduate medicine. Flexibility in curriculum can be created using virtual learning. This is a needs assessment of traditional problem-based learning (PBL) and the interest in virtual learning as part of the PBL experience.

Methods Used: This is a qualitative and quantitative study utilizing focus groups and an electronic survey of first and second year medical students at UBC. The data from the focus groups was analyzed using constant comparative analysis to identify themes and codes. These themes were then used to determine questions for the electronic survey. Quantitative survey data was analyzed using a Chi-square test.

Summary of Results: Two focus groups of 1st and 2nd year students were undertaken to identify themes associated with traditional versus virtual PBL learning. The dominant theme from 1st and 2nd year focus groups was concern over the loss of life-skills acquired during face-to-face PBL. The second most prevalent theme identified was the benefit of flexibility and convenience associated with virtual PBL learning. 73% of 1st year and 17% of 2nd year students responded to the electronic survey. 59% of 1st year and 43% of 2nd year students felt that face-to-face interaction of PBL was “critically” or “strongly important” (p < 0.005). 29% of 1st year and 61% of 2nd year students wanted a hybrid of both virtual and traditional PBL (p < 0.005). 17% of 1st year students and 36% of 2nd year students felt that the addition of virtual PBL would be most beneficial during the 2nd undergraduate year (p < 0.005). 66% of 1st year students did not want virtual PBL as part of their undergraduate curriculum.

Conclusions: 1st year students were more strongly guarded than 2nd year students about using virtual PBL. Both groups felt it could be complementary in 2nd year. Respondents felt that a “hybrid” of a virtual and face-to-face experience later in 2nd year training would allow students to benefit from flexibility and convenience provided by virtual learning.

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CHANGES IN NURSING EDUCATION IN UGANDA SINCE 2005

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Purpose of Study: A well-trained and motivated stock of health workers sufficient in numbers and distribution is necessary for health systems development. In Africa, especially Uganda, educating and training nurses is key to the nation’s unmet health needs and health system improvements. Interest in improving nursing education in Uganda has grown, as nations attempt to meet the Millennium Development Goals. Little is known about the number, character, and status of nursing education in African nations. The purpose of this study is to identify and examine changes in Uganda’s nursing education, specifically admissions, curriculum, faculty, and teaching methods since 2005.

Methods Used: Six graduate students, three from the University of Washington in Seattle and three from Makerere University in Kampala, conducted a cross-sectional mixed methods study at six Ugandan nursing schools in the summer of 2011. We conducted 34 in-depth interviews on the issues of changes in curriculum and teaching methods, research activities, and student leadership preparation. Participants included 9 deans, academic heads, and principals and 25 professors. We conducted 5 focus groups with six to ten nursing students to assess student experiences and motivations. Analysis of transcripts identified major themes, comparing and contrasting patterns within and between interviews and focus groups. For quantitative data we collected registrar reports and strategic plans detailing the number of enrolled and graduated students and staffing levels from 2005 to 2011.

Summary of Results: We identified 11 themes related to changes in nursing education: workforce, infrastructure, departmental autonomy, funding from global health initiatives, institutional collaborations, nursing structure cadre, admissions programs offered, teaching and assessment methods, student leadership preparation, and community immersion. Overall, there has been an upward trend in the number of applicants at all institutions, however, the number of professors did not increase proportionately.

Conclusions: Changes in Ugandan nursing schools reflect the country’s effort to produce a more robust workforce to improve health through improvements in student and professor training and support, infrastructure, and use of evidence-based teaching and assessment methods.
72 FEMALE MEDICAL STUDENT PERSPECTIVES ON THEIR PROFESSIONAL INTERACTIONS WITH FEMALE PHYSICIANS
Lubliner E1,2, George S1, Hayes-Bautista DE2 1Charles Drew University, Los Angeles, CA; and 2UCLA, Los Angeles, CA.
Purpose of Study: This exploratory study attempts to fill the research gap on female medical student perspectives, varied by race, on their gendered professional relationships with higher-ranking female physicians. With an increasing “feminization” of medicine and a continued lack of minority representation, this research seeks to examine the quality of medical education for female medical students, particularly minority women. By identifying facilitating factors and barriers to communication amongst women, strategies will be proposed for improved communication. Facilitating positive interactions between women early in their training will likely improve the retention and advancement of female and minority female physicians.
Methods Used: Using a modified Grounded Theory approach, this qualitative research uses in-depth interviews with a purposeful sample of 18 female medical students (6 White, 6 African-American, 6 Latina). After transcription, open coding was performed and data was examined line-by-line for potential themes. Subsequently, a few selected transcripts were reviewed by another investigator to ensure agreement on the final analysis.
Summary of Results: Preliminary data suggests that relationships between female medical students and female physicians are affected by rank, specialty, and gender differences. Overall, interactions between female students and female attendings were positive; whereas interactions with female residents varied. While participants were asked about all specialties, they consistently mentioned OB/GYN and surgery as having the most challenging gendered interactions. Facilitators for successful interactions included: finding common ground as women, increased mentorship, and acceptance of differences. Barriers included: competition, higher expectations of women, and a culture of hierarchy.
Conclusions: The continued underrepresentation of women and minorities in academia significantly impacts the quality of their medical education and consideration to pursue academic medicine. Notably, there is an absence of “community” between women in medicine. By designing interventions addressing gender issues between women and the lack of diversity in academic medicine, medical schools can ensure a physician workforce equipped to care for a diverse patient population, effective teamwork, and improved patient care.

73 THE JOINT COMMISSION CLINICAL ASTHMA CARE MEASURES AND HOSPITALIZATION OUTCOMES
Fassl B1, Nkoy F1, Stone B1, Uchida D1, Maloney C1 1University of Utah, Salt Lake City, UT; and 2Intermountain PCMC, Salt Lake City, UT.
Purpose of Study: The Joint Commission (TJC) introduced 3 Children’s Asthma Care (CAC 1-3) core measures to improve the quality of pediatric inpatient asthma care. Little data exists regarding the impact on asthma outcomes. Objectives of this study are to examine changes in 1) provider compliance with CAC 1-3 measures and 2) asthma hospitalization outcomes following implementation of a pediatric asthma care process model (CPM).
Methods Used: We used a Quality Improvement study design. We included children age 2–17 years admitted between 1/1/2005 and 12/31/2010 with a primary discharge diagnosis of asthma. We implemented a pediatric asthma CPM designed to standardize inpatient asthma care and to support compliance with CAC measures. The study was divided into 3 periods: 1) pre-implementation (1/1/2005 to 12/31/2007), 2) CPM implementation (1/1/2008 to 3/31/2009) and 3) post-implementation (04/01/2009 to 12/31/2010). We measured changes in provider compliance with TJC-CAC measures 1–3 and associated changes in hospitalization outcomes including death, pediatric intensive care unit transfer, length of stay, costs, resource utilization, and asthma readmission to either an emergency department or hospital within 6 months of hospital discharge. Logistic regression analysis controlling for age, sex, race, insurance type and intervention period was used to evaluate changes in compliance and outcomes following CPM implementation.
Summary of Results: 1865 children were admitted for acute asthma. Compliance with TJC measures pre- and post-CPM implementation were 99% vs.100% for CAC-1; 100% vs.100% for CAC-2 and 0% vs. 87% for CAC-3 (p < 0.01). Increased compliance with the CAC-3 measure was associated with a sustained decrease in 6 months hospital asthma readmissions from 24% (p < 17% pre- to 12% post-implementation). No change in other outcomes was observed.
Conclusions: Implementation of the asthma CPM was associated with improved compliance with CAC-3 and with a delayed but significant and sustained decrease in hospital asthma readmission rates. This the first study to report a significant and sustained reduction in asthma readmissions after introduction of the TJC inpatient asthma care core measures.

74 MEDICAL ASSISTANTS’ PERCEIVED ROLES AND PREFERRED TRAINING METHODS IN COMMUNITY HEALTH CLINICS
Chon CY, Tu S 1University of Washington, Seattle, WA.
Purpose of Study: Medical Assistants (MAs) raise the quality of patient care in ambulatory settings. Despite MAs’ significance in team-based primary care models, such as the Patient-Centered Medical Home (PCMH), not much is published on their training or their needs. This study examines MAs’ perceived roles and preferred on-site training, in particular in the context of culturally and linguistically diverse patient populations.
Methods Used: Two focus groups were held at two community health clinics. MAs were interviewed (n = 19; 52% report spending ≥75% of time with limited English proficient (LEP) patients). The moderator guide was based on the Jenkins Tetrahedral model, which shows that interrelationships among learning goals, learner characteristics, and materials determine the appropriate training strategy. Based on the coding and analysis of interviewed transcripts, themes related to MAs’ roles and training emerged.
Summary of Results: MAs Roles and Needs: MAs who see themselves as communication liaisons want huddle time with providers to increase team effectiveness. They also want acknowledgment for their efforts from the staff. MAs as Educators: MAs working with LEP patients prefer simple explanations, demonstrations, visual aids and translated materials. Specific Training Requested: Language is the key barrier to care. More language, cultural and interpersonal communications training is needed. Preferred Training Methods: Demonstrations, shadowing, webinars, refreshers, courses, and resource-based learning. Hands-on strategy is effective for skills training, updating knowledge, and bridging the gap between academic and clinical experience. Firsthand learning increases MAs’ sense of responsibility and importance in the team. Least Effective Training Methods: Lecture-style talks, pressure-driven learning, and authoritative teaching.
Conclusions: Our exploratory study shows that MAs have a positive attitude toward training and favor participatory learning. To enhance MA roles and the success of PCMH, we recommend the Jenkins model for initial needs analysis at the individual level, acknowledging that it requires greater emphasis on community learning. We suggest training methods that can be tailored to clinic needs and the evolving experience of MAs, while emphasizing team-building skills.

75 CAPABILITIES AND REFERRAL PATTERNS OF HEALTH FACILITIES IN THE BIBIANI-ANHWIASO-BEKWAI DISTRICT IN RURAL GHANA
Han SH1,2, Rickard DH1 1UCLA David Geffen School of Medicine, Los Angeles, CA; and 2Charles Drew University, Los Angeles, CA.
Purpose of Study: While there exist studies on health care in Ghana at the district level, little is reported about smaller health facilities and resources available at these facilities. As these are the initial points of contact with health care for most people in rural Ghana, it is important to understand what resources are available and how cases become escalated to a hospital level.
Methods Used: Fifteen of the 21 public and private health facilities in the Bibiani-Anhwiaso-Bekwai (BAB) District were surveyed over a 2-week period. Questionnaires were administered to a senior staff member at each of 3 hospitals, 3 health centres, 7 clinics, and 2 Community Health Planning Services (CHPS). Data was analyzed using MS Excel.
Summary of Results: Only hospitals have doctors on staff. The BAB district has approximately 3.4 physicians per 100,000 people, compared to 267 per 100,000 people in the USA. Nurses comprise 83% of health care delivery staff. Despite being a malaria endemic region, only 7 of 15 facilities surveyed had malaria test kits available. Most facilities must refer patients to
hospitals to obtain basic laboratory tests other than pregnancy and hemoglobin count. Referrals to hospitals are necessary for many non-basic treatments. The most common reasons for referrals were severe malaria, anemia, diarrhea, and delivery complications.

**Conclusions:** 1. Access to physicians is very limited and only in hospitals. Nurses comprise the majority of health care delivery staff. 2. Health centres, clinics, and CHPS have substantially less availability to resources than hospitals. 3. Most referrals beyond basic primary care are sent to the one publically owned hospital in the district.

**Summary of Results:** Cell viability assays were performed to increasing concentrations of PLX4032 and the MEK1/2 inhibitor, AZD6244. Protein expression levels of phospho-ERK, total ERK, PDGFRB, EGFR, and tubulin were evaluated by western blot. Triplicate qPCR reactions normalized to tubulin were used to determine relative RTK RNA expression levels. Secondary mutations were assessed using bi-directional sequencing of gDNA.

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**Summary of Results:** SKMEL28 and M263 PLX4032 resistant lines are also resistant to AZD6244 in cell viability assays. By qPCR, PDGFRB is upregulated in M263 PolyR (100×) and M263 R3 (>30×), SKMEL28 PolyR over-expresses EGFR (>100×), and both PDGFRB and EGFR are upregulated in SKMEL28 R1 (50× and 20×, respectively). These results are confirmed at the protein level by western blot. M263 and SKMEL28 cell lines do not have secondary mutations in N-RAS or C-Raf elevation, and upregulation of receptor tyrosine kinases (RTK) in alternative survival signaling. Here we seek to characterize how four patient derived melanoma cell lines, SKMEL28, M263, NK, and RP develop resistance to PLX4032.

**Purpose of Study:** ZELBORAF (Vemurafenib/PLX4032) was recently approved by the FDA for late stage metastatic melanoma in patients with V600E B-RAF mutations. While extremely effective, most patients eventually develop resistance to the drug. Hypotheses for resistance mechanisms to B-RAF inhibitors include secondary mutations in B-RAF, MAPK reactivation through secondary mutations in N-RAS or C-Raf elevation, and upregulation of receptor tyrosine kinases (RTK) in alternative survival signaling. Our results suggest that miR-9 targets of miR-9, we searched the computational algorithm TargetScan. We performed quantitative real time RT-qPCR, western blotting, and immunofluorescence to validate miR targets in: primary mouse cell lines overexpressing miR-9 generated from K15.KrasG12D.Smad4--/-.mice tumors and human head and neck SCC cell lines, Cal27 and FaDu. We assayed tumor growth in vivo by subcutaneous injection of tumor cell lines in the flank of immunocompetent mice. We determined chemoresistance-signaling by a transcriptional luciferase assay and a small inhibitory RNA (siRNA) screen.

**Summary of Results:** miR-9 targets the adherence junction tumor suppressors α-catenin and E-cadherin in mouse and human head and neck SCC cell lines respectively. Injection of overexpressing miR-9 mouse tumor cells in vivo resulted in the development of highly metastatic SCC in mice. Consistently, knockdown of miR-9 in vivo resulted in muted tumor growth and inhibited metastasis. Significantly, other groups have demonstrated that decreased α-catenin and E-cadherin levels correlate with tumor grade and metastatic status in human SCC. Mouse cells overexpressing miR-9 had increased expression of the Apc/Cbeta1, a chemoresistance gene, and were resistant to Docetaxel induced cell death. Docetaxel increased the transcriptional response of the pro-survival signaling pathway nuclear factor-kappa B (NFκB) in a dose-dependent manner with higher reporter activity in miR-9 over-expressing cells. siRNA inhibition of β-catenin abrogated Apc/Cbeta1 expression.

**Conclusions:** Our results suggest that miR-9 is an oncogenic microRNA in skin SCC and involved in metastasis and chemoresistance.

**References:**

1. Access to physicians is very limited and only in hospitals.
2. Health centres, clinics, and CHPS have substantially less availability to resources than hospitals.
3. Most referrals beyond basic primary care are sent to the one publically owned hospital in the district.

**Journal of Investigative Medicine • Volume 60, Number 1, January 2012 Western Regional Meeting Abstracts**

**76 MECHANISMS OF RESISTANCE TO THE B-RAF INHIBITOR ZELBORAF IN FOUR MELANOMA CELL LINES**

Garg E1, Kong X2, Shi H2, Moriceau G2,1,3,4,1 David Geffen School of Medicine at UCLA, Los Angeles, CA; 1David Geffen School of Medicine at UCLA, Los Angeles, CA; 2David Geffen School of Medicine at UCLA, Los Angeles, CA; 3David Geffen School of Medicine at UCLA, Los Angeles, CA; and 4David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** ZELBORAF (Vemurafenib/PLX4032) was recently approved by the FDA for late stage metastatic melanoma in patients with V600E B-RAF mutations. While extremely effective, most patients eventually develop resistance to the drug. Hypotheses for resistance mechanisms to B-RAF inhibitors include secondary mutations in B-RAF, MAPK reactivation through secondary mutations in N-RAS or C-Raf elevation, and upregulation of receptor tyrosine kinases (RTK) in alternative survival signaling. Our results suggest that miR-9 targets of miR-9, we searched the computational algorithm TargetScan. We performed quantitative real time RT-qPCR, western blotting, and immunofluorescence to validate miR targets in: primary mouse cell lines overexpressing miR-9 generated from K15.KrasG12D.Smad4--/-.mice tumors and human head and neck SCC cell lines, Cal27 and FaDu. We assayed tumor growth in vivo by subcutaneous injection of tumor cell lines in the flank of immunocompetent mice. We determined chemoresistance-signaling by a transcriptional luciferase assay and a small inhibitory RNA (siRNA) screen.

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**Conclusions:** Our results suggest that miR-9 is an oncogenic microRNA in skin SCC and involved in metastasis and chemoresistance.

**Hematology and Oncology I Concurrent Session**

**1:30 PM Thursday, January 26, 2012**

**77 MIR-9, A TUMOR SUPPRESSOR MICRONRNA, TARGETS ADHERING JUNCTION PROTEINS RESULTING IN SKIN SQUAMOUS CELL CARCINOMA: IMPLICATIONS FOR METASTASIS AND CHEMORESISTANCE**

Reddi A, White R, Wang X University of Colorado, School of Medicine, Denver, CO.

**Purpose of Study:** Squamous cell carcinoma (SCC) is the second most common form of skin cancer. MicroRNAs (miRs), small noncoding RNAs that suppress gene expression by targeting miRNA, have emerged as potential regulators of tumor-initiating cells (TICs). In a mouse model of SCC, initiated by Kras activation and Smad4 loss, we identified miR-9 as a marker of the TIC “side population.” miR-9 expression, in our model, was associated with highly metastatic passed tumors and chemoresistance. In the present study we investigated tumor suppressor targets of miR-9 that mediate SCC oncogenesis.

**Methods Used:** To determine SCC tumor suppressor targets of miR-9, we searched the computational algorithm TargetScan. We performed quantitative real time RT-qPCR, western blotting, and immunofluorescence to validate miR targets in: primary mouse cell lines overexpressing miR-9 generated from K15.KrasG12D.Smad4--/-.mice tumors and human head and neck SCC cell lines, Cal27 and FaDu. We assayed tumor growth in vivo by subcutaneous injection of tumor cell lines in the flank of immunocompetent mice. We determined chemoresistance-signaling by a transcriptional luciferase assay and a small inhibitory RNA (siRNA) screen.

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**Conclusions:** Our results suggest that miR-9 is an oncogenic microRNA in skin SCC and involved in metastasis and chemoresistance.
these cancer genomes also possessed a mutation in mismatch repair gene MSH6, suggesting a potential mechanism for hypermutation.

Conclusion(s): Our results suggest that AII may regulate mSHMT via cMyc/p53 mediated signaling. These findings indicate that mSHMT expression and thereby, may provide rationale for developing inhibitors of DNA-damaging therapy, and is synthetically lethal to BRCA2-deficient cancer cells. 3E10 therefore has potential as a targeted agent selective for cancer cells deficient in DNA repair, which is relevant to numerous human malignancies. 3E10 is distinct from all antibodies currently approved for cancer therapy, and the application of a cell-penetrating anti-DNA antibody to the treatment of cancer represents a completely new paradigm in antibody-based cancer therapy.

81 THE ROLE OF COXSAKIE-ADENOVIRUS RECEPTOR AS A SENESCENCE BIOMARKER DURING RECTAL CANCER TREATMENT

Grobman LE1, Wu DY1,2, Dong DZ2, Wu PC1,2 University of Washington, Seattle, WA; and 3VA Puget Sound, Seattle, WA.

Purpose of Study: The treatment of human cancer with chemotherapy has been associated with therapy-induced cellular senescence (TCS), whereby tumor cells enter a transitional state of cell-cycle arrest or senescence. The majority of cells progress to cell death, but a subset reenter the cell cycle to resume proliferation leading to cancer progression. Coxsackie adenovirus receptor (CAR) distinguishes these states in vitro, with high CAR expression in cells that can escape senescence, and low CAR expression in senescent cells destined for cell death. The purpose of this pilot study is to characterize in vivo CAR biomarker expression in rectal cancer patients undergoing combined modality therapy.

Methods Used: Pretreatment biopsy and surgical resection specimens were collected from 28 rectal cancer patients from an institutional tumor repository including 16 treated with preoperative (neo)adjuvant chemotherapy and 12 who underwent surgery alone. CAR expression was assayed by immunohistochemical (IHC) staining and scored on staining intensity (0 = no stain, 1 + = light stain, 2 + = moderate stain, 3 + = marked stain) in paraffin-embedded breast tumor tissue sections. Finally, pathway map was predicted for identified proteins by Gene Go software.

Conclusion(s): SHMT is a vital enzyme required for folate-mediated one carbon metabolism necessary for de novo purine biosynthesis. While the role of mSHMT has been reported in ovarian and breast cancer biology, it is not clear how this protein is regulated in tumor tissues. Our findings from breast cancer cell lines along with human tumor specimen, suggest that mSHMT may be used as a valid biomarker in breast tumor specimen with high arginase expression and thereby, may provide rationale for developing inhibitors of arginase for therapeutic purposes.

80 TARGETING CANCER WITH A CELL-PENETRATING ANTI-DNA ANTIBODY

Ji E1, Chan G2, Dalal S1, Geiger E1, Xu X1, Peterson-Roth E1, Liu Y1, Hegan DC1, Liu Y1, Sweasy JB1, Rockwell S1, Gera J2, Nishimura RN2, Weisbart RH2, Glazer PM1 1Yale University School of Medicine, New Haven, CT; and 2Veterans Affairs Greater Los Angeles Healthcare System, Sepulveda, CA.

Purpose of Study: 3E10 is a rare cell-penetrating anti-DNA antibody that has not previously been associated with any cytotoxicity. In testing 3E10 as a molecular delivery vehicle we unexpectedly discovered that 3E10 alone sensitizes cancer cells to DNA-damaging therapy. The purpose of this study was to explore this phenomenon and evaluate the utility of 3E10 in cancer therapy.

Methods Used: The impact of purified 3E10 or 3E10 Fv (single chain 3E10 variable fragment) on MCF-7, HeLa, U251, U87, or PEO1 (BRCA2+) breast cancer cells deficient in DNA-damaging therapy, and is synthetically lethal to BRCA2-deficient cancer cells. 3E10 therefore has potential as a targeted agent selective for cancer cells deficient in DNA repair, which is relevant to numerous human malignancies. 3E10 is distinct from all antibodies currently approved for cancer therapy, and the application of a cell-penetrating anti-DNA antibody to the treatment of cancer represents a completely new paradigm in antibody-based cancer therapy.

CONCLUSIONS: We have discovered that a rare cell-penetrating anti-DNA antibody, 3E10, impairs DNA-damaging therapy, and is synthetically lethal to BRCA2-deficient cancer cells. 3E10 therefore has potential as a targeted agent selective for cancer cells deficient in DNA repair, which is relevant to numerous human malignancies. 3E10 is distinct from all antibodies currently approved for cancer therapy, and the application of a cell-penetrating anti-DNA antibody to the treatment of cancer represents a completely new paradigm in antibody-based cancer therapy.

82 AURISTATIN DRUGS DECREASE LONG-TERM SURVIVIN LEVELS AND INDUCE APOPTOSIS IN HUMAN PANCREATIC CANCER (PANC-1) CELLS

Park JS1, Asuncion MM2, Aspe JRB3, Pettit GR2, Wall NR1 1Loma Linda University; Loma Linda, CA; 2Loma Linda University, Loma Linda, CA; 3Arizona State University, Tempe, AZ.

Purpose of Study: Recently, a class of drugs called Auristatins has been identified as potentially effective against pancreatic cancer. Current research has shown that aside from improved selectivity and killing, inducing apoptosis instead of necrosis and reducing cellular levels of Survivin, an exocytosed apoptosis inhibitor that enhances the survival of neighboring cancer cells, may also increase the overall efficacy of a chemotherapeutic
agent. Thus, we investigated whether Auristatins accomplished these functions when administered to human pancreatic cancer cells.

Methods Used: The human pancreatic cancer cell line PANC-1 was used. Dose-response curves were constructed via flow cytometry, using as the response the amount of G2/M cell cycle arrest 24 hours after treatment (Auristatin 15-PE (15-PE), Auristatin PYE (PYE), Auristatin TP (TP), and Auristatin 6AQ (6AQ)). The drugs were then administered at 500 μM and their effects were analyzed at 24, 48, and 72 hours against non-treated controls. Annexin-V flow cytometry was utilized to quantify viable cell numbers, necrosis, and apoptosis, and Western blots, to assay for Survivin levels.

Summary of Results: G2/M cell cycle arrest was demonstrated in about 60% of the cell population of each treatment sample by 24 hours, and a reduction in cell numbers and significant apoptotic activity was detected in all samples after 48 hours of treatment. Decreased levels of Survivin in cells treated with 15-PE or PYE and increased levels in samples treated with TP or 6AQ were detected at 24 hours. Increased Survivin levels were detected in all samples by 48 hours. After 72 hours, Survivin levels dipped below control levels in samples treated with 15-PE, PYE, and TP, but remained above control levels in cells treated with 6AQ.

Conclusions: While each drug tested reduced PANC-1 cell numbers via apoptosis, only Auristatins 15-PE, PYE, and TP repressed Survivin levels below control levels at 72 hours. Increased 24-hour Survivin levels induced by TP and 6AQ and increased 48-hour Survivin levels in all samples were most likely the results of a response to stress. Further studies correlating cell viability to Survivin levels are pending.

83
A POTENTIAL THERAPY FOR HIGH-RISK B-CELL LEUKEMIA: TARGETING HEALTH DISPARITIES IN HISPANIC CHILDREN

Martinez SR1, Bennett T2, Francis O2, Weldon D1, Payne KJ1,2,1Loma Linda University, Loma Linda, CA; 2Loma Linda University, Loma Linda, CA; and 3Loma Linda University, Loma Linda, CA.

Purpose of Study: Childhood high-risk B-cell acute lymphoblastic leukemia (B-ALL) can be classified into several subtypes based on genetic and functional anomalies. Chromosomal alterations resulting in over-expression of the CRLF2 protein have recently been associated with high-risk B-ALL and poor outcome. This defect occurs at a frequency that is five times higher in Hispanic children than others and is thus the most important biological component of childhood cancer health disparities identified to date. Normally, CRLF2 acts as a receptor component for the growth factor TSLP. The JAK2-STAT5 pathway is activated downstream of TSLP/CRLF2 interactions in normal cells. While there is speculation that TSLP may not be required for signals downstream of CRLF2 in B-ALL with deregulated CRLF2 (CRLF2d B-ALL), the activation status of the JAK2-STAT5 pathway in this disease remains to be elucidated.

Methods Used: We are conducting studies using flow cytometric analysis of two CRLF2d B-ALL cell lines to determine if TSLP activates the JAK2-STAT5 pathway leading to increased cell survival or proliferation. A related project in our laboratory is examining the ability of a natural product to inhibit TLSP-mediated-induced signals in normal B cells.

Summary of Results: Our preliminary data show that STAT5 phosphorylation is dependent on TLSP stimulation in the two CRLF2d B-ALL cell lines. Here we show that the natural product described above inhibits TLSP-mediated STAT5 phosphorylation in both CRLF2d B-ALL cell lines. Ongoing studies are examining the effect of TLSP on the survival and proliferation of CRLF2d cell lines and the ability of the natural product to inhibit the impact of TLSP on these activities.

Conclusions: These data show that STAT5 is not constitutively activated in two CRLF2d B-ALL cell lines, but rather is induced by TLSP. We also show that TLSP-induced STAT5 phosphorylation can be inhibited by a natural product and thus identify this product as a potential novel therapeutic agent for the treatment of high risk CRLF2d B-ALL that contributes to health disparities in Hispanic children.

84
FAR-RED FP-BASED TRIPLE MODALITY REPORTER FOR IN VIVO IMAGING

Felsen C, Whitney M, Yang J, Tsiens R UCSF, La Jolla, CA.

Purpose of Study: We report optimization of a triple modality reporter system that combines genes encoding a fluorescent protein (FP), luciferase enzyme (Luc), and thymidine kinase (Tk) for long-term, sensitive tracking of tumor growth in live animals by fluorescence, bioluminescence, and positron emission tomography, respectively.

Methods Used: Our triple reporters improve on previous designs by replacing GFP or mRFP1 with a further red FP for which fluorescence depth-attenuation is less than that of shorter wavelength FPs. We have included self-cleaving viral 2A sequences between each component to ensure equal initial stoichiometry of each reporter without creating a fusion protein. In selecting an optimal far-red FP, mPlum, mNeptune, E2-Crimson, and infrared FP (IFP) were compared for optical attenuation by overlaying tissue and brightness in tumor cells both with purified protein and identically constructed expression vectors that differed only in the identity of their FP.

Summary of Results: Although purified IFP had the lowest fluorescent signal attenuation with increasing depth, HT1080 cells stably expressing IFP were relatively dim in cell culture and xenografts. E2-crimson was the brightest FP as a single reporter in HT1080 cells by microscopy, FACS, and tumor epifluorescence. However, E2-Crimson, mPlum, and mNeptune had comparable brightness in the triple reporter for stable and transiently transfected cells. Overall, FP brightness in cell culture was lower in the triple reporters than in single and double reporters (FP+Luc or FP+Tk). Yet, luciferase activity of codon-optimized firefly luciferase Luc2 and truncated HSV-1 wtK were not significantly different between the double and triple reporter contexts. In subcutaneous xenografts of HT1080 and PC-3 cells stably expressing the E2-Crimson-Luc2-WtK reporter, ~500 cells could be reliably detected by bioluminescence and increased to ~2500 by far-red epifluorescence.

Conclusions: Though bioluminescence remains more sensitive than epifluorescence for macroscopic imaging, the new FPs have narrowed the gap and are essential for FACS, microscopy, and calibration of injectable optical probes. These multimodality reporters will optimize detection and sensitive, quantitative monitoring of tumor growth in vivo, for evaluation of non-genetic, injectable imaging agents for early tumor detection, fluorescence-guided surgery, and novel cancer therapeutics.

85
NOVEL MICROARRAY TECHNOLOGY DISCOVERS INI1 DELETIONS AND COPY NUMBER SIGNATURES THAT CORRELATE WITH CLINICAL OUTCOME IN EWING’S SARCOMA

Schiffman J1, Jahromi M1, Putnam A2, Wright J1, Spraker H1, Zhou H2, Randall RL1, Jones K1, Lessnick S1, University of Utah, Salt Lake City, UT; 2University of Utah, Salt Lake City, UT; and 3University of Utah, Salt Lake City, UT.

Purpose of Study: Ewing’s sarcoma (ES) is the second most common primary bone tumor, with dismal outcomes for metastasis or relapse. Less than 300 cases are diagnosed per year in the United States which makes biology studies difficult. Microarray technologies have improved the molecular understanding of many cancers, but have been minimally applied to ES. Novel approaches now permit microarray analysis of archived formalin-fixed paraffin-embedded (FFPE) samples, opening the door for genomic studies on rare tumors. Our goal was to analyze primary and metastatic tumors from ES patients, and to correlate copy number alterations (CNAs) with clinical outcome.

Methods Used: Genomic DNA was extracted from FFPE samples (40 primary, 12 metastatic, and 32 paired normal bone marrows). We analyzed samples with OncoscanTM FFPE Express (Affymetrix) with 330,000 targeted SNP probes for known cancer genes. We correlated CNAs with clinical features including age, tumor site, metastasis, relapse, and survival. We validated CNA effects on protein expression by immunohistochemistry (IHC).

Summary of Results: We identified novel homozygous deletions in INI1 (SMARCB1). IHC confirmed INI1 protein loss in 7.5% of our cohort (N = 40) and 10% in a cohort from the Children’s Oncology Group (N = 31). We detected novel gains in CEBRB, corresponding to protein expression. Focal and whole chromosome CNAs correlated with outcome in 8 loci (20q13.13 [CEPRB], MYC, 16q24.1, 16q23.3–24.1, trisomies: 5, 8, and 20), including a multivariable CNA index highly predictive of survival (100% vs. 39%, P < 0.001). We identified RELN gene changes unique to 25% of metastatic samples.

Conclusions: We report the first SNP microarray results in archived FFPE tissues in ES. We identified novel CNAs, including the first description of...
INII loss and focal CEBPB gain. We created a multivariable CNA index that may be useful for ES risk-stratification in future clinical trials and provides candidate targets for drug development. The ability to obtain high resolution, genome-wide CNA results in FFPE tumors will increase our understanding of ES tumorigenesis and can identify new therapeutic targets.

86 DEVELOPING A PHOTONOVELA FOR LATINO ADOLESCENT AND YOUNG ADULT CANCER SURVIVORS

Strength KH1, Doose-Peña M2, Millán R2, Morales S1,2, Perez M1, Enriquez F3, Barboza E3, Casillas J2, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA; 1University of California Los Angeles, Los Angeles, CA and 2PADRES Contra El Cancer, Toluca Lake, CA.

Purpose of Study: To develop the research protocol that will be employed by the community-academic partnership guiding the creation of the photonovela intervention. Adolescent and young adult (AYA) cancer survivors can experience medical and psychological late effects placing them at increased risk for morbidity and mortality secondary to cancer treatment at a young age. Vulnerable populations, such as Latinos, may be at higher risk given the lack of culturally-relevant, age appropriate health education materials. A non-profit organization serving the Latino childhood cancer community (PADRES) and UCLA developed a research partnership to create an educational intervention called a photonovela (illustrated booklet). The photonovela will address key survivorship messages: 1)cancer stigma, 2)risk for late effects, 3)need for survivorship care plan/treatment summary, and 4)need for continuous health insurance.

Methods Used: Literature review was conducted to identify methodologies used in photonovela development: a)the use of a community advisory group to explore key messages and b)consensus methods to gain expert opinions on content. Inclusion criteria: a)search terms included photonovela, health education, childhood cancer survivor, RAND consensus, and Delphi panel, b)search engines used were PubMed, PsycINFO, CINAHL Plus, Web of Science, and Google Scholar, c)published between 1975 and 2011, and d)written in English.

Summary of Results: Key concepts identified were used in the protocol: 1)Characteristics of successful photonovelas: language and health literacy level appropriate to audience, target audience identifies with characters/storyline, entertainment-education strategy to incorporate educational messages; 2)Engage community members using focus groups; 3)RAND modified Delphi method was identified as the most relevant consensus method to determine key concepts in the photonovela.

Conclusions: Using a systematic literature review a protocol was identified as the most relevant consensus method for use in the creation of the photonovela targeted toward Latino AYA cancer survivors and their families.

Maternal and Infant Medicine

Concurrent Session

1:30 PM Thursday, January 26, 2012

87 LINEAR GROWTH FALTERING BEGINS IN EARLY POSTNATAL PERIOD IN AN INDIGENOUS POPULATION OF MAYAN DESCENT

Berngard SC1, Bishop J1, Westcott J1,2, Krebs N1,2, Kindem M2, Garces A1,2, Mazariegos M1,2, Kosso-Thomas M2, Wright L2, Hambidge M1,2,3 1University of Colorado, Denver, Aurora, CO; 2RTI, Research Triangle Park, NC and 3FANCAP, Guatemala City, Guatemala.

Purpose of Study: Mean length-for-age Z-score (LAZ) is exceptionally low by 6 mos of age in populations of Mayan descent. The stage in early infancy at which this decline occurs is uncertain, as is the relationship to fetal growth. The objective of this study was to track changes in linear growth from birth to 6 mos of age.

Methods Used: This was a longitudinal anthropometric study from birth to 6 mos. Subjects were 253 indigenous infants (127 M/126 F) in the Western Highlands of Guatemala. Anthropometric measurements were acquired in the home (birth) and community health centers (3 and 6 mos). Z-scores (LAZ; weight-for-age, WAZ, and weight-for-length, WLZ) were calculated using 2009 WHO growth standards. ANOVA was performed for the three time-points with Tukey (HSD) post-hoc analysis evaluating the difference between time-points.

Summary of Results: Mean Z-scores for birth, 3 and 6 mo were LAZ: -1.09, -2.00, -2.25, and WAZ: -0.92, -0.98, -1.03 respectively. Longitudinal differences in means are presented in the table.

Conclusions: The characteristically low mean LAZ at age 6 mo in this population is related both to low birth length and to linear growth failure in the first 3 months of post-natal life.

88 TOBACCO EDUCATION FOR CHILDREN AND PARENTS IN BUTTE, MONTANA

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Purpose of Study: Butte is a historic mining town in southwestern Montana with a population of 34,200 people. Tobacco use is a major public health concern in Butte, given that 26.1% of adults are current smokers and 28% of women smoke during pregnancy. Smoking increases the chance of developing heart disease, which is the leading cause of death in Butte. It is also known that 90% of adult smokers begin smoking before age 18. The purpose of this project was to design and implement a tobacco education program for children and their parents in the Butte community.

Methods Used: The populations used for this project were the Butte YMCA summer camp kids, ages 5 through 12, and the parents who use the Butte YMCA. An hour-long curriculum for children was designed, including five age-appropriate and interactive activities based on published literature. The activities focused on the short-term & long-term effects of smoking, the cost of smoking, the decreased lung capacity of smokers, portrayals of smoking in popular media, and activities that are possible if an individual stays smoke-free. An informational brochure was designed for parents and was placed at the YMCA front desk. The brochure included general information about smoking, specific facts about smoking in Butte, five literature-supported ways to prevent kids from smoking, and local resources for tobacco cessation.

Summary of Results: Nine children attended the workshop during the YMCA summer camp session. They were engaged and excited about the activities and many of them had family members who smoked, so they were an ideal target group for the intervention. The kids made drawings showing positive activities they could do if they do not smoke and these were arranged on a poster and displayed at the YMCA. The informational brochures for parents were placed on the front counter and positive feedback was received about the brochure design.

Conclusions: This was a useful pilot project addressing tobacco use in Butte, Montana. It is likely that the children who attended the workshop will be less likely to smoke in the future, especially if these educational messages are repeated frequently. The project was made more sustainable with the use of a brochure for Butte parents. The curriculum and brochure designed in this project were effective tools for spreading awareness about smoking in the Butte community.

89 IMPLEMENTATION AND ASSESSMENT OF A PERINATAL HEALTH EDUCATION PROGRAM IN RURAL NEPAL

Crandall H, Levy D, Nkoy F, Fassi A University of Utah, Salt Lake City, UT.

Purpose of Study: Newborn and maternal mortality rates in Nepal are among the highest in Asia. We implemented and assessed a perinatal health education program (PHEP) for community based lay providors (CBP) in rural Nepal. The objectives were to 1) determine knowledge acquisition of CBP who completed the training program; 2) describe changes in compliance with perinatal preventive measures and birth outcomes and 3) report communities' perceptions of the program.

Methods Used: We designed and implemented a ten lesson training program for CBP in twelve townships of Baglung district. We used a multimodal evaluation to assess the effectiveness of the PHEP. CBP completed pre and
post-training exams to assess knowledge acquisition. We used pregnancy report cards and family interviews to determine CBP compliance with PHEP recommendations to teach pregnant women and their families about appropriate prenatal, intrapartum and postpartum care. We reviewed government records and interviewed CBP and families to compare compliance with maternal and child health (MCH) indicators before and after PHEP training completion. We conducted focus groups of community members to evaluate perception of the PHEP.

**Summary of Results:** 192 CBP completed the training. Knowledge about preventive measures during pregnancy, appropriate intrapartum and neonatal care increased from 83% to 95%, 81% to 95% and 76% to 95% respectively (p<0.01). More than 92% of pregnant women received counseling about MCH care including pregnancy danger signs, birth preparedness and newborn care. There was improved compliance with MCH indicators regarding preventative measures and birth outcomes: prenatal iron use increased from 74% to 97%; four antenatal care visits increased from 37% to 82%; skilled provider attendance at births increased from 31% to 72% and health facility-based deliveries increased from 1% to 52%. Focus groups showed that community members had knowledge of the program and felt CBP were effective at promoting improved care.

**Conclusions:** This PHEP was effective at improving CBP knowledge of prenatal, intrapartum and postpartum care. This program was associated with improved compliance with MCH indicators. There was high community acceptance and strong support of the PHEP. Future studies will evaluate the effect of the PHEP on maternal and newborn morbidity and mortality.

90 BUILDING A COMMUNITY-BASED NUTRITION MONITORING PROGRAM IN RURAL MALAWI CHILDicare CENTERS

**Purpose of Study:** Namwera, a rural village in southeastern Malawi, experiences among the highest rates of under-five malnutrition in the world. Despite a decentralized treatment campaign by the government, there is currently a weak system of identifying severely acute malnourished children. The aim of this project is to increase the number of early active case findings by training volunteer caretakers in acute malnutrition screening at village-run daycares (Community-based Childcare Centers; CBCCs).

**Methods Used:** A needs-assessment was conducted with community leaders to confirm the burden of malnutrition and to guide priorities for the project. A two-day program in nutrition monitoring was held with the volunteer caretakers. The first class reviewed key information for the volunteers to share with caregivers of high-risk children, including hygiene, the Malawi six-food groups and signs of malnutrition. The second session provided tools for screening (use of the mid-upper arm circumference (MUAC) strip and edema assessment) and the protocol for referring cases to the community health worker. The program was created in partnership with the Ministry of Health campaign through the Namwera AIDS Coordinating Committee.

**Summary of Results:** A total of 13 caretakers from four CBCCs were trained in the program. A practical with 16 children confirmed the quality of MUAC and edema training. Each caretaker was provided with a health education handbook, a MUAC slip and a registry to begin biweekly screening of the 357 children in four CBCCs. The Namwera health worker and a University of Malawi researcher will conduct quarterly audits of this program. A one-year review will assess whether this pilot project should disseminate to the remaining 97 CBCCs in the district.

**Conclusions:** This program provided daycare volunteers the screening tools to increase early enrollment for childhood malnutrition treatment in their village. This project aligned efforts among the local players in childhood nutrition and promotes sustainability by involving well-respected caretakers. Further efforts to ensure food security during the rainy season, gender equality and access to clean water and electricity should be considered to decrease the burden of childhood malnutrition in Namwera.

91 REDUCING MATERNAL MORTALITY AND MORBIDITY IN MANGOCII, MALAWI THROUGH COMMUNITY-LEVEL PROMOTION OF BIRTH PREPAREDNESS

**Purpose of Study:** Delays in seeking skilled healthcare pose significant risks for laboring women in Malawi, where a woman’s risk of dying from a pregnancy-related condition is 1 in 18. These potentially fatal delays for women in Mangochi District can be due to ignorance of the consequences in delaying treatment, a desire to have a traditional, unskilled delivery, and a lack of preparedness for accessing a healthcare facility. Through community-based discussion groups this project sought to overcome some of these barriers so as to reduce maternal mortality and morbidity in Mangochi.

**Methods Used:** Four community health workers guided discussions in four different villages to emphasize the consequences of delaying access to skilled care. The discussions also encouraged pregnant women and their families to create birth plans. Visual aids developed by Family Care International were used to reinforce these messages. In addition, village healthcare volunteers were trained at the Malawi Children’s Village (MCV) on these topics to lead discussions in their own villages. Education materials were secured for use by village health workers for future discussions. Three assessment questions were asked at the beginning and end of the discussions and training to determine retention of key points.

**Summary of Results:** Discussion groups were held in 4 different villages and were attended by a total of 167 people. Forty-nine village healthcare volunteers were trained to lead discussions in their 37 home villages on birth preparedness and complication readiness, and this training will be reinforced at regular monthly meetings at MCV. Participants were able to successfully answer questions related to key points at the end of the discussion and demonstrated an interest and curiosity in maternal health by asking their own questions.

**Conclusions:** The project improved local awareness of the health benefits of hospital-based delivery and the benefits of a birth plan. Sustainability will depend on the continued efforts of local healthcare workers. Future discussion groups should target family decision makers, including husbands and older relatives. Follow-up assessment is needed to determine if the intervention leads to increased rates of hospital-based deliveries.

92 DENTAL CAVITY PREVENTION THROUGH FLUORIDE EDUCATION IN SANDPOINT, IDAHO

**Purpose of Study:** The City of Sandpoint stopped adding fluoride to the municipal water supply in July 2010. Since North Idaho is deficient in natural fluoride, much of the population now lives without supplemental fluoride. Sandpoint Water District supplies four cities, which host more than 10,000 residents. Fueled by negative publicity, the local population is skeptical of fluoride and is resistant to community-wide interventions citing a breach of personal rights. The purpose of this project is to create awareness of fluoride deficiencies, educate the population using culturally sensitive media, and provide access to fluoride supplements.

**Methods Used:** Parents of young children in Sandpoint were interviewed to determine what materials would convince them to pursue fluoride treatment. A literature review was conducted to determine the best methods of reaching the community and provide evidence-based facts. Physicians and dentists were recruited to volunteer at fluoride health fairs, and an educational handout targeted at a 6th-grade reading level was created in a non-authoritative question-and-answer format. Local health professionals and the Panhandle Health District (PHD) were both contacted to initiate a fluoride campaign.

**Summary of Results:** In response to community input, educational materials were developed and well received by parents of young children in downtown Sandpoint. Discussions with healthcare professionals highlighted the need for fluoride programs, and seven physician and dental offices volunteered to provide free fluoride prescriptions at fluoride health fairs beginning this fall. All project materials were given to the PHD for reproduction, and three health clinics adopted the educational handout as part of their educational materials. The Statewide Oral Health program may also use these materials beyond the Idaho Panhandle in the future.

**Conclusions:** Overcoming local ideology and misinformation are primary concerns for this project and future interventions. To meet this challenge, local healthcare professionals must work to establish viable ways to provide fluoride supplements to underserved children. The PHD and local healthcare professionals have recognized fluoride as an important community issue, and this project serves as a starting point to reintroduce fluoride through educational and provider-based campaigns.
93 TEEN PREGNANCY PREVENTION IN OTHELLO, WASHINGTON
Louw C University of Washington, Seattle, WA.

Purpose of Study: Othello, a small town in Eastern Washington, has the highest teen pregnancy rate in the state. Attributing factors in the area include both a lack of parent communication and a lack of available resources about safe sex practices. Teen pregnancy can lead to a lower educational attainment by the teen parents, increased likelihood of poverty for the teen mother and possible behavioral problems in the children of the teen parents. Columbia Basin Health Association (CBHA) provides medical care to the population of Othello regardless of their ability to pay. The purpose of this project is to increase CBHAs provider communication with young, female patients (11-14 yrs) about safe sex practices. Many teen pregnancies in Othello occur between the ages of 15-19, therefore it is critical to begin communication before that age.

Methods Used: Polling community members and CBHA personnel revealed a need to address the high teen pregnancy rate. Providers indicated an interest in supplementing well-child visits with culturally sensitive, bilingual materials. To identify and address the key contributing factors of teen pregnancy in the materials, a literature review was performed. Inquiry into the available resources at the Othello Library exposed a need for additional resources and contact with the library system was established.

Throughout the development of the materials, providers and community members were consulted.

Summary of Results: An educational brochure was created in both English and Spanish about teen pregnancy, sexually transmitted infections, efficacy of contraceptives as well as a panel for patients to reflect upon their goals for the future. Persistent contact with the Mid-Columbia Libraries’ administration resulted in nine books relating to teen pregnancy being added to the Othello Library collection. Providers at the CBHA clinic were given an individual presentation of the development of the brochures and their intended use, as well as a list of books and website resources to refer patients to.

Conclusions: CBHA personnel and community members recognize the teen pregnancy epidemic in Othello and implementation of this project resulted in a revitalization of the seriousness of the issue. Although the fight against teen pregnancy will likely be a prolonged effort in Othello, the providers at CBHA now have new tools in their arsenal to fight the battle.

94 PREVENTION OF UNINTENDED TEEN PREGNANCY IN RURAL PERU THROUGH EDUCATION AND EMPOWERMENT OF ADOLESCENT GIRLS
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Purpose of Study: The high prevalence of unintended pregnancies among adolescents is a significant public health concern in the small town of Yantalo, Peru. Early pregnancy can pose serious medical risks for the mother and child, as well as social repercussions for the entire community. The responsibility of a new baby often causes girls to drop out of school, limiting their future life options. They also have a higher probability of being single mothers and becoming financially dependent on extended family members, perpetuating a cycle of poverty. The aim of this project was to educate women on the health risks of MIP and of the free resources available to prevent malaria. The project encouraged students to expand their future life options, and increased participants’ knowledge of sexuality and contraception methods. For many of the girls it was a new experience to think abstractly about their personal goals, and to be introduced to the idea that they can influence their own destinies. Continued efforts are needed to inspire youth to attain their full potential and to educate them about reproductive health, enabling them to make informed and responsible decisions about their sexual lives in the future.

Conclusions: This project encouraged students to expand their future life options, and increased participants’ knowledge of sexuality and contraception methods.

95 PREVENTING MALARIA IN PREGNANCY THROUGH HEALTH EDUCATION IN RURAL UGANDA
Shipe M University of Washington, Seattle, WA.

Purpose of Study: Malaria is the leading cause of morbidity and mortality in the rural district of Kiboga in Central Uganda, and pregnant women represent a disproportionate number of high acuity cases. In Kiboga, malaria is the leading cause of maternal deaths and is the likely cause of the high rate of spontaneous abortions and low-weight births. Despite the high number and severity of cases, women are largely unaware of the dangers of malaria in pregnancy (MIP) and of the free resources available to prevent malaria. The purpose of this project was to educate women on the health risks of MIP and teach them how to prevent it to protect themselves and their unborn children.

Methods Used: A community health assessment and interviews with patients revealed that MIP is a major cause of morbidity and mortality. Following a literature review of the topic, an educational campaign was chosen to help reduce the burden of MIP. To target women who attend antenatal classes, educational materials were created in the local language, Luganda. Nurses were trained to use the materials during health education talks, which were given during daily antenatal classes at Kiboga Hospital. To target the community, two types of posters highlighting key points from the talks were created in Luganda and hung throughout the hospital and community.

Conclusions: The education health project on MIP empowers women to protect themselves and their children from malaria and encourages them to access available resources. The posters and health education talks will continue to teach women about MIP in and around Kiboga Hospital. With increased investment in the future the project could be expanded to other health centers and rural sites via village health teams so the entire community can avoid the devastating consequences of malaria on pregnant women.

96 PROMOTING INFANT AND CHILD NUTRITION THROUGH COMMUNITY EDUCATION IN THE PERUVIAN SIERRA
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Purpose of Study: Undernutrition accounts for an estimated 50% of deaths worldwide and can contribute diseases such as diarrhea, pneumonia, measles and malaria in rapidly growing infants and children. In Peru, undernutrition is most commonly caused by lack of variety and quality of food, rather than inadequate access to nutrient-rich food. Inadequate complementary feeding practices of children under 3 years are an important cause of undernutrition and educational interventions in food secure regions have been shown to reduce undernutrition.

Methods Used: A community health assessment of the Andean city of Huancayo, Peru indicated that infant and child undernutrition, specifically complementary feeding practices, is a community concern. Six community health center and rural sites surrounding Huancayo were chosen for an educational outreach program, based on previously established relationships with T’ikani, a local NGO. In partnership with T’ikani, a workshop was created that communicated the importance of sound nutrition and food hygiene for preventing disease. A variety of educational techniques were used, including a small theater demonstration, an interactive presentation and discussion, and a group preparation and sharing of a nutrient-rich meal. Based on community

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requests, participants were also taught a protocol to treat intestinal parasites using papaya seeds.

**Summary of Results:** A total of 93 families, representing over 100 children under the age of 3, participated in the workshops. Each family received a region-specific, culturally relevant cookbook and a chart outlining the nutritional benefits of locally available foods. Community participation varied at each site from 28.6% to 126.9% of expected attendance. Teachers from Tikani were trained in current complementary feeding recommendations, and were given all educational materials for future distribution and use.

**Conclusions:** This project increased community knowledge of recommended complementary feeding practices for children under the age of 3. The impact of this project will depend on the continued reinforcement of these recommendations. The trained teachers at Tikani intend to continue to visit homes in the community to provide ongoing education. Future evaluation is needed to assess whether this project will lead to significant changes in child nutrition and health in the target communities.

**97 CONTRACEPTIVE EDUCATIONAL OUTREACH FOR AT-RISK TEENS IN OTHELLO, WA**

Hahn M 1,2

**University of Washington, Seattle, WA.**

**Purpose of Study:** Teen pregnancy is an ongoing concern for Othello, WA and surrounding areas. The most recent data from the Washington State Department of Health shows that Adams County had the highest teen pregnancy rate in the state, at 13.3%, more than three times the state average. Unintended pregnancies pose challenges to teen mothers and their families, but can also sacrifice the educational futures of these teens and put significant financial burdens on the state.

A lack in formal education about contraceptives and sexual health is an important contributing factor to these high rates. Until 2009, Othello High School taught an “Abstinence Only” program, but recently introduced “F.L.A.S.H.”, a comprehensive curriculum to be taught at the freshman level. This was a necessary change; however, it left the upper-class students without access to this educational improvement.

Research has shown that a comprehensive sexual health curriculum results in fewer unwanted pregnancies. Thus, the purpose of this project was to expand these educational advancements by providing comprehensive sexual health education to at-risk teens in Othello, targeting upper-class students.

**Methods Used:** An educational session was arranged for a class of students, grades 10-12, at Othello High School. A presentation was developed focusing on abstinence, contraceptives and local resources. Models were used to demonstrate many contraceptive methods. Pamphlets summarizing the contraceptive methods were distributed to the students in English and Spanish.

**Summary of Results:** Results: Twenty-five students attended the educational session. Questions were used to prompt discussion and introduce topics. All students received a summary pamphlet. Students were enthusiastic to share their knowledge and participated actively in the discussion.

**Conclusions:** Teen pregnancy is not an issue we can solve overnight; however, working with Othello High School to increase at-risk teens’ education will help them act more responsibly. These continued efforts will ensure that the youth of Othello have the knowledge to prevent unwanted pregnancies at all ages.

**Neonatal – Pulmonary I**

**Concurrent Session**

1:30 PM

Thursday, January 26, 2012

**98 MACROPHAGE POLARIZATION & BRONCHOPULMONARY DYSPLASIA**


**USC, Los Angeles, CA.**

**Purpose of Study:** In previous studies we showed elevated TGF-beta (TGFb) is a predictor for BPD and the ability of lung macrophages to express IL-10 is protective. Macrophages exhibit significant phenotypic plasticity. Depending on the microenvironment, they undergo “polarization” that either propagates inflammation (M1 polarized), or promotes tissue repair (M2 polarized). Little is known about lung macrophages in neonates and how TGFb impacts them. In this study we characterized polarization of macrophages obtained from the lungs of human premature neonates and determined their response to TGFb.

To examine the mechanism, we generated & characterized transgenic mice that carry macrophage-specific homozygous inactivation of the gene for TGFb receptor II (TBRII).

**Methods Used:** Tracheal aspirates (TA) was obtained from neonates born at various gestational ages. Macrophages were isolated and sorted by flow cytometry using antibodies specific for M1 or M2 polarization. Macrophages were treated with IL-10 and gene expression was analyzed by Real-time-PCR.

Macrophage-specific inactivation of TBRII was accomplished by mating between the Lyz22-cre driver line & TBRII flox/flox mice. TBRII inactivation was confirmed by genotyping and western blot. Macrophages from double-transgenic Lyz22-cre; TBRII flox/flox bone marrow cells were isolated and treated with M1 or M2 inducers. RNA and protein were quantified using Real-time-PCR & western blot analyses.

**Summary of Results:** Macrophages from neonates born at ~28 weeks gestation exhibited distinct dysregulation of IL-10-induced M2 polarization. TGFb inhibited M2 polarization in human neonatal macrophages. IL4, an M2 inducer, activated M2 gene expression in WT mouse macrophages. Addition of TGFb inhibited IL4 induced polarization. TGFb upregulated M1 gene expression in WT mouse macrophages. Inactivation of TGFb receptor appeared to enhance M2 polarization of macrophages in response to IL4.

**Conclusions:** To our knowledge, this is the first study to characterize lung macrophage polarization in human neonates. Our studies in genetically altered mice suggest that macrophage-specific inactivation of TBRII leads to M2-skewed polarization. Since M2 polarization is critical for tissue remodeling, further studies are underway to elucidate if TBRII deletion is protective against lung injury in BPD mouse models.

**99 NF-κB INHIBITORY PROTEINS DICTATE CELLULAR SURVIVAL IN RESPONSE TO MITOCHONDRIAL STRESS**

Wright C 1, Agboke F 1, Muthu M 2, Mundy M 3, Demery P 2,3

**Univ of Colorado Denver, Denver, CO; 2 Univ of Pennsylvania, Philadelphia, PA and 3 CHOP, Philadelphia, PA.**

**Purpose of Study:** Oxidant stress contributes to lung injury in preterm infants. The transcription factor NF-κB regulates the cellular response to oxidant stress. The pathway leading to oxidant stress-induced NF-κB activation remains to be elucidated. We sought to characterize the role the Inhibitory Kappa-B (IκB) protein in mediating the cellular response to oxidant stress.

**Methods Used:** Murine embryonic fibroblasts(MEF) derived from wild type(WT) and IκBδ knock-in mice(AKBI), in which the IκBα gene is replaced by the IκBδ cDNA, were used for this study. MEF cells were exposed to serum starvation(SS, serum free DMEM) for up to 48 hours. Cell viability was assessed by trypan blue exclusion(TBE), and reactive oxygen species(ROS) were measured by DCF. Mitochondrial stress was assessed by caspase-9 activity. Apoptosis was assessed by Western blot of caspase-3 and PARP, and by caspase-3 activity. NF-κB pathway activity was assessed NF-κB luciferase activity, Western blot of cytosolic IκBα, and nuclear p65. The specific effect of IκBδ was evaluated by transient overexpression of IκBδ in WT MEF exposed to SS. The Mouse Apoptosis Array(NABiosciences) was used to assess gene expression. Experiments were repeated in triplicate.

**Summary of Results:** After 48h of SS, WT MEF had >40% mortality; at this time point AKBI mice had 85% survival(p<.05). ROS production increased significantly in both cell lines following SS, although only WT MEF showed increased caspase-9 activity(p<.05). WT MEF exposed to SS showed increased apoptosis by caspase-3 activity, and caspase-3 and PARP cleavage(p<.05). Following SS, WT MEF demonstrated IκBδ cytosolic degradation, and both decreased nuclear p65 and NF-κB luciferase activity(all p<.05), with no significant changes in AKBI. IκBδ overexpression in WT MEF prevented caspase-3 cleavage following exposure to SS. Significant differences in gene expression between the cell lines was noted.

**Conclusions:** These data demonstrate that individual IκB isoforms are responsible for mediating specific responses to mitochondrial stress. Cells overexpressing IκBδ have improved survival following exposure to oxidant...
stress. This suggests that manipulation of this pathway could have therapeutic applications for neonates exposed to oxidative stress.

100 IUGR ALTERS DNA AND HISTONE METHYLATION OF THE ELASTIN GENE IN NEWBORN RAT LUNG

Purpose of Study: Intrauterine growth restriction (IUGR) increases the risk of postnatal lung disease and impairs lung development. Lung development depends on programming of elastin expression during a critical developmental window. In the rat, this critical window begins at birth. Programming of the elastin gene expression may be influenced by epigenetic modifications including methylation of both DNA and histone proteins. Methylation of histone 4, lysine 20 (H4K20Me) along the elastin gene is dependent upon PPARy. We showed that IUGR decreases rat lung elastin and PPARy expression at birth. We hypothesize that IUGR alters H4K20Me, as well as DNA methylation, along the elastin gene in newborn rat lung.

Methods Used: IUGR was induced by bilateral uterine artery ligation in rat dams at E19 of gestation (term 21 days). Bisulfite sequencing was used to assess DNA methylation within exon 1 of the elastin gene in newborn IUGR and control rat lung. ChIP was used to assess H4K20Me levels along the elastin gene in the same samples.

Summary of Results: Results are reported as IU/GR as % of gender-specific control. Intrauterine growth restriction (IUGR) increases risk of postnatal lung disease and impairs lung development. Lung development depends on programming of elastin expression during a critical developmental window. In the rat, this critical window begins at birth. Programming of the elastin gene expression may be influenced by epigenetic modifications including methylation of both DNA and histone proteins. Methylation of histone 4, lysine 20 (H4K20Me) along the elastin gene is dependent upon PPARy. We showed that IUGR decreases rat lung elastin and PPARy expression at birth. We hypothesize that IUGR alters H4K20Me, as well as DNA methylation, along the elastin gene in newborn rat lung.

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Conclusion: Intrauterine growth restriction (IUGR) increases risk of postnatal lung disease and impairs lung development. Lung development depends on programming of elastin expression during a critical developmental window. In the rat, this critical window begins at birth. Programming of the elastin gene expression may be influenced by epigenetic modifications including methylation of both DNA and histone proteins. Methylation of histone 4, lysine 20 (H4K20Me) along the elastin gene is dependent upon PPARy. We showed that IUGR decreases rat lung elastin and PPARy expression at birth. We hypothesize that IUGR alters H4K20Me, as well as DNA methylation, along the elastin gene in newborn rat lung.

102 CURCUMIN BLOCKS HYPEROXIA-INDUCED PULMONARY ALVEOLAR TYPE II CELL AND LIPOFIBROBLAST APOPTOSIS
Villarreal P, Sakurai R, Li Y, Torday J, Rehan VK. Harbor UCLA Medical Center, Torrance, CA.

Purpose of Study: To determine the effect of curcumin on hyperoxia-induced lung cellular apoptosis in neonatal rat lungs under in vitro and in vivo conditions. We have recently shown that curcumin, the Indian spice in turmeric, blocks hyperoxia-induced neonatal lung injury. However, the underlying mechanism(s) and the cell-types involved in this protection are not fully known. Since curcumin has potent anti-apoptotic properties, we hypothesized that it blocks the hyperoxia-induced cellular apoptosis of both alveolar type II (ATII) cells and lipofibroblasts (LIF).

Methods Used: Embryonic day 19 ATII cells and LIF were exposed to 21% or 95% O2 for 1-24h following 1h pretreatment with curcumin. Cell proliferation (thymidine incorporation) and apoptosis (Western blot analysis for p53, Bcl-2, Bax, and cleaved caspase-3, and confocal immunofluorescence staining for caspase-3), were performed. For in vivo studies, 1-day old Sprague Dawley rat pups were exposed to: normoxia (21%O2), normoxia + hyperoxia (7d exposure to 95%O2), or hyperoxia (7d exposure to 95%O2) + curcumin (5 mg/kg BW). Curcumin was administered i.p. once daily. At the end of the experimental period, the pups were sacrificed and the lungs analyzed for apoptosis markers by Western blotting and immunofluorescence staining.

Summary of Results: Initially, we established that in vitro hyperoxia exposure results in time-dependent decreases ATII cell and LIF proliferation, accompanied by an increase in apoptosis. 1h curcumin (5 μM) pretreatment blocked the hyperoxia-induced decrease in cell proliferation (decrease in thymidine incorporation) and increase in cellular apoptosis (decrease in Bcl-2/Bax ratio, and increases in cleaved caspase-3 and p53) in both ATII cells and LIFs. Similarly, parenteral curcumin administration blocked the in vivo hyperoxia-induced increase in ATII cell and LIF apoptosis. Further studies on the mechanistic basis for this curcumin-mediated protection against cellular apoptosis are in progress.

Conclusion: Curcumin, in addition to its previously documented role of accelerating neonatal lung maturation, blocks the hyperoxia-induced increase in cellular apoptosis in both ATII cells and LIF, offering a potential mechanism for protection against Bronchopulmonary Dysplasia (Grant Support: HD067319;HD-051857; HL107118).

103 NEONATAL HYPEROXIA INCREASES LUNG ELASTIN AS WELL AS ALTERS LUNG STRUCTURE IN MALE IUGR RATS

Purpose of Study: Intrauterine growth restriction (IUGR) increases risk of bronchopulmonary dysplasia (BPD), with males more severely affected. BPD is characterized by excessive expression and aberrant accumulation of elastin, and alveolar simplification. Potential causes for these characteristics are related to mechanical ventilation and oxygen exposure related to chronic hypoxia. We demonstrated that elastin expression and elastic fiber deposition are decreased in IUGR rats, in the absence of a secondary postnatal insult. However, whether the lung of former IUGR rats is susceptible to additional changes after a second postnatal insult, such as hyperoxia, is not known. We hypothesize that mild hyperoxia exposure will increase elastin expression and elastic fiber deposition, as well as induce structural changes, in the IUGR rat lung compared to the control rat lung.

Effect of curcumin on hyperoxia-induced cell and lipofibroblast apoptosis
Methods Used: IUGR (induced by uterine ligation) and control rat pups were exposed to 60% oxygen or room air from postnatal days 3-6, then room air to postnatal day 21 (d21). Lungs assessed at d21 included normoxic control (NC), hyperoxic control (HC), and hyperoxic-IUGR (H-IUGR). Elastin mRNA transcript levels, elastin fiber deposition, and lung structure was quantified.

Summary of Results: Male H-IUGR lungs had increased elastin mRNA expression and elastic fiber deposition relative to NC lungs and HC lungs. Hyperoxia did not affect elastin mRNA or elastic fiber deposition in any group of female lungs. Male H-IUGR lungs had increased tissue density and airway wall thickness relative to NC lungs and HC lungs. Male H-IUGR lungs also had decreased secondary septal volume density relative to NC lungs and HC lungs. Hyperoxia only increased airway wall thickness in female HC relative to NC lungs.

Conclusions: The male IUGR rat lung is susceptible to increased elastin expression, elastic fiber deposition, and lung structural changes in response to postnatal mild hyperoxia, that was not severe enough to affect control lungs. Our data are intriguing because only male lungs are affected. We speculate that the initial insult of IUGR alters the transcriptional regulation of elastin gene in a sex-specific manner, rendering it hyper-responsive to a “second hit” that otherwise does not cause lung injury.

104 PERINATAL VITAMIN D EFFECTS ON LUNG DEVELOPMENT DETERMINE THE ASTHMA PHENOTYPE

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Purpose of Study: Though there are strong epidemiologic data suggesting a link between perinatal vitamin D (VD) deficiency and childhood asthma, the molecular mechanisms involved are unknown. Using a rat model, we have recently shown VD's spatial- and temporal-specific effects on alveolar epithelial-mesenchymal interactions known to be involved in perinatal lung maturation, particularly lipofibroblast apoptosis, a critical step in alveolar septation. However, whether VD supplementation during the perinatal period overcomes the effects of VD deficiency on perinatal lung maturation is not known.

Methods Used: 4 weeks prior to pregnancy, Sprague-Dawley rats were started on the following 4 dietary regimens, which were continued through pregnancy and lactation i) No cholecalciferol added diet ii) 250 IU/kg iii) 500 IU/kg or iv) 1000 IU/kg cholecalciferol added groups. After delivery, the pups were sacrificed on postnatal day 21. Blood and lung tissue were collected to determine VD (25(OH)D3 and 1,25(OH)2D3) levels and markers of alveolar epithelial-mesenchymal differentiation, respectively. Specific markers examined included the parathyroid hormone-related protein receptor (PTHrP-R), paxogenesis, proliferator-activated receptor (PPAR), adipo-cytes differentiation-related protein (ADRP) (markers of mesenchymal differentiation), leptin receptor, surfactant protein (SP) B C (markers of epithelial differentiation), surfactant phospholipid synthesis, and Bcl-2/Bax (apoptosis marker).

Summary of Results: Vitamin D deficiency (no cholecalciferol added groups) resulted in altered LIF (decreased PTHrP, ADRP, and ATII differentiation (decreased SPB, SP, and surfactant phospholipid synthesis), consistent with the lung asthma phenotype, accompanied by increased lung cellular apoptosis (decreased Bcl-2/Bax ratio). Vitamin D supplementation blocked the majority of these changes, the optimal effects seen with 500 IU/kg cholecalciferol supplementation.

Conclusions: Perinatal VD deficiency alters alveolar epithelial-mesenchymal signaling, suggesting induction of the asthma phenotype in the affected offspring. Perinatal VD supplementation at 500 IU/kg effectively blocks the effects of perinatal VD deficiency, providing a strong rationale for adequate VD supplementation during the perinatal period for the prevention of childhood asthma (Grant Support: HL107118).

105 ERYTHROPOIETIN TREATMENT REDUCES THE INCIDENCE OF BRONCHOPULMONARY DYSPLASIA IN PRETERM INFANTS

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Purpose of Study: To determine whether erythropoietin treatment for anemia of prematurity contributed to a reduced incidence of bronchopulmonary dysplasia (BPD) in preterm infants.

Methods Used: An IRB approved retrospective study using the neonatal database for patient identification and data retrieval. Our study population was composed of all live born neonates with a birth weight of 500-1500 grams and gestational age of 22-32 weeks admitted to the Neonatal Intensive Care Unit (NICU) of a single academic center from 1994 to 2007. Our primary objective was to determine whether erythropoietin reduced the incidence of BPD.

Summary of Results: A total of 733 patients were included in the study, of which 342 treated with erythropoietin. Preliminary results show the incidence of BPD was 29% in the erythropoietin treated infants and was 41% in those not treated with erythropoietin, p=0.0008. After adjusting for significantly different risk factors (gestational age, birth weight, Apgar scores at 5 minutes, dexamethasone, sepsis, maternal diabetes and Vitamin A administration) between the erythropoietin and non-erythropoietin groups, the adjusted odds ratio of BPD was 0.37 (95% confidence interval: 0.24 to 0.56, p=0.0001). The BPD rate was associated with the age at initiation of erythropoietin treatment: 16% at 4 weeks or less, 39% at 5 to 8 weeks, and 67% at ≥ 9 weeks of life (p<0.0001).

Conclusions: There was an association between erythropoietin treatment and reduction in BPD incidence in preterm infants. The lowest incidence of BPD was observed in infants treated with erythropoietin before 4 weeks of age.

106 KINETICS OF HBNO METABOLISM IN NEWBORN LAMBS

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Purpose of Study: Nitric oxide (NO) binds rapidly to the Fe2+ heme of deoxyhemoglobin to produce iron-nitrosyl hemoglobin (HBNO). In vitro and under anoxic conditions HBNO is a stable compound with a half-life of several hours. However, the rate of release of NO from HBNO in vivo is not well understood. To characterize the kinetics of HBNO disappearance in vivo, we infused HBNO into newborn lambs and measured its rate of disappearance. HBNO bioactivity was also assessed by measuring changes in systemic blood pressure and exhaled NO.

Methods Used: Experiments were conducted on anesthetized, mechanically ventilated newborn lambs. HBNO (50% saturation) was prepared by exposing deoxygenated ovine blood to pure NO gas, and was administered to lambs as an intravenous bolus over 30 sec to achieve an initial HBNO saturation of 4-5%. Nine blood samples were collected over 20 min and HBNO and methemoglobin (MetHb) were measured by spectrophotometry.

Summary of Results: HBNO disappeared by first-order decay (rate constant 14.4 s-1), and MetHb concentrations increased reaching a plateau of 2.1% 15 min post-injection. Arterial blood pressure fell transiently from 85±5 to 70±7 mmHg, reaching a nadir within 3 min of the HBNO bolus and returning to baseline levels within 15 min. Exhaled NO increased in those not treated with erythropoietin infants of VPD at 3 min of HBNO injection, and returned to baseline within 10 min.

Conclusions: These data demonstrate that HBNO is more labile in vivo than previously thought. However, its rate of disappearance is still many orders of magnitude slower than the rate at which NO binds to Hb, suggesting
the low physiological concentrations of HbNO do not release vasoactive amounts of NO.

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NEONATAL RESUSCITATION PROGRAM TEAM TRAINING FOR HIGH RISK PREMATURE INFANTS: IMPROVING PATIENT OUTCOMES USING SIMULATION

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Purpose of Study: The Neonatal Resuscitation Program (NRP) was designed for managing compromised, term infants immediately following delivery. Premature infants’ resuscitation needs, risks, and vulnerabilities differ from those of the term infant. The premature infant is at higher risk for cerebral circulatory alterations during CPR (chest compressions and/or epinephrine). Infants who receive extensive CPR have an increased risk of mortality and severe neurological injury. This study assessed the impact of a simulation-based team training program on reducing the need for CPR in the delivery room during resuscitations of premature infants. The program included a novel checklist for applying NRP to the very low birth weight population.

Methods Used: Retrospective cohort study, infants <1500 grams at birth were included. Outcome measures: need for chest compressions and epinephrine administration in the delivery room, 1 and 5-min Apgar scores, and occurrence of severe IVH (grade 3 or 4). Baseline demographics and outcomes between groups were compared using x2 and Mann Whitney U-test. SigmaStat version 3.0 was used.

Summary of Results: 117 infants were included. Demographics were similar in the infants born before and after the training with respect to gestational age, birth weight, and male gender. Following the team training program, the percentage of infants who received chest compressions in the delivery room decreased from 18.8% to 3.8% (p = 0.028). There was no statistical difference in the percentage of infants requiring epinephrine administration in the delivery room (6.3% before and 3.8% after, p = 0.84), infants with a 1-min Apgar <4 (29.7% before and 41.5% after, p = 0.25), infants with a 5-min Apgar <7 (31.3% before and 37.7% after, p = 0.589) or those with severe IVH (15.6% before and 7.3% after, p = 0.039).

Conclusions: Implementing a check-list driven simulation-based team training program for managing high-risk preterm resuscitations was associated with a significant reduction in the need for chest compressions in the delivery room.

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IUGR DECREASES STEAROYL-COA DESATURASE MRNA AND PALMITOLEIC ACID LEVELS IN NEWBORN RAT LUNG

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Purpose of Study: Intrauterine growth restriction (IUGR) increases the risk of bronchopulmonary dysplasia (BPD), which is characterized by impaired alveolar formation. In humans and rats, alveolar formation depends on the transcriptional regulator, PPARgamma. We demonstrated that IUGR decreases PPARgamma expression in the newborn rat lung. Stearoyl-CoA desaturase (SCD) is an important downstream target of PPARgamma in the lung. SCD catalyzes the rate-limiting step in synthesis of palmitoleic acid (C16:1). Palmitoleic acid contributes to surfactant synthesis and alveolar formation. However, the effect of IUGR on SCD and palmitoleic acid levels in the rat lung is unknown. We hypothesize that IUGR will decrease SCD and palmitoleic acid levels in newborn rat lung compared to control lung.

Methods Used: IUGR was induced by bilateral uterine artery ligation in the pregnant rat. SCD mRNA levels were measured in lung tissue harvested at birth (d0) from IUGR and control rat pups. Lung fatty acid composition of both IUGR and control rat pups was determined by gas chromatography.

Summary of Results: IUGR decreased mRNA transcript levels of SCD (58.0 ± 4.4%) in d0 rat lung compared to controls. IUGR also decreased palmitoleic acid levels in d0 rat lung when compared to controls (78.3 ± 1.1%*). P<0.01

Conclusions: We conclude that IUGR reduces both SCD mRNA levels as well as levels of a key SCD product, palmitoleic acid, in lung tissue of newborn rat pups. Interestingly, the observed change in mRNA and lipid levels parallels the observed change in PPARgamma expression in IUGR. We speculate that the down regulation of SCD and palmitoleic acid levels in IUGR is a result of direct action by PPARgamma on SCD transcription.

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EVIDENCE FOR A VASOCATIVE METABOLITE OF NITRIC OXIDE IN WHOLE BLOOD

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Purpose of Study: In whole blood, free nitric oxide (NO) has a half-life orders of magnitude shorter than the transit time of blood flow from the lungs to the body. However, inhaled NO therapy results in peripheral vaso-dilation, suggesting the presence of a circulating vasoactive NO metabolite. NO can bind reversibly with the heme of deoxyhemoglobin (HbNO). We hypothesized that HbNO could act as a circulating vasoactive species.

Methods Used: Stock syringes of ~50% HbNO were made by exposing deoxygenated whole blood to NO gas. Boluses were then given intravenously to newborn lambs to an initial HbNO concentration of 2 to 5 μM while arterial blood pressure (ABP) and exhaled NO (eNO) gas were measured. HbNO was measured by spectrophotometry. HbNO was injected either <5 min or ~60 min after being made.

Summary of Results: HbNO was stable in the stock syringes for more than 2 hours. As shown in the figure, injection of HbNO <5 minutes old resulted in a fall in ABP (17.4±1.0%) and rise in eNO (11.8±1.8 ppb). However, responses were markedly reduced or absent (no change in ABP and eNO increase of 4.8±1.7 ppb) for HbNO injected 60 min after it was made, despite no difference in the concentrations of HbNO being injected.

Conclusions: These results confirm the presence of a vasoactive metabolite of NO in whole blood. However, the results suggest HbNO is not the metabolite as ABP was not affected by HbNO injected more than 60 min after it was made. Further studies are under way to identify the metabolite.
LIMITING FEEDING CHANGES APOPTOSIS AND PROLIFERATION IN THE LUNG, BRAIN, AND LIVER OF CHRONICALLY VENTILATED PRETERM LAMBS


Purpose of Study: Preterm neonates who develop neonatal chronic lung disease (CLD) often fail to thrive because of feeding intolerance. The effect of inadequate feeding on molecular participants in organ injury is not known. Our preterm lamb model of neonatal CLD provides opportunity to test the role of nutrition. Preterm lambs supported by mechanical ventilation (MV) develop lung and brain injury. Enteral feeding is complicated by residual milk in the stomach. In contrast, preterm lambs supported by nasal high-frequency ventilation (HFV) do not develop lung and brain injury. Enteral feedings are tolerated. Whether the outcomes are related to feeding tolerance is unknown. We hypothesized that limiting feeding of preterm lambs supported by nasal HFV will change injury parameters in the lung and brain.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV or nasal HFV (n=4 each) for 21d. An unpaired group of PT lambs (paired feeding group) was supported by nasal HFV and limited to the same amount of ewe’s milk that is tolerated by PT lambs supported by MV. Apoptosis (cleaved caspase 3) and proliferation (proliferating cell nuclear antigen, PCNA) were assessed by immunoblot.

Summary of Results: The paired feeding group tolerated less milk daily (mL/Kg/d; p<0.05) than the nasal HFV group, and the same amount as the MV group. At 21d, body weight of the groups was not different. In the lung, cleaved caspase 3 (cc3) protein abundance was less (p<0.05), and PCNA protein was more (p<0.05) in the paired feeding group than the nasal HFV group (p<0.05), and the same as the MV group. In the brain, cc3 protein abundance was not different among the groups. Brain PCNA protein abundance, on the other hand, was less (p<0.05) in the paired feeding group than the nasal HFV group (p<0.05), and the same as the MV group.

Conclusions: Limiting nutrition to chronically ventilated preterm lambs may contribute to poor lung and brain outcomes by changing mediators of proliferation. IGF-1 may be relevant because it is subject to epigenetic changes that may depend on nutrition. (HL110002, HL062875, HL056401, HD141075).

Neonatology General I
Concurrent Session
1:30 PM
Thursday, January 26, 2012

PHASE I TRIAL OF NEONATAL ERYTHROPOIETIN IN PERINATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Purpose of Study: Hypothermia improves outcome of perinatal hypoxic-ischemic encephalopathy (HIE), a cause of neonatal encephalopathy; yet >40% of cooled infants die or exhibit moderate-severe disability. Animal studies suggest high-dose erythropoietin (Epo) is neuroprotective in HIE via mechanisms that differ from hypothermia. Neuroprotection is achieved in animals who achieve plasma Epo concentrations of 6,000-15,000 mU/mL. We hypothesized that early high-dose Epo is well-tolerated in neonates receiving hypothermia for HIE. Epo doses of 1000 and 2500 U/kg achieved plasma concentrations that are neuroprotective in animal models.

Methods Used: In this multicenter dose-escalation open-label study, we gave Epo 250 (N=3), 500 (N=6), 1000 (N=7) and 2500 U/kg/dose (N=8) IV to 24 infants receiving hypothermia for HIE. Infants received up to 6 total doses of Epo, administered QOD starting at 24h of age. We measured serum Epo levels, and monitored safety until hospital discharge.

Summary of Results: Patients received an average of 4.7 doses. Mean length of hospital stay was 12 days. See Figure for plasma Epo concentrations measured in the first 21 patients. Drug was cleared rapidly with no accumulation of Epo. No deaths or other significant adverse effects, such as hypertension, thrombosis and polycythemia, were observed. Conclusions: Early high-dose Epo is well-tolerated in neonates receiving hypothermia for HIE. Epo doses of 1000 and 2500 U/kg achieved plasma concentrations that are neuroprotective in animal models.

EPIGENETICS OF TRANSGENERATIONAL TRANSMISSION OF IN UTERO NICOTINE-INDUCED ASTHMA


Purpose of Study: Perinatal nicotine exposure alters the normal differentiation of the lung mesenchymal cells in the fetal lung by stimulating the Wnt pathway, resulting in the asthma phenotype in the offspring, and PPARγ agonists can inhibit this effect. However, whether the in utero nicotine-induced asthma risk is transmitted transgenerationally, or PPARγ agonists would have any effect on this process is not known.

Methods Used: Time-mated Sprague Dawley rat dams received either placebo or nicotine [1 mg/kg, s.c.], once daily from day 6 of gestation to postnatal day (PND) 21. Following delivery, at PND21, generation 1 (F1) pups were either subjected to pulmonary function tests, or killed to obtain their lungs and tracheas to determine the relevant protein markers and for tracheal tension studies. Some F1 animals were used as breeders to generate F2 pups, but without any exposure to nicotine in the F1 pregnancy. F3 pups were similarly generated. At PND21, F2 and F3 pups underwent studies similar to those performed on F1 pups. As the putative basis for the transgenerational (TG) effect of nicotine on asthma, epigenetic changes in the lungs and gonads of the F1 offspring were determined. Lastly, we determined if the PPARγ agonist rosiglitazone (RZG) inhibited the nicotine-induced epigenetic changes and TG asthma risk.

Summary of Results: In comparison to the control group, with perinatal nicotine exposure only to F0 rats (N=12), 1) F1 through F3 pups demonstrated the asthma phenotype (changes being more pronounced in males) even though F2 and F3 rats were not exposed to nicotine; 2) the increase in the tracheal constriction response was seen exclusively in males; 3) global DNA methylation increased in the testes, decreased in the ovaries, but did not change in the lung; 4) histone (H3) acetylation increased in the lungs and testes, but did not change in the ovaries; and 5) all of these changes were blocked by RZG administration.

Conclusions: Germline epigenetic marks imposed by exposure to nicotine during pregnancy can become permanently programmed and transferred through the germline to subsequent generations, a ground-breaking finding, which shifts the current asthma paradigm, opening up many new avenues to explore (HL75405, HD51857, HD058948, HL55268, and 17RF01790).
113 GENDER-SPECIFIC PERINATAL NICOTINE-INDUCED ASTHMA IN RAT OFFSPRING

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Purpose of Study: We have recently suggested that in utero nicotine down-regulation of homeostatic mesenchymal PPARγ signaling might contribute to asthma. Here, we have exploited an in vivo rat model of asthma to determine if the effects of perinatal nicotine exposure on offspring pulmonary function and mesenchymal markers of airway contractility in both tracheal and lung parenchymal tissue are gender-specific, and whether the protection afforded by the PPARγ agonist rosiglitazone (RGZ) against the perinatal nicotine-induced effect is also gender-specific.

Methods Used: Purin-fed pregnant rat dams received either a placebo, nicotine (1 mg/kg, sc.), or nicotine (1 mg/kg, sc. + RGZ (3 mg/kg, ip.) daily from embryonic day 6 until postnatal day (PND) 21. Pups were delivered spontaneously and breast-fed ad libitum. At PND 21 lung resistance, compliance, and tracheal contractility were determined. In addition, expression of the structural and functional mesenchymal markers of airway contractility (α-SMA, smoothelin, Collagen I and III) were also determined by immunoblotting and immunostaining.

Summary of Results: Compared to controls, perinatal nicotine exposure caused a significant increase in airway resistance, and a decrease in airway compliance following a methacholine challenge in both genders, as well as the male-specific effects on airway compliance, and tracheal contractility were determined. In contrast, expression of the mesenchymal markers of contractility, were observed exclusively in males. Concomitant treatment with RGZ normalized the nicotine-induced alterations in pulmonary function in both genders, as well as the male-specific effects on airway contractility on α-SMA, smoothelin, Collagen I and III was attenuated by RGZ.

Conclusions: Perinatal nicotine exposure causes gender-specific predisposition to childhood asthma, providing a powerful phenotypic model for unequivocally determining the underlying nature of the cell-molecular mechanism for this disease. Grant Support: NIH (HL75405, HD51857, 2Stanford University School of Medicine, Stanford, CA.

114 HEME OXYGENASE-1 DEFICIENCY PROMOTES NECROTIZING ENTEROCOLITIS DEVELOPMENT IN A MURINE MOUSE MODEL

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Purpose of Study: Intestinal inflammation is an initial step in necrotizing enterocolitis (NEC) development, which can rapidly progress to mucosal destruction and wall necrosis. Heme oxygenase-1 (HO-1) has been implicated in the pathogenesis of NEC.

Methods Used: To induce NEC, 7- to 10-day-old HO-1−/− and wildtype (WT) pups were removed from moms and fed 20g/kg formula (1g Similac 60/40 in 10mL Esbilac) 5g by OG every 4h for 48h. On D15 and 7, pups were exposed to 5%O2/95%N2 for 1min. Controls (WT, HO-1−/−) were treated similarly. After 48h, the small intestine, proximal colon, and liver were harvested and sectioned for H&E staining. NEC severity was blindly scored by a pathologist (0-4). For HO-1 induction, 6d-old WT pups were given 30-mu mol heme/kg BW OG and HO activity in liver and intestinal tissues was measured 24h later. Mouse PCR array for endothelial cell activation, injury, angiogenesis, and vaso-specific markers were performed on NEC liver tissues.

Summary of Results: Basal intestinal HO activity was similar for WT and Het pups but increased significantly in liver and small intestine of WT pups after giving heme as an HO-1 stimulator. In contrast, HO activation in Het pups was impaired. Comparing NEC scores, we found a significant difference between WT and Het NEC of 1.15±0.7 (n=24) and 2.1±1.0 (n=20), respectively. Our observed NEC incidence was 20% for WT vs. 45% for Het pups with a mortality rate of 56% and 86%, respectively. NEC livers showed increases in portal-periporal activity and fatty changes of hepatocytes, with both more dominant in Het NEC livers. PCR array analyses showed increases of 2.2-2.4-; 3.0-; 4.0-; and 1.8-fold in angiotensinogen, chemokine ligand-2, IL-6, serpine-1, and von Willebrand Factor, respectively, in Het NEC livers.

Conclusions: A partial deficiency in HO-1 promotes experimental NEC development, possibly involving liver and vascular changes and affecting thrombotic and inflammatory endothelial pathways. We speculate that HO-1 induction may be protective in the early stages of NEC development.

115 INCREASED VARIABILITY OF FECAL BILE ACID LEVELS IN INFANTS THAT DEVELOP NECROTIZING ENTEROCOLITIS

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Purpose of Study: Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency of premature infants. We have shown that bile acids (BA) are significantly elevated in neonatal rodents with NEC, with a positive correlation to severity of disease. Further, removal of BAs decreased NEC incidence and severity. The purpose of this study is to determine if there are differences in fecal BA levels in premature infants that develop NEC compared to premature infants that do not develop disease.

Methods Used: Fecal samples were prospectively collected from premature infants meeting the inclusion criteria: birth weight (BW) of ≤ 1800 g, estimated gestational age (EGA) ≤ 34 weeks and less than 30 days old prior to initiation of enteral feeding. Sample collection occurred over multiple days of life (range 5-53 days), with a mean of 33.8 ± 13.1 samples per subject. Fecal samples were weighed, mixed with an equal volume of sterile, distilled water, homogenized and centrifuged to separate the fecal water from the fecal pellet. Total BA levels were determined from the collected fecal water using the Diazyme Total Bile Acid Kit. The coefficient of variation (CV) for total fecal BA levels was calculated for each patient’s time sequence of samples.

Summary of Results: BA levels from 8 infants (median EGA, 29 weeks; median BW, 1050 g) were analyzed. Of these subjects, 2 developed NEC. Subjects with NEC displayed cyclic increases in total BA levels not observed in subjects without NEC. These variations were independent of both the composition and amount of enteral nutrition given. The CV for subjects with NEC diagnoses was 1.040 and 1.138; the mean CV for non-NEC subjects was 0.401 ± 0.177 (range 0.23 - 0.67). Thus, the CVs for infants that developed NEC were at least 50% greater than the largest CV among non-NEC subjects.

Conclusions: These data suggest that variability in total fecal BA levels is altered in premature infants that develop NEC and that BAs play a role in NEC pathophysiology. These variations in BA levels could be utilized as a predictive test for disease development.

116 PRETERM BIRTH AND ASSOCIATED VENTILATION ARE NOT RELATED TO HIGHER LEVELS OF LIVER MARKERS OF HEPATOBLASTOMA IN PRETERM LAMBS

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Purpose of Study: Very-low birth weight (VLBW) is a potent risk factor for hepatoblastoma. The pathogenesis of hepatoblastoma is not known, although it may be related to perinatal exposures associated with VLBW. Preterm birth and associated ventilation support are risk factors for poor growth. Emerging data from our studies suggest that preterm lambs supported by mechanical ventilation (MV) for 3d and subsequently weaned from ventilation grow less and have a reduced marker of hepatocyte proliferation (cell nuclear antigen) compared to controls, although this was not statistically significant. We reasoned that our model might provide insight regarding the relationship between a) preterm birth and associated ventilation and b) expression of markers of hepatocyte proliferation (hepatoblastoma). We hypothesized that preterm birth and associated ventilation would be related to higher levels of liver markers of hepatocyte proliferation (hepatoblastoma).

Methods Used: Pregnant ewes were given dexamethasone before delivery of preterm (PT) lambs (~125d gestation; term ~150d). The PT lambs were delivered via cesarean section. Lambs were ventilated for 3 days postnatal (DPN) and then weaned to room air. Blood was collected from the jugular vein for determination of bile acid (BA) levels. Liver samples were analyzed for markers of hepatocellular proliferation (proliferating cell nuclear antigen, PCNA).

Summary of Results: BA levels were significantly higher in PT lambs compared to full-term (FT) lambs (P < 0.05). PCNA levels were also significantly higher in PT lambs compared to FT lambs (P < 0.05). There was no significant difference in PCNA levels between lambs ventilated for 3DPN and lambs ventilated for 3DPN and then weaned to room air. There was also no significant difference in BA levels between lambs ventilated for 3DPN and then weaned to room air and lambs ventilated for 3DPN and then weaned to room air and then ventilated again for 3DPN.

Conclusions: Preterm birth and associated ventilation are not related to higher levels of liver markers of hepatoblastoma in preterm lambs.
intubated, given surfactant, supported by MV for 3d, weaned to and supported by nasal HFV for 3d, and weaned from ventilation support and lived for 10-11wk more (‘PT weaned’; n=6). Other lambs were born at term gestation (~3 wk after the PT lambs were delivered) and lived for 8-9 wk more (‘T+8wk control’; n=6). At the end of the respective study periods (2mo of age after term gestation), liver tissue was analyzed by immunoblot for markers of hepatoblastoma (alpha-fetoprotein (AFP), beta-catenin, and notch2).

**Summary of Results:** Hepatic notch2 protein abundance was ~60% lower (p<0.05) in ‘PT weaned’ lambs compared to ‘T+8wk control’ lambs. Neither hepatic AFP nor beta-catenin protein abundance was different between the 2 groups.

**Conclusions:** Contrary to our hypothesis, preterm birth and associated ventilation are not related to higher levels of liver markers of hepatoblastoma. Instead, notch2 protein level is lower. AFP and beta-catenin protein levels are not changed. We speculate that being preterm and associated ventilation does not create liver markers of hepatocyte proliferation (hepatoblastoma). (HL110002, HL062875, HL056401, HD41075).

### 118 COMPARISON OF CD34 SUBSETS IN TERM AND PRETERM NEONATES

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**Purpose of Study:** Circulating endothelial progenitor cells (EPC) are bone marrow derived cells capable of participating in vascular repair. EPCs may play an important role during development especially in premature infants. There are no reference values for EPC frequency in neonatal blood. EPC frequency may be different in preterm infants compared to term infants and may be affected by clinical illnesses. Further understanding of EPCs in newborns may lead to novel treatment approaches.

**Methods Used:** Blood samples were collected on day 1 and weekly for 3 weeks from hospitalized neonates. Flow cytometry was used to determine frequency of CD34+ cells and CD34+CD45-, CD34+VEGFR2+ and CD34+CD45-VEGFR2+ subsets in whole blood leukocytes (WBL), mononuclear cell fraction (MNC), or both. EPCs were defined as CD34+CD45-VEGFR2+ cells. Prospective clinical data were collected to examine associations between EPCs and clinical illnesses. Comparisons between term and preterm were done using Wilcoxon rank sum test. Associations with gestational age were examined with Spearman correlation coefficients. Statistical tests were 2 sided at a significance level of 0.05.

**Summary of Results:** Thirty patients and 71 blood samples were studied. On day 1, median CD34+, CD34+CD45-, and CD34+VEGFR2+ cell per million WBL were higher in preterm than in term infants with p<0.05 (4969 vs 1366; 151 vs 49; 58.6 vs 12.8). Median CD34+CD45- per million MNC was higher in preterm than in term infants (180 vs 80.6, p=0.0445). Median EPC values in preterm vs term infants were 2.35 vs 0.9 per million WBL (p=0.03) and 4.7 vs 1.7 per million MNC (p=0.458). There was a statistically significant inverse correlation between each CD34 subset and gestational age (p<0.03). No clear pattern of change in EPCs was noted over time, but one patient who developed necrotizing enterocolitis had a 23-fold increase in MNC EPCs from day 1.

**Conclusions:** Preterm infants have higher levels of CD34 subsets, including circulating EPCs than term infants. These levels are inversely related to gestational age.

### 119 EXTRACORPOREAL MEMBRANE OXYGENATION INDUCES INFLAMMATORY MEDIATORS IN NEONATES BORN WITH CONGENITAL DIAPHRAGMATIC HERNIA

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**Purpose of Study:** Infants with congenital diaphragmatic hernia (CDH) often require extracorporeal membrane oxygenation (ECMO). However, ECMO may induce alterations in inflammatory mediators potentiating the risk for tissue damage. We hypothesized that 1. exposure to ECMO would alter both pro- and anti-inflammatory mediator expression in neonates born with CDH and 2. that inflammatory mediators would increase following packed red blood cell (PRBC) transfusions, a frequent event during ECMO.

**Methods Used:** We collected whole blood samples from neonates with CDH (n=6) before, during, and after ECMO. We then characterized expression of 13 plasma inflammatory mediators (Th1: IFN-γ, IL-12, IL-2; Th2: IL-4, IL-5, IL-10, IL-13; Other: IL-1β, IL-6, IL-8, TNF-α, IL-2R, CD40 ligand) using LumineX® technology. We also analyzed expression of these same mediators in patient samples before and after blood transfusions, including measurements in the PRBC units themselves.

**Summary of Results:** Exposure to ECMO induced alterations in inflammatory mediator levels in all 6 patients tested. Inflammatory mediators rose over the first 24 hours before approaching baseline. The increases in TNF-α reached statistical significance (mean 7.6 vs 29.3 pg/mL; p<0.05). Alternatively, plasma expression of CD-40 ligand and IL-2 receptor decreased with ECMO initiation. Elevated inflammatory mediator levels were found for 11 of the 13 analytes tested in stored PRBC samples prior to transfusion (n=75). PRBC transfusion induced increases in IFN-γ, IL-10, IL-6, and IL-8 although none reached statistical significance.

**Conclusions:** We conclude that ECMO alters inflammatory mediator levels in patients born with CDH. Increased levels of inflammatory mediators are found in stored PRBC units, and subsequent transfusion of these units into neonates results in increased inflammatory mediator expression. We speculate that 1. exposure to the ECMO circuit induces a robust inflammatory response incorporating elements of Th1, Th2, and monocytic responses and 2. that transfusion of cytokine-laden PRBCs may influence the clinical response of neonates on ECMO.

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120 PROBIOTIC USE IN CYANOTIC CONGENITAL HEART DISEASE

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Purpose of Study: Term infants with cyanotic congenital heart disease (CCHD) are at increased risk for necrotizing enterocolitis. Little is known about the intestinal microbiota in these high-risk infants. We sought to investigate the composition of the fecal microbiota and the impact of administration of probiotic Bifidobacteria longum sp infants in neonates with CCHD.

Methods Used: Sixteen infants with CCHD were enrolled in this randomized, placebo-controlled pilot trial. Infants received either B. infantis (4.2 x 10^9 cfu twice daily) or placebo for 8 weeks or until hospital discharge. Stool specimens were collected at baseline and then weekly. For comparison, serial stool specimens from 6 healthy term infants without heart disease were collected at similar time points. All specimens were analyzed by terminal restriction fragment length polymorphism (TRFLP) and quantitative reverse transcription PCR (qPCR).

Summary of Results: Two infants were withdrawn from the study prior to beginning treatment (one was transferred to another facility, one at parental request), the baseline stool specimens of these infants were included. Principal component analysis of TRFLP data revealed marked similarity between the two groups of infants with heart disease, both differed significantly from the group of infants without heart disease. B. infantis was found in 14/16 infants with heart disease with baseline stool with <0.1% bifidobacteria compared to 4 of 6 infants without heart disease. 5 of 6 infants treated with B. infantis had at least one stool with >10% bifidobacteria, compared with 3 of 9 infants in the placebo group and 4 of 6 infants without heart disease.

Conclusions: The intestinal microbiota of infants with congenital heart disease differs from that of infants without heart disease. Likely contributing factors include hospitalization, antibiotic administration, and chronic cyanosis. Administration of probiotic B. infantis increased the percentage of bifidobacteria transiently.

121 EFFECT OF SUPERIOR CERVICAL GANGLION REMOVAL ON CEREBRAL BLOOD FLOW DURING PERIODS OF ACUTE HYPERTENSION IN PRETERM AND TERM LAMBS

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Purpose of Study: The role of the superior cervical ganglion (SCG) in cerebral autoregulation is controversial. We have previously shown that stimulation of the SCG reduces cerebral blood flow (CBF) on the stimulated side without affecting CBF on the contralateral side. In the current study we test the null hypothesis that the SCG does not influence CBF during changes in mean arterial pressure (MAP).

Methods Used: Premature lambs 120-124 d (n=11) and 2-week-old term lambs (n=10) were anesthetized and mechanically ventilated. Arterial PCO2 in mean arterial pressure (MAP). Stimulation of the SCG reduces cerebral blood flow (CBF) on the stimulated side, whereas in the contralateral side, the CBF remains unchanged.

Summary of Results: Two infants were withdrawn from the study prior to beginning treatment (one was transferred to another facility, one at parental request), the baseline stool specimens of these infants were included. Principal component analysis of TRFLP data revealed marked similarity between the two groups of infants with heart disease, both differed significantly from the group of infants without heart disease. B. infantis was found in 14/16 infants with heart disease with baseline stool with <0.1% bifidobacteria compared to 4 of 6 infants without heart disease. 5 of 6 infants treated with B. infantis had at least one stool with >10% bifidobacteria, compared with 3 of 9 infants in the placebo group and 4 of 6 infants without heart disease.

Conclusions: The intestinal microbiota of infants with congenital heart disease differs from that of infants without heart disease. Likely contributing factors include hospitalization, antibiotic administration, and chronic cyanosis. Administration of probiotic B. infantis increased the percentage of bifidobacteria transiently.

122 THE TIMING OF SURGICAL INTERVENTION AND CLINICAL PREDICTORS OF MORTALITY IN INFANTS REFERRED TO A NEONATAL INTENSIVE CARE UNIT FOR NECROTIZING ENTEROCOLITIS

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Purpose of Study: Necrotizing enterocolitis (NEC) is the most common surgical emergency affecting the intestinal tract in premature infants. Intestinal perforation is one indicator prompting surgical exploration; however, other indicators are not well defined. The purpose of this study was to define clinical parameters that correlate with early (within 12 hours of admission) or late (more than 12 hours) surgical intervention in infants admitted to a tertiary level neonatal intensive care unit (NICU) with a diagnosis of NEC in relation to mortality.

Methods Used: Data from NICU admission and CPQCC logs from 1/06-10 were reviewed. Seventy cases of NEC in premature infants were confirmed.

Summary of Results: Forty-four percent of the infants were in the early surgery group, 31% were in the late surgery group, and the remaining were medically managed. Infants in the early surgery group had a higher mortality than those in the late surgery group (p=0.05). Black infants had the highest mortality independent of the timing of surgery, whereas in the late surgery group, a history of PDA only predicted mortality for Black male infants. Five-minute Apgar score was not significantly different between the two surgery groups. In infants who had surgery, there was a significant correlation between mortality and a lower pH, greater base deficit, higher lactate and more prolonged PTT and PT at admission, although only an elevated lactate was significant in predicting mortality (p<0.05).

Conclusions: Preliminary data suggest that clinical illness severity scoring independent of perforation may contribute to the decision for surgical intervention either early or late and that earlier referral of Black male infants with NEC, particularly with a history of PDA, may increase this cohort's chance of survival. Further analyses to elucidate the number of infants with suspected or confirmed perforation, the type and extent of surgical intervention, among other variables may better define factors linked to mortality and outcome.

123 USE OF AN OXYGEN SATURATION HISTOGRAM INCREASES TIME INFANTS ARE WITHIN TARGET SATURATION RANGE

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Purpose of Study: The Keep Oxygenation at Appropriate Levels for Age (KOALA) protocol provides guidelines for adjusting supplemental oxygen to maintain oxygen saturations (SpO2) 88-95% in our NICU. When KOALA was initially instituted there was an increased compliance in maintaining appropriate SpO2; however, over time compliance waned. We aimed to improve compliance with prescribed oxygen saturation ranges by incorporating histogram data into the charting to improve target SpO2 range compliance.

Methods Used: This study is an observational analysis of SpO2 histogram data. Infants with a birth weight < 1500 grams were eligible, if they required a FiO2 >0.25 for >25% of the time. Infants with cyanotic heart disease and persistent pulmonary hypertension were excluded. Data was obtained from the histogram function from a Masimo pulse oximeter. Nursing staff was taught to obtain the SpO2 histogram for their shift. From March to September 2011, nursing staff charted the histogram output in the electronic medical record. Data was assessed for improvement in KOALA protocol compliance.

Summary of Results: During the study period, 36 infants were observed. There was a significant increase in time infants spent within the target SpO2 range, from 55% to 62% (p=0.001) (Table 1). Time spent above and below target range was significantly decreased (p=0.001).

Conclusions: Nurses serve as gatekeepers for administration of supplemental oxygen. Reporting the SpO2 histogram output increases awareness.
The level of understanding of brain death is low among the
medical student body in a four year accredited U.S. medical school. This knowledge gap persists among graduating students as most do not attain an expert understanding. The investigators identified areas of knowledge gaps and compared brain death expertise throughout the curriculum progression.

**Summary of Results:** The overall response rate was 69% (212 of 306 students). Mean scores were 3.1, 3.9, 4.1, and 4.0 (out of 5) among first through fourth year classes respectively. Understanding of brain death differed across the medical school classes (p < 0.0001). 33% (N = 70) of all students attained scores of 5 indicating an expert level of understanding brain death. By class; 18% of first year students demonstrated expert levels of understanding, compared to 31% of second year students, 48% of third year students, and 39% of fourth year students.

**Conclusions:** The level of understanding of brain death is low among the student body in a four year accredited U.S. medical school. This knowledge gap persists among graduating students as most do not attain an expert understanding of brain death. A more comprehensive brain death curriculum should be implemented in order to adequately equip physicians with this fundamental knowledge.

**Purpose of Study:** A lack of understanding of brain death has been demonstrated among physicians, and may stem from knowledge deficits at the medical school level. The authors sought to evaluate current understanding of brain death and knowledge gaps among U.S. medical students at a single center.

**Methods Used:** Using a validated “Understanding Brain Death” survey tool, the authors surveyed the student body at an accredited four year medical school. A score of 5/5 on this scale indicated an expert level of understanding. The investigators identified areas of knowledge gaps and compared brain death expertise throughout the curriculum progression.

**Conclusions:** If the result is that there is no tonotopic organization of auditory cortex in patients with schizophrenia even while attending to pitch or laterality, it will suggest that the architecture underlying tonotopy in the auditory cortex is not responsive to top-down, task relevant reorganization in the same manner as in healthy subjects. This alteration in organization of the auditory cortex may in turn influence higher order cognitive processes by altering the perception of incoming auditory stimuli. Grant support: R25 MH080859.
127 SYSTEMATIC ANALYSIS OF TREATMENT STRATEGIES AND OUTCOMES FOR MALIGNANT EPIDERMOID TUMORS
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Purpose of Study: Epidermoid tumors are rare congenital lesions that arise from ectodermal remnants during embryogenesis. While these lesions are considered benign and tend to have a favorable prognosis following surgical resection, they may upon rare occasion undergo malignant transformation which has a poor prognosis. In this systematic analysis, we reviewed treatment strategies and analyzed survival outcomes for every case of malignant epidermoid tumor reported in order to better characterize optimal therapeutic strategies.
Methods Used: A comprehensive literature review was conducted in order to identify all known cases of malignant transformation of intracranial epidermoid tumor. Treatment options were analyzed for survival data according to the following therapeutic groups: medical management/ shunt placement, chemotherapy, stereotactic radiosurgery (SRS), and surgery plus multiple (2+) adjuvant therapies. Survival data was compared to treatment outcomes for patients receiving only surgical resection, as reported in our previous study. Information regarding tumor location, sex, age, and interval to malignancy was also analyzed.
Summary of Results: We identified 58 cases of intracranial epidermoid tumor with malignant degeneration. Thirty-three patients (56.9%) were male and twenty-five (43.1%) were female. Average age of malignant degeneration was 53.6 years, with mean interval from initial epidermoid symptom onset to diagnosis of malignancy being 6.0 years. Average survival regardless of therapy was 11.8 months, ranging from 1 day post operation to 5 years. Mean survival outcomes for groups treated with medical management/ shunt placement, chemotherapy, SRS, and multiple postoperative adjuvant therapies were 5.3 months, 25.7 months, 29.2 months, and 36.3 months, respectively. Outcomes for the groups including chemotherapy, SRS, and multiple postoperative adjuvant therapies were statistically significant compared to surgical resection alone. There was no detectable difference between treatment groups regarding age, sex, or interval to malignant degeneration.
Conclusions: While there remains a lack of consensus regarding the best approach to the management of patients with malignant epidermoid tumors, our systematic analysis characterizes and confirms the added benefit of adjuvant therapies.

128 CORTICAL ATROPHY AND GENOMIC BIOMARKERS IN COGNITIVELY NORMAL ELDERLY AND MCI
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Purpose of Study: Mild cognitive impairment (MCI) is a transitional state between normal cognitive functioning and Alzheimer’s disease (AD). Understanding the genetic background of MCI and AD and its relationship to global cortical atrophy may assist in early diagnosis and may help to explain the pathogenesis of this disease.
Methods Used: We investigated the relationship between genotypic and gray matter MRI parameters in MCI and 37 cognitively normal (NC) subjects. Genotyping was conducted at the onset of enrollment. The MRIs were spatially and intensity normalized and skull-stripped. Cortical surfaces were parameterized, flattened and warped. Tissue segmentation was conducted and gray matter maps were created. Linear regression models were created to investigate the association between the APOE4, TOMM40 and CLU genotypes and gray matter thickness. Significance and correlation maps were created to visualize areas of association.
Summary of Results: Our results showed multiple areas of negative association between the genotypes and gray matter thickness, which followed a pattern similar to that seen in AD. A negative association was observed between APOE4 and the bilateral precuneal, right frontal and right parietal areas. TOMM40 (rs1575580) showed a negative association with the bilateral precuneal areas. TOMM40 (rs2075650) showed a negative association in the bilateral precuneal, left cingulate, right parietal and right frontal areas. AD showed a negative association in the right temporal lobe. Unfortunately, the results did not survive correction for multiple comparisons.
Conclusions: By using cortical atrophy as a quantitative phenotype, we attempted to identify susceptible genes in MCI. Further research with a larger sample size is warranted to clarify these relationships and their role in the pathological changes in MCI and AD.

129 TRANSPLANTATION OF INDUCED PLURIPOTENT NEURAL PROGENITOR CELLS AND CHONDROITINASE ABC IN A HYDROGEL MATRIX AFTER STROKE
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Purpose of Study: Shortly after a stroke, a reactive glial scar forms that establishes a physical barrier inhibiting neuronal communication with the affected region. In addition, cells within the glial scar secrete chondroitin sulfate proteoglycans (CSPGs) that have a strong inhibitory effect on neuroregeneration. We hypothesize that if the inhibitory properties of the post-stroke glial scar can be eliminated, then transplantation of neural progenitor cells (NPC) into a stroke cavity will have improved migration, differentiation, and integration within the host.
Methods Used: An ischemic stroke was created in 24 mice via left carotid artery ligation followed by stereotactic infusion of a potent vasoconstrictor into the left striatum. Seven days later, the mice were divided into 4 groups: 1) control, 2) cABC alone, 3) NPCS alone, or 4) cABC plus NPCs. To prevent immunologic activation against the NPCs, all mice were treated with daily cyclosporine A via subcutaneous micro-osmotic pumps. The NPC have inducted pluripotency derived from the transcription factors Oct3/4, Klf4, Sox2, and c-myc. The CABC and/or NPC were dissolved in a hydrogel matrix before stereotactic infusion into the stroke cavity. Fourteen days after selected therapy, the mice were perfused and sectioned for immunohistochemistry.
Summary of Results: cABC was effectively concentrated to 0.2 units/ul, dissolved in the hydrogel matrix, and maintained biologically activity at body temperature. The CABC at a dose of 0.1 units/mouse demonstrated effective gradient of the inhibitory CSPGs found within the post-stroke glial scar. This was evidenced by an enhancement of 2B6 staining and elimination of WFA staining around the stroke cavity when compared to control.
Conclusions: To date, we are the first group to show that cABC maintains enzymatic activity within a hydrogel. This strategy is advantageous because it allows for target delivery of cABC into the post-stroke glial scar while avoiding toxic global CNS exposure. The ability to concentrate cABC to 0.2 units/ul is 40 times greater than previous published reports and this is critical when infusing into the volume limited space of the brain. cABC dose of 0.1 units/mouse leads to effective degradation of the inhibitory CSPGs found within the glial scar and spares healthy surrounding neural tissue.

130 ALPHA-SYNUCLEIN Oligomer-INDUCED CALCIUM ACTIVITY IN PURE ASTROCYTE MODEL
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Purpose of Study: Parkinson’s disease (PD) is a neurodegenerative disorder characterized by death of dopaminergic neurons in the substantia nigra, resulting in impairment of proper motor functions as well as dementia. Current literature indicates that abnormal aggregation of neuropeptide called alpha-synuclein (α-syn) in neuronal pre-synaptic terminals most likely is the cause of the pathogenesis. (Polymeropoulos et al 1996; Walsh et al., 2004). Despite their predominance in number in the CNS, astrocytes and their roles in the underlying mechanism leading to neuronal death remain largely unknown.
Methods Used: We isolated pure rat astrocyte cultures as in vitro model for PD pathogenesis and tested for the direct effect of alpha-synuclein oligomers in astrocyte calcium activity. Fluorescent microscopy utilizing a calcium indicator Fluor-4AM was used to obtain astrocyte images over a time at randomly selected fields of view.
Summary of Results: Our preliminary results have shown that application of 3 different concentrations of alpha-synuclein oligomer, 2.33, 5, and 7 μM, produces a statistically significant difference in the percentage of cells that produced intracellular calcium transients, or oscillation in calcium concentration (Chow, S, Yu, D, MacDonald, C L, et al., 2010): averaging 81.81% in the treatment groups and 18.01% in the control group. The average number...
Male Sprague-Dawley (8 weeks, 150-190 g) rats were subjected to a translational acceleration of at least 150g and to a rotational acceleration of 600g. The purpose of the study was to investigate the effects of these acceleration levels on the brain. The results showed that the brains of the rats subjected to these accelerations showed signs of damage, including regions of edema, necrosis, and hemorrhage. These findings are consistent with previous studies that have shown that these acceleration levels can result in mild traumatic brain injury (mTBI) in rats.

Our next approach is to investigate specific astrocyte protein expressions as well as mathematically model the signaling dynamics to better understand the implication of our data. The outcome of this project may have an implication in expanding current treatment strategies of PD through discovering a novel target for therapy in astrocyte. Moreover, understanding astrocyte functions and the nature of their interaction with neuronal disease pathways may expand current understanding of not only the onset of neurodegenerative disorders, but also of the different aspects of the brain.

**Summary of Results:**
- There was a significant reduction in the incidence of PNALD when compared to a standard lipid regimen.
- The primary outcome was PNALD, defined as a conjugated bilirubin of greater than 2 mg/dL for two consecutive blood draws over at least two weeks.
- Chi-squared tests, the Wilcoxon signed-rank test and t-tests were used to compare control and experimental data.

**Conclusions:** Lipid minimization is associated with a reduction in the incidence of PNALD associated with a lower incidence of PNALD when compared to a standard lipid regimen.

**Methods Used:** Surgical patients with necrotizing enterocolitis, gastrochisis, and jejunoileal atresia admitted to our institution over a 6-year period from 2005 to 2011 were retrospectively reviewed. The control group (132 patients) was admitted between 2005-2008, while the experimental group (83 patients) was admitted between 2009-2011. Weekly liver function tests for each patient were recorded. The primary outcome was PNALD, defined as a conjugated bilirubin of greater than 2 mg/dL for two consecutive blood draws over at least two weeks. Chi-squared tests, the Wilcoxon signed-rank test and t-tests were used to compare control and experimental data. A multivariable logistic regression model was constructed to model the association of lipid minimization with the development of PNALD.

**Conclusion:** Lipid minimization is associated with a reduction in the incidence of PNALD when compared to a standard lipid regimen.
Purpose of Study: Atlanta-occipital dissociation (AOD) injuries must be rapidly diagnosed due to the potential for significant patient morbidity and mortality. Despite the significant danger posed by cranio-ocular instability, accurate diagnosis of AOD remains difficult due to a lack of reliable radiodiagnostic criteria. The aim of this study is to evaluate the utility of a simplified crano-cervical interval (CCI) in detecting AOD in comparison to five standard diagnostic techniques.

Methods Used: CTs of the cervical spine were reviewed in 20 patients with upper cervical injury including 10 with AOD. Images underwent blinded review by a radiologist, two orthopedists, and two medical students. The five standard measurements for AOD (BDI, BAI, Powers’ ratio, Sun’s, Lee’s X-line) and the proposed CCI were applied for determination of sensitivity, specificity, and positive and negative predictive values. Abnormal CCI was defined as a distance >2.5 mm at point of greatest separation between occipital condyle and C1 lateral mass. Measurement was taken bilaterally on sagittal CT at midpoint of the lateral mass (Image). Interobserver agreement was also tabulated.

Summary of Results: For continuous measures, data is expressed as mean ± sd (Table). CCI had a sensitivity, specificity, PPV, and NPV for AOD at 1.0, 0.84, 0.87, and 1.0 respectively. Sensitivity for CCI was significantly larger than the next sensitive measurement, BDI (1.0 vs. 0.70, p < .001). BDI, BAI, and CCI show good to excellent agreement between readers on data from all patients and all raters, with ICC’s of 0.83, 0.78, and 0.88 respectively. Poor agreement between readers is seen with Sun’s ratio and Powers’ ratio, with ICC’s of 0.31 and 0.40 for all raters on all patients. Poor agreement is also seen in assessment of abnormality of Lee’s lines, with a Light’s kappa coefficient of 0.30 for all raters on all patients.

Conclusions: The simplified CCI has the highest diagnostic sensitivity for AOD among all other radiodiagnostic criteria and provides a useful tool to detect AOD.

135 COMPARISON OF EXTRACORPOREAL SHOCKWAVE STONE DISSOLUTION AND URETEROSCOPIC HOLMIUM LASER STONE FRAGMENTATION FOR THE TREATMENT OF URINARY STONES

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Purpose of Study: The harmful effects of radiation are well known to physicians. As a result, physicians are urged to practice the ALARA principle to maintain radiation exposure “as low as reasonably achievable.” Since fluoroscopy is a frequently used tool in many diagnostic and therapeutic surgical procedures, identification of techniques to decrease radiation exposure is important. The purpose of this study is to compare fluoroscopy time and success rates between two methods routinely used to treat urinary calculi including ureteroscopic holmium laser stone fragmentation (URS) and extracorporeal shockwave renal stone fragmentation (SWL).

Methods Used: A retrospective review of patients treated with SWL or URS was conducted between January 2007 and June 2011 at a single center (n = 426). Fluoroscopy time, operative time, perioperative complications, stone size, stone location, and postoperative outcomes were compared using a Student’s t-test and chi-square (α = 0.05).

Summary of Results: Mean fluoroscopy time for SWL was nearly three times longer than that of URS stone surgery (157.8 vs. 55.7 s, respectively, p < 0.001). The mean operative time was longer for URS (69.6 vs. 46.2 min.; p < 0.001). URS had a higher overall stone free rate (84.6% vs. 72.5%; p = 0.005) and also had a higher stone free rate for renal stones than SWL (86.9% vs. 69.8%; p = 0.001). Stone free rates for ureteral stones were similar between the two procedures, (86.7% vs. 82.6%; p = 0.372). However, patients undergoing URS had longer hospitalization times (0.32 vs. 0.042 days; p < 0.001).

Conclusions: Both procedures had low hospitalization times and high success rates, however the fluoroscopy time was much longer with SWL. Radiation exposure should be considered when selecting a treatment modality.

136 CLINICAL LIVER TRANSPLANT OUTCOMES IN PATIENTS WITH PULMONARY HYPERTENSION

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Purpose of Study: Patients with severe pulmonary hypertension (pHTN) are at increased risk for worse outcomes post-liver transplant (LT) including pulmonary complications, delayed liver function, graft loss, and decreased survival. This study evaluates outcomes and complications for a large number of LT patients with mild to moderate pHTN.

Methods Used: This is a retrospective review of data from 2001 to 2011. All cases of pHTN were diagnosed with echocardiogram and categorized according to standard criteria: low mild 25-29 mmHg; mild 30-34 mmHg; moderate 35-44 mmHg; severe ≥45 mmHg. Our center protocol excludes most patients with known moderate and severe pHTN from LT. Median follow-up was 65 months. Outcomes included early liver function, ventilator days, intensive care unit (ICU) days, hospital length of stay (LOS), and graft and patient survival.

Summary of Results: Cardiac and pulmonary records for 1263 patients were reviewed. There were 102 patients with confirmed pHTN (8%); 63 low mild, 30 high mild, and 9 moderate. The patients with pHTN were older (p < 0.001) and had a higher donor age (p = 0.01). Comparing pHTN patients to non-pHTN patients (means): ventilator days 6 vs 4 (p = 0.02); ICU days 11 vs 7 (p = 0.01); LOS 18 vs 15 days (p = 0.08). Patient survival was: 90-day 95% vs 93% (p = 0.95); 1-year 82% vs 88% (p = 0.14), with 1-year graft survival 79% vs 87% (p = 0.05). There was a significant trend with increasing severity of pHTN towards more days on the ventilator, in the ICU, and overall LOS. There were no group differences for risk of myocardial infarction, stroke, or deep venous thrombosis. Cox regression failed to demonstrate a significant difference in long-term patient survival when accounting for MELD score, hepatitis C infection, and donor and recipient age.

Conclusions: These results demonstrate worse clinical outcomes for patients with any pHTN. Such patients must be carefully evaluated prior to LT as even patients with mild pHTN will require more hospital resources and are at risk for poorer long-term outcomes. A possible cause for the worse outcomes is the older age for the recipients with pHTN. It is unclear from these data if older patients with cirrhosis are at higher risk of pHTN when compared to younger cirrhotic patients.

137 FLUOROLESS VERSUS CONVENTIONAL URETEROSCOPY: A COMPARISON STUDY

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Purpose of Study: The US FDA has issued a recommendation to decrease radiation from fluoroscopy, CT and nuclear medicine imaging. During the course of a ureteral stone episode, a patient is at risk for multiple doses of radiation both from diagnostic sources such as computed tomography (CT) as well as therapeutic sources with fluoroscopy routinely employed extensively during endoscopic stone treatment. The purpose of this study is to compare the safety and feasibility of performing ureteroscopic laser lithotripsy to remove urinary stones entirely without image guidance. No previous study has reported complete upper urinary tract endoscopic stone treatment without fluoroscopy or ultrasound. In addition we compared the outcomes of a cohort of fluoroscopy patients to a group of conventional ureteroscopy patients.

Methods Used: A retrospective review of 25 patients who received ureteroscopic lithotripsy treatment without fluoroscopic or other imaging was performed and the outcomes of the procedure were analyzed to determine safety and efficacy. In addition this cohort was compared to a cohort of conventional ureteroscopy patients performed during the same time period. Continuous variables were compared using a paired two-tailed student’s t-test and chi-square (α = 0.05).
Summary of Results: All 25 fluoroscopy procedures were successfully completed with no requirement of intraoperative image guidance including fluoroscopy. In addition there were no complications in the fluoroscopy group. When the two groups were compared there was no difference in gender, age, BMI, stone laterality, stone size, or need for additional procedures. There was a significantly lower operative time in the fluoroscopy group (61 vs. 100 min; p < 0.01) and a markedly lower fluoroscopy time in the fluoroscopy group (0.00 vs. 28.4 sec; p < 0.01) compared to the conventional group.

Conclusions: In select patients, an experienced surgeon can safely and effectively perform fluoroscopy ureteroscopic stone removal. Application of this technique reduces in radiation exposure with no increased operative time or complications.

Methods Used: Thirty-seven children underwent ETV or posterior fossa tumor resection for the treatment of clinically and radiologically confirmed hydrocephalus. T2-weighted axial MR images of the orbit were obtained and tumor resection was performed to treat the pediatric hydrocephalus. A post-operative ONSD was measured just behind the optic globe pre- and post-surgical intervention. The ONSD appears to diminish, in response to measures to reduce hydrocephalus. Findings such as optic bulging and tortuosity also supported the clinical significance of ONSD reduction.

Summary of Results: There was significant reduction in the ONSD post ETV (n = 19) and posterior fossa tumor resection surgery (n = 18). The average pre-operative ONSD was 6.42 mm versus 5.73 mm post-operatively (p < 0.0001, paired t-test). There was also a 90% (p < 0.0001, chi-square) and 61% (p = 0.005, chi-square) reduction in optic bulging and tortuosity, respectively after surgery. The magnitude of ONSD reduction was similar in both ETV and tumor resection group. After intervention, all 37 patients experienced a decline in function less pronounced than Group 2, at 76% of baseline 6 hours after brain death was induced. Group 3 experienced a decline in function less pronounced than Group 2, at 76% of baseline 6 hours after brain death. Cytokine results showed comparable serum IL-6 concentrations between Group 1 and Group 3, at 67 pg/mL and 42 pg/mL respectively. Group 2 had a grossly elevated serum level of IL-6 at 1256 pg/mL. The contractility data is representative of two animals in Groups 1 and 3, and three animals in Group 2, while the cytokine data is representative of one animal from each group pending analysis of the remaining animals.

Conclusions: There appears to be a correlation between higher plasma concentration of IL-6 and depressed myocardial contractility, supporting the intervention of hemoadsorption of cytokines to attenuate brain death-induced ventricular dysfunction. A larger sample is necessary to determine whether these results are reproducible and statistically significant.
Method Used: A retrospective chart review was performed at 3 institutions between February 1993 and May 2011, of which 127 patients who presented with entombed stents qualified for our study. Patient demographics, surgical approach, and clinical outcomes were gathered and analyzed using a Student’s t-test and chi-square (α = 0.05).

Summary of Results: In the unimodal approaches (n = 60), procedures included cystoscopy (n = 17), ureteroscopy (n = 25), extracorporeal shockwave therapy (n = 13), and a percutaneous approach through the kidney (n = 5). Among multimodal therapies (n = 67), the most common multimodal approach was a combination of extracorporeal shockwave therapy + ureteroscopy + cystoscopy (n = 22). Median indwelling stent time was similar (11.8 vs. 13.5 months) when comparing the unimodal and multimodal treatment groups, respectively (p = 0.49). Multimodal treatments had a higher success rate of 82.1% versus the 61.7% success rate of unimodal treatments in a single setting (p = 0.01). The complication rates did not differ in multimodal treatments compared to unimodular therapies (31.3% vs. 22.4%; p = 0.27).

Conclusions: Because multimodal treatment demonstrated a higher success rate, this approach should be considered for patients with entombed stents rather than unimodal treatments.

142 DETERMINING VOLUME OF KIDNEY STONES IMPLEMENTING OSIRIX SOFTWARE
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Purpose of Study: The determination of stone burden is crucial in endourology to accurately predict stone size and surgical complexity, but it is often accessed using two-dimensional measurements on computed tomography (CT) or plain films. Three-dimensional stone volume would be a more accurate estimate of stone burden, but there is no easily applied technique to measure volume. The purpose of this study was to determine the feasibility and accuracy of OsiriX computer software to calculate three-dimensional stone volume.

Methods Used: CT images were taken of 124 urinary stones, ranging from 5.58 to 31.42 mm in diameter that were randomly placed within the kidneys of a human cadaver. Volumes of the kidney stones were calculated using OsiriX imaging software using 1.25, 2.5, and 5 mm slice reconstruction and were then compared with stone volumes determined using water-displacement. Repeated measures ANOVA and least squares mean analysis (α = 0.05) were performed on the collected data.

Summary of Results: It was determined that OsiriX calculated kidney stone volumes for stones >1 mL with a median error of 4.17% (1.25 mm slice thickness), 4.89% (2.5 mm slice thickness), and 5.58% (5 mm slice thickness). However, there was a significant difference (p < .001) in mean error when using stones <1 mL at 5 mm cuts (40.8%) compared to 1.25 mm (24.2%) and 2.5 mm cuts (30.1%). The OsiriX software was fast and easy to use and could determine stone volume in an average of 10.3 seconds.

Conclusions: OsiriX computer software is fast and easy to use for the calculation of three-dimensional stone volume in stones greater than 1 cc. However, error increases as stone size decreases, but may be reduced by the use of 1.25 mm slice reconstruction. Use of this free software program to calculate stone volume could prove to be a valuable clinical and research tool for predicting larger stone volumes.

143 SOFT TISSUE DAMAGE BY OSCILLATING SAW BLADE DURING TOTAL KNEE ARTHROPLASTY
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Purpose of Study: Iatrogenic intraoperative damage to medial collateral ligament during total knee arthroplasty is an uncommon, yet devastating, complication that threatens the success of the surgery. While the cutting tip of the blade is intuitively deemed to be hazardous to the soft tissue, the contribution of the side of the blade to the soft tissue damage has been ignored. We believe that changes in the design of the blades can reduce the risk of tissue damage. The hypotheses of this study were (1) some blade tip designs have less risk of tissue damage, and (2) changes in the design of the side of the blade will reduce the risk of tissue damage.

Methods Used: Fresh frozen bovine tendon specimens (5 × 5 × 20 mm) were prepared for biomechanical testing. After being secured into a materials testing machine, each specimen was tensioned at 100 N. A surgical saw with blade was placed on sliding tracks facing the specimen. 3 different blades were used. The saw was pushed into the specimen using a dead weight to initiate cutting. The tip-cutting and side-cutting were achieved by changing the orientation of the saw. The process was recorded with high-speed cameras to measure the time required to cut the tendon.

Summary of Results: We found that the rounding off the side of the blade decreases the cutting rate by 3 to 10 folds.

Conclusions: The risk of intraoperative damage to medial collateral ligament can be reduced by rounding off the side of the oscillating bone saw blade; this modification can further fortify the success rate of total knee arthroplasty.

144 WHITE MATTER INTEGRITY IN INSULIN AND FFNF IMPPLICATED IN BULIMIA NERVOSA NERVOSA
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Purpose of Study: This study investigated brain white matter (WM) functionality in bulimia nervosa (BN) in order to better characterize brain function in this disorder.

Methods Used: Twenty-one control women (CW, mean age 27 ± 7 years) and 19 women with BN (mean age 25 ± 5 years) underwent diffusion tensor imaging (DTI) of the brain to calculate fractional anisotropy (FA; giving an indication of WM axon integrity) and the apparent diffusion coefficient (ADC; reflecting WM cell damage). Additionally, these measures were correlated with behavioral data collected.

Summary of Results: Insula and fornix FA were significantly reduced in BN and FA values in those regions were negatively correlated with state and trait anxiety in CW but not BN. ADC values were increased in BN in the fornix, frontal WM regions, and the superior longitudinal fasciculus. BN ADC values were positively related to bulimia symptoms and adverse childhood events.

Conclusions: WM integrity is disturbed in BN, and fornix and insula WM axon abnormalities are particularly implicated in BN, as previously reported in anorexia nervosa. Bulimic behavior and adverse childhood life events seem to be directly related to WM cell break down in BN.

145 A PROFILE OF DEPRESSED MEDICAL STUDENTS
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Purpose of Study: The aims of the study are: (1) To determine the prevalence of depressive symptoms in a national sample of medical students; (2) to identify correlates of depressive symptoms, and; (3) to test the buffering role of social support in reducing depression symptoms.

Methods Used: This cross-sectional study, used data from 2,682 medical students from 36 U.S. accredited medical schools who completed a 10-minute, web-based Health and Lifestyle Questionnaire in 2005. The measures in the questionnaire included: a 43-item Readjustment Rating Scale (SRRS), a 10-item Alcohol Use Disorder Identification Test (AUDIT), a 15-item social support index, and a 10-item Center for Epidemiologic Studies Depression Scale (CES-D).
Summary of Results: The sample consists of 40.0% male, 59.9% female. The average CES-D score was 12.6 (SD = 10.3). Of the sample, 18.4% had mild depressive symptoms (CES-D score 5-10), 26.0% had severe depressive symptoms (CES-D score ≥16). With the exception of illicit drug use and social support, none of the independent variables showed significant relationship with severity of depressive symptoms among the students who scored ≥16 on the CES-D. Results of stepwise multiple regression analysis show that among students who scored ≥16 on the CES-D and controlling for the confounding effect of age, gender, year in medical school, smoking, drinking, illicit drug use; stressful life events continued to be associated with severe depressive symptoms (β = 0.69, p < 0.01). None of the covariates predicted CES-D scores except for illicit drug use (β = 1.33, p < 0.05). In addition, students who had more social support showed lower relationship between stress and severity of depressive symptoms (β = -0.37, p < 0.05). Cross-sectional data reveal that stress is prevalent in medical students and are significantly associated with the number of stressful life events. In addition, the presence of social support is a protective factor that buffers the negative psychological impact of stressful events on medical students. Our next step is to identify source(s) of stress and support, to develop effective interventions and coping skills.

146 CHARACTERIZATION AND THERAPEUTIC POTENTIAL OF INDUCTED PLURIPOTENT STEM CELL-DERIVED CARDIOVASCULAR PROGENITOR CELLS
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Purpose of Study: Cardiovascular progenitor cells (CPCs) have been identified within the developing mouse heart by expression of the transcription factors Nkx2.5 and Isil. Detailed study of endogenous CPCs has been limited due to the lack of specific cell-surface markers needed to isolate them and the absence of suitable conditions to expand them in vitro. We sought to identify specific cell-surface markers to label endogenous embryonic Isil+ CPCs and functionally validate these CPC markers in induced pluripotent stem cell (iPSC)-derived Isil+ progenitors. Furthermore, we developed conditions that would allow for the propagation and characterization of these CPCs and protocols for their clonal expansion in vitro and transplantation in vivo.
Methods Used: Total RNA from CPCs was isolated (Qiagen RNasy), amplified (Illumina RNA Amplification kit) and gene expression quantified using Illumina microarrays. Fluorescence Activated Cell Sorter at the UCLA Core Flow Cytometry Laboratory was used to quantify Flt1+/Flh4+ cells. Differentiation was assessed by PCR and immunostaining for a panel of cardiovascular markers. Summary of Results: To identify cell surface markers for the isolation of CPCs from iPSCs, we analyzed the transcriptome of Isil+ CPCs. This analysis of Isil+/Flh4+ mouse CPCs identified a panel of surface markers expressed on Isil+ CPCs. Comparison of these markers revealed that the combination of Flt1+/Flh4+ best identified and facilitated the purification of Isil+ CPCs from embryonic hearts as well as differentiating iPSCs. To investigate their in vivo potential to differentiate into cardiomyocytes (CM), Flt1+/Flh4+ cells were isolated from GFP+ murine iPSCs, maintained in proliferation medium, and transplanted into syngeneic adult hearts. Three weeks post-CPC transplantation, hearts were harvested and immunofluorescence imaging demonstrated robust engraftment and differentiation into mature adult CMs in vivo.
Conclusions: We have demonstrated that the combination of cell surface markers Flt1 and Flh4 specifically identify an Isil+ CPC with trilineage cardiovascular potential in vitro and robust ability for engraftment and differentiation into CMs in vivo post transplantation.

147 DEPRESSION IS COMMON IN TB PATIENTS AND IS ASSOCIATED WITH TREATMENT ABANDONMENT
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Purpose of Study: Tuberculosis (TB) is associated with poverty, stigma and marginalization, which are risk factors for psycho-morbidity, but little is known about the mental health of TB patients. We therefore studied interactions between TB, depression, socio-demographic factors and TB treatment adherence among the urban poor.
Methods Used: Over 7 years, patients with newly diagnosed or recurrent TB and randomly selected healthy controls from shantytowns in Lima were evaluated in a case control study and the patients were then followed-up to determine their treatment outcome. Each participant provided demographic and socio-economic data and completed a Beck Depression Inventory (BDI). Depression scores were adjusted for overlap with the physical symptoms of TB. Poverty was assessed with a composite socio-economic index. Data were analyzed with linear and logistic regressions.
Summary of Results: TB patients (n = 1,734) had frequent depression (53%), severe depression (15%) and suicidal ideation (4.7%). Depression was more common and depression scores were higher in than in randomly selected healthy members of the same community (n = 470; both P < 0.005), independently of poverty, education and other cofactors. For TB patients, higher depression scores were independently associated with female gender, poverty, incomplete schooling, illicit drug use, perceived discrimination and longer delay in seeking medical care for TB symptoms (all P < 0.01). Furthermore, a prior history or current episode of treatment abandonment was significantly related to current depressive state (OR 1.8, P < 0.001).
Conclusions: Depression was highly prevalent among newly diagnosed TB patients and especially associated with prior treatment abandonment. TB programs may optimize disease control, treatment adherence and quality of life by diagnosing and addressing the mental health issues that affect TB patients.

148 METHYLATION IN REGIONS OF EXECUTIVE FUNCTION IN THE DEVELOPING HUMAN BRAIN
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Purpose of Study: Despite growing recognition of the importance of DNA methylation for development, the nature and plasticity of DNA methylation remains poorly understood. We performed methylation studies on candidate genes in fetal brain regions responsible for executive function, in order to determine regional methylation status through early brain development, and to determine to what extent a peripheral sample (buccal swab) reflects the central nervous system.
Methods Used: Fetal tissue samples were obtained from 4 whole brain specimens 14-22 weeks gestation and the following regions dissected: dorsal premotor cortex, anterior cingulate cortex, and a peripheral (cheek) sample. DNA was isolated using a commercial DNA isolation kit. Methylation profiling was performed using a methylation BeadChip array (Illumina, USA) on the following genes: dopamine receptor 2 and 4 (DRD2, DRD4), catechol-O-methyltransferase (COMT), and dopamine transporter 1 (DAT1). DNA was converted with sodium bisulfite, amplified (Illumina RNA Amplification kit) and gene expression quantified using Illumina microarrays. Fluorescence Activated Cell Sorter at the UCLA Core Flow Cytometry Laboratory was used to quantify Flt1+/Flh4+ cells. Differentiation was assessed by PCR and immunostaining for a panel of cardiovascular markers. Summary of Results: To identify cell surface markers for the isolation of CPCs from iPSCs, we analyzed the transcriptome of Isil+ CPCs. This analysis of Isil+/Flh4+ mouse CPCs identified a panel of surface markers expressed on Isil+ CPCs. Comparison of these markers revealed that the combination of Flt1+/Flh4+ best identified and facilitated the purification of Isil+ CPCs from embryonic hearts as well as differentiating iPSCs. To investigate their in vivo potential to differentiate into cardiomyocytes (CM), Flt1+/Flh4+ cells were isolated from GFP+ murine iPSCs, maintained in proliferation medium, and transplanted into syngeneic adult hearts. Three weeks post-CPC transplantation, hearts were harvested and immunofluorescence imaging demonstrated robust engraftment and differentiation into mature adult CMs in vivo.
Conclusions: We have demonstrated that the combination of cell surface markers Flt1 and Flh4 specifically identify an Isil+ CPC with trilineage cardiovascular potential in vitro and robust ability for engraftment and differentiation into CMs in vivo post transplantation.

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Summary of Results: Of the 170 CpG sites in the selected genes, 57 were in COMT, 69 in DAT1, 22 in DRD2, and 22 in DRD4. These CpG sites were distributed across the promoter, 5'UTR, first exon, gene body, and 3'UTR. Preliminary results indicated that it was possible to detect significant variability in methylation at 77 of these CpG sites. There were no detectable differences between methylation at the left and right hemispheres in the brain regions examined, and few significant differences between methylation at CpG sites within brain regions and methylation in cheek samples. Methylation status decreased with increasing gestational age for all 4 genes in all regions.
Conclusions: It is possible to identify regions of epigenetic variation in developmentally important genes in fetal brain samples. Moreover, brain and cheek tissues shared similar DNA methylation patterns within the same individual at the genes of interest. Variably methylated gene regions represent a new target for understanding biological diversity during early development.
EFFECT OF Dipeptidyl Peptidase-IV Inhibitor Treatment on Post-prandial Glucagon and Glucagon-like Peptide-1 Levels in Patients with Type 1 Diabetes: An Investigator-initiated, Double-blind, Randomized, Placebo-controlled Trial

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Purpose of Study: Peripheral insulin resistance in type 1 diabetes may be related to increasing body mass index (BMI), subcutaneous insulin delivery and a small, but significant, paradoxical rise in glucagon after meals. Dipeptidyl peptidase-IV (DPP-IV) inhibitors increase glucagon-like peptide-1 (GLP-1) resulting in a decrease in the paradoxical post-prandial rise of glucagon. This study evaluated the effects of sitagliptin, a DPP-IV inhibitor approved for patients with type 2 diabetes, in adult patients with type 1 diabetes (off-label). Our previous small pilot study evaluating the use of sitagliptin in patients with type 1 diabetes showed a statistically significant improvement in glucagon control, insulin dose and HbA1c while patients were taking sitagliptin.

Methods Used: This investigator-initiated, multi-center, double-blind, randomized, parallel, 20-week study enrolled 141 adult subjects with type 1 diabetes. The primary outcome was post-meal reduction in 4-hour glucagon area under the curve (AUC) following a meal challenge test with Boost® DM. Subjects received sitagliptin 100 mg/day or matching placebo for the 16-week study period following a 4-week run-in phase. A subset of 100 patients were blinded continuous glucose monitors (CGM) for 5 separate 7-day periods during the study. Secondary endpoints included changes in HbA1c, insulin dose, weight, hypoglycemia and GLP-1 and glucose-dependent insulinotropic peptide (GIP) levels and CGM data analysis.

Summary of Results: The baseline characteristics were similar between the two groups. The results from this trial are currently being analyzed.

Conclusions: We predict that sitagliptin use in type 1 diabetes will improve glucagon control (HbA1c) with a potential reduction in insulin dose or weight by decreasing the paradoxical rise in glucagon after meals. We further predict that the drug will be effective in increasing post-meal GLP-1 and GIP levels, similar to what occurs in patients with type 2 diabetes.

150 CAN THE TIMED UP AND GO DEFINE SEVERITY OF FALL RISK?

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Purpose of Study: We sought to determine whether Timed Up and Go (TUG) time could be used to predict fall risk in patients with type 1 diabetes. To our knowledge, TUG time has not been previously examined.

Methods Used: Patients from an outpatient fall prevention clinic in Seattle were enrolled in a prospective chart review study. Patients were sorted into low-, medium- and high-risk groups based on their TUG time (<9, 10-19, and ≥20 seconds, respectively) at their first clinic appointment. Nonparametric and t-tests were used to compare these groups on demographics, comorbidities associated with falling, modifiable fall risk factors, and fall-related healthcare use.

Summary of Results: Statistically significant differences were observed between the 3 groups in the percent with cognitive impairment (low-risk 0% vs. medium-risk 14% vs. high-risk 58%, P < 0.01), coronary artery disease (0% vs. 19% vs. 17%, P < 0.01), obesity (0% vs. 16% vs. 25%, P < 0.01) and mean number of comorbidities (1 vs. 2 vs. 2 comorbid conditions, P = 0.02). Non-significant trends across groups were noted for use of 24 medications, (63% vs. 76% vs. 83%), presence of a gait or balance disorder (75% vs. 89% vs. 92%), lower extremity weakness (63% vs. 70% vs. 83%), poor visual acuity (25% vs. 35% vs. 50%), and depression (25% vs. 35% vs. 50%). The medium- and high-risk groups were more likely to be prescribed a hypoglycemic medication and less likely to be taking a vitamin D supplement. More serum vitamin D levels tended to be lower among those in the high-risk group (32.7 vs. 31.6 vs. 23.0 ng/mL).

Conclusions: Both statistically significant differences and non-significant trends were seen between the three groups defined by TUG time. The TUG test is easy to administer, and fall risk factor profiles based on TUG time have relevance both for future fall prevention research as well as for clinicians and aging service providers seeking to match patients at risk for falling with the most appropriate fall prevention program.

151 LIMITING FEEDING CHANGES APOPTOSIS AND PROLIFERATION IN THE LIVER OF PRETERM LAMBS SUPPORTED BY NASAL HIGH-FREQUENCY VENTILATION

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Purpose of Study: Feeding intolerance is a frequent problem with preterm neonates who develop neonatal chronic lung disease (CLD). The consequence of inadequate feeding on molecular participants in organ injury is unknown. Our preterm lamb model of neonatal CLD provides opportunity to test the role of inadequate feeding because preterm lambs supported by mechanical ventilation (MV) for 21d repeatedly have residual milk in their stomach. In contrast, preterm lambs supported by nasal high-frequency ventilation (HFV) for 21d rarely have residual milk in their stomach. Associated with prolonged MV is poor somatic growth and decreased hepatocyte proliferation. Whether decreased hepatocyte proliferation, as an index of liver injury, is related to inadequate feeding is not known. We hypothesized that limiting feeding of preterm lambs supported by nasal HFV for 21d will change injury indicators in the liver.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV for 21d or nasal HFV for 21d (n = 4/group). A third group of PT lambs (‘paired-feeding’ group) was supported by nasal HFV and limited to the same amount of ewe’s milk that is tolerated by PT lambs supported by MV. Apoptosis (cleaved caspase 3) and proliferation (proliferating cell nuclear antigen, PCNA) were assessed by immunohistolot.

Summary of Results: The paired-feeding group tolerated less milk daily (mL/Kg/d; P < 0.05) than the nasal HFV group, and the same amount as the MV group. At 21d, body weight of the groups was not different. In the liver, cleaved caspase 3 protein abundance was the same among the groups. On the other hand, PCNA protein was less (p < 0.05) in the paired-feeding group than the nasal HFV group (p < 0.05), and the same as the MV group.

Conclusions: Limiting nutrition to chronically ventilated preterm lambs may contribute to poor liver outcome by reducing hepatocyte proliferation. IGF-1 may be a relevant growth factor because it is subject to epigenetic changes that may be determined by nutrition. (HL110002, HL062875, HL056401, HD41075)

152 DE NOVO MICRODELETION OF XPL1 TARGETING THE MONOAMINE OXIDASE A AND B GENES IN A MALE INFANT WITH EPISODIC HYPTONIA: A GENOMICS APPROACH TO PERSONALIZED MEDICINE

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Purpose of Study: Monoamine oxidase A and B play key roles in deaminating neurotransmitters, biogenic metabolites, and dietary amines. Patients deficient in one or both enzymes have distinct metabolic and neurologic profiles. MAOdeficient patients exhibit normal clinical characteristics and behavior, while MAOdeficient patients have borderline cognitive deficiency and impaired impulse control. Patients who lack both MAOA and MAOB tend to have the most extreme laboratory values (urine serotonin 3-4 times normal; urine dopamine 3-5 times normal; marked elevations in O-methylated amine metabolites and marked decreases in deaminated metabolites) in addition to severe mental deficiency and behavioral problems. Mice lacking maoa and moab exhibit decreased proliferation of neural stem cells beginning in late gestation and persisting into adulthood. These mice show significantly increased monoamine levels, particularly serotonin, as well as anxiety-like

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behaviors as adults, suggesting that brain maturation in late embryonic development is adversely affected by increased serotonin levels. 

Methods Used: We report the case of a male infant with a de novo XIp11.2 microdeletion targeting the MAOA and MAOB genes. The concentrations of monoamine substrates were measured in urine, serum, and CSF after dietary manipulation.

Summary of Results: This newly recognized X-linked disorder is characterized by severe cognitive deficiency and unusual episodes of hypotonia, which resemble absence seizures, but have no EEG correlate. A customized low tyramine diet was implemented in an attempt to normalize the monoamine profile of our patient.

Conclusions: Our study represents only the second recognized case of such a deletion and the first to treat this disorder through dietary manipulation. The use of serotonin synthesis inhibitors like p-chlorophenylalanine and p-ethylphenylalanine could potentially be even more effective in lowering serotonin levels in the absence of monoamine oxidase enzymes.

153 EFFECT OF PHYSICIAN FOLLOW-UP AND SPECIALTY DIFFERENCES ON 30-DAY READMISSION FOR HEART FAILURE PATIENTS

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Purpose of Study: To determine whether heart failure patients who have an outpatient physician visit within 30 days after discharge have a lower rate of 30-day readmission than patients without such a visit. The study also examines whether the medical specialty of the physician seen at the first outpatient visit has an effect on the rate of 30-day readmission.

Methods Used: The study examined 1265 Medicare Advantage patients discharged with a principal diagnosis of heart failure from an academic medical center between June 2005 and July 2010. Only those hospitalizations not preceded by another hospitalization within 30 days were included. Inpatient and outpatient records were examined to determine if a rehospitalization occurred within 30 days and if an outpatient visit occurred within 30 days of these index hospitalizations. Outpatient visits occurring after a rehospitalization were not included. Medical staff rosters were used to determine the identity and specialty of physicians who provided the initial post-discharge outpatient care. The study examined the relationship between 30-day readmissions and outpatient visits within 30 days using bivariable and multi-variable analyses.

Summary of Results: Of heart failure patients who saw a physician within 30 days after discharge, 17.0% had a 30-day readmission, compared to 29.8% of patients who did not see a physician. Compared to a reference group of patients who had no outpatient visit, the adjusted odds ratio for 30-day readmission for patients who first saw a cardiologist was 0.33. The odds ratios for patients seen by primary care and other specialty physicians were 0.48 and 0.49, respectively.

Conclusions: The study suggests that patients discharged for heart failure should have physician follow-up within 30 days after discharge to reduce the risk of 30-day readmission. The follow-up should be with a cardiologist for the greatest reduction in readmission risk.

154 MECHANISMS OF RESISTANCE TO THE B-RAF INHIBITOR ZELBORAF IN FOUR MELANOMA CELL LINES

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Purpose of Study: ZELBORAF (Vemurafenib/PLX4032) was recently approved by the FDA for late stage metastatic melanoma in patients with V600E B-RAF mutations. While extremely effective, most patients eventually develop resistance to the drug. Hypotheses for resistance mechanisms to B-RAF inhibitors include secondary mutations in B-RAF, MAPK reactivation through secondary mutations in N-RAS or C-RAF elevation, and upregulation of receptor tyrosine kinases (RTK) in alternative survival signaling. Here we seek to characterize how four patient derived melanoma cell lines, SKMEL28, M263, NK, and RP develop resistance to PLX4032.

Methods Used: Cell viability assays were performed to increasing concentrations of PLX4032 and the MEK1/2 inhibitor, AZD6244. Protein expression levels of phospho-ERK, total ERK, PDGFRB, EGFR, and tubulin were evaluated by western blot. Triplicate qPCR reactions normalized to tubulin were used to determine relative RTK RNA expression levels. Secondary mutations were assessed using bi-directional sequencing of gDNA.

Summary of Results: SKMEL28 and M263 PLX4032 resistant lines are also resistant to AZD6244 in cell viability assays. By qPCR, PDGFRB is upregulated in M263 PolyR (>100×) and M263 R3 (>30×), SKMEL28 PolyR over-expresses EGFR (>100×), and both PDGFRB and EGFR are upregulated in SKMEL28 R1 (50× and 20×, respectively). These results are confirmed at the protein level by western blot. M263 and SKMEL28 cell lines do not have secondary mutations in N-RAS and none of the resistant lines exhibit high p-ERK expression on western blot compared to their baseline parental counterparts. NK and RP resistant lines exhibit little RTK upregulation, but have high p-ERK expression at the protein level, with no secondary mutations in B-RAF, N-RAS, or H-RAS.

Conclusions: The data suggests SKMEL28 and M263 resistant cell lines escape B-RAF targeting through a MAPK-redundant pathway dependent on RTK upregulation, while the NK and RP resistant cell line data support resistant mechanisms through MAPK-reactivating survival signaling.

155 DECREASED INTRACELLULAR AND EXTRACELLULAR PRODUCTION OF THE T HELPER 1 CYTOKINE IL-17 BY CORD BLOOD MONONUCLEAR CELLS MAY CONTRIBUTE TO NEONATAL INFECTIONS

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Purpose of Study: Human neonates and immunocompromised hosts are uniquely susceptible to severe and overwhelming bacterial and fungal infections. Defective neonatal polymorphonuclear leukocyte (PMN) activation and movement contribute to this increased susceptibility. The T helper 1 (Th1) lymphocytes produce cytokines. Following stimulation and intracellular transcription these cytokines are secreted extracellularly to affect target tissues. The Th1 cytokine interleukin 17 (IL-17), has been described to act on fibroblasts and endothelial cells to recruit PMNs to sites of microbial invasion. Here, we examine cord blood MMCs production of IL-17 and measure intracellular IL-17 compared to adult controls.

Methods Used: Whole blood was collected from adults and umbilical cord blood from term deliveries. Mixed MMCs were isolated and stimulated with phytohemagglutinin (PHA), group B streptococcus (GBS) or E. coli, and then incubated for 24 hours in tissue culture medium. IL-17 production was measured utilizing Luminex multianalyte technology. Phorbol myristate acetate (PMA) stimulated intracellular IL-17 production was measured by flow cytometry.

Summary of Results: In response to stimulation with PHA, GBS, or E. coli, IL-17 production was significantly diminished in cord blood. PHA (cord n = 14, mean = 0.2 pg/mL; adult n = 16, mean = 455 pg/mL; p = 0.023). GBS (cord n = 10, mean = 0.2 pg/mL; adult n = 12, mean = 10.9 pg/mL; p = 0.004). E. coli (cord n = 10, mean = 0.0 pg/mL; adult n = 12, mean = 12.5 pg/mL, p = 0.061). Flow cytometry results demonstrate decreased PMA stimulated intracellular IL-17 production in the cord blood cells compared to cells from adults (cord n = 6; MFI = 0.0%; adult n = 5; MFI = 13.9%; P < 0.01).

Conclusions: IL-17 has a profound effect on the immune response to bacterial and fungal infections. For instance, IL-17 production is markedly deficient in autosomal dominant Hyper IgE (Job Syndrome) patients who suffer recurrent bacterial and candida infections. This study is the first to describe defective production of intracellular and extracellular IL-17 by neonatal MMCs; which may contribute to the human neonates increased susceptibility to microbial infections.

156 BUMPED KINASE INHIBITORS BLOCK MALARIA TRANSMISSION TO MOSQUITOES

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Purpose of Study: Current antimalarial drugs allow continued transmission of malaria from infected persons to mosquitoes and then back to people. Effective control and eradication of malaria will require new tools to prevent
transmission. Plasmodium calcium dependent protein kinase 4 (CDPK4) is essential for exflagellation of microgametes, sexual reproduction and infection of the mosquito host and is a potential drug target to block mosquito transmission. Plasmodium CDPK4 (PfCDPK4) has a unique ATP binding site which renders CDPK4 differentially sensitive to bumped kinase inhibitors (BKIs). Thus, we sought to synthesize a large panel of BKIs and characterize their in vitro activity against PfCDPK4, selectivity over human protein kinases, and in vivo activity against Plasmodium microgametocytes in both murine models and human blood samples.

Methods Used: A large panel of BKIs was synthesized by previously described methods. In vitro activity of BKIs against PfCDPK4 was determined using a nonradioactive Kinasegel luciferase assay. BKIs that displayed potency against PfCDPK4 were screened for in vitro activity against human protein kinases using a radioactive γP-ST ATP activity assay. In vivo studies included administering BKIs to mice infected with Plasmodium berghei as well as human blood samples containing P. falciparum microgametocytes both of which were fed to Anopheles mosquitoes. In both studies, microgametocyte exflagellation in mouse and human blood samples, ookyst formation in the mosquito midgut, and sporozoite production in the Anopheles salivary glands were measured.

Summary of Results: BKIs selectively inhibit PfCDPK4 over human protein kinases and prevent the exflagellation of Plasmodium microgametes. Administration of BKIs to mice stops the transmission of P. berghei to mosquitoes. Finally, addition of BKIs to blood containing P. falciparum gametocytes stops exflagellation of microgametocytes and blocks the infection of mosquitoes.

Conclusions: BKIs are non-toxic, selective inhibitors that block malaria transmission to mosquitoes, have a low likelihood of generating resistance, and are thus excellent leads for further drug development.

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IUGR INCREASES DNA METHYLATION OF THE PPAR-GAMMA PROMOTER 2 IN RAT VISCERAL ADIPOSE TISSUE

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Purpose of Study: Intrauterine growth restriction (IUGR) increases the risk for visceral obesity in humans and animal models, with males more affected. We have shown in adolescent male rats, that IUGR increases deposition of visceral adipose tissue (VAT) and mRNA levels of the pro-adipogenic transcription factor, PPARγ2, with no effect in female rats. Increased expression of the PPARγ gene may be influenced by epigenetics. Epigenetic modifications include DNA methylation. However, it is unknown if IUGR alters DNA methylation of the PPARγ2 promoter in male VAT. We hypothesize that IUGR will alter DNA methylation of PPARγ2 in adolescent male rat VAT at d21.

Methods Used: IUGR was induced by uterine artery ligation on day 19 of gestation in Sprague Dawley rats. VAT was harvested from offspring at postnatal day 21. Methylation changes in the PPARγ promoter 2 were detected using bisulfite modification and sequencing.

Summary of Results: IUGR increased DNA methylation of the PPARγ2 promoter 2 in male rat VAT (140 ± 12%)*. In contrast, IUGR did not significantly alter DNA methylation of PPARγ2 promoter 2 in female adolescent rat VAT (88 ± 17%)*. *p < 0.05.

Conclusions: In conclusion, IUGR increases PPARγ2 promoter methylation in VAT of adolescent male rats. Interestingly, we observed increased DNA methylation in association with increased mRNA levels of PPARγ2. We speculate that histone modifications along the PPARγ gene, are also affected by IUGR and that in combination these changes contribute to the increased PPARγ mRNA observed in IUGR rat VAT.

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NUCUAL THICKENING AND CYSTIC HYGROMAS: PREDICTING POSTNATAL OUTCOMES FROM PRENATAL ULTRASOUNDS

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Purpose of Study: To determine the prevalence and odds ratios of chromosomal anomalies and pregnancy outcomes in babies found to have nuchal thickening, cystic hygromas or lymphatic malformations during routine prenatal ultrasound.

Methods Used: We queried the UW ultrasound database for abnormal prenatal ultrasounds occurring between 2002 and 2008. We obtained a sample of 326 patients, 76 were excluded because they did not follow up for treatment at UWMC or demonstrated abnormalities outside the scope of our investigation, leaving a final study population of 250. We retrospectively charted all fetal structural abnormalities, chromosomal anomalies and pregnancy outcomes in this population. Prevalence and odds ratios of various postnatal outcomes were calculated based upon these prenatal findings.

Summary of Results: A preliminary review of study results suggests that cystic hygromas are a statistically more powerful predictor for fetal chromosomal anomalies including trisomy-21, Turner's and Patau syndrome, as compared to nuchal thickening alone. Furthermore, babies found to have cystic hygromas are much more likely to undergo elective or spontaneous termination of pregnancy. Lymphatic malformations, on the other hand, are not related to chromosomal anomalies and have a much higher rate of spontaneous resolution in utero as compared to cystic hygromas.

Conclusions: Prenatal ultrasound is standard procedure with numerous diagnostic capabilities yet a great degree of variability exists among physician's opinions regarding the significance of various findings. Confounding terminology and contradictory conclusions among studies has further obscured the physician's ability to interpret prenatal ultrasounds. We believe that our research provides the clinician with a clearer understanding as to the clinical relevance of nuchal thickening vs. cystic hygromas. This information will ultimately provide for better prenatal counseling to parents and allow the clinician to make more educated decisions about subsequent diagnostic testing and patient management.
The Dorsal Medial Hypothalamus Mediates Pain Hypersensitivity Induced by Chronic Stress

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Purpose of Study: Stress and pain are closely linked through common neural circuits, as reflected in the dual effects of stress on pain thresholds: acute, intense stress decreases sensitivity to pain via neural pathways in the midbrain and brainstem, whereas prolonged but less severe stress causes increased sensitivity to pain (hyperalgesia) through yet unknown pathways. Prolonged stress also increases heart rate, blood pressure, and core temperature, all mediated by the hypothalamus. Direct stimulation of the dorsal medial region of the hypothalamus (DMH) in anaesthetized rats reproduces these physiological stress responses and also increases pain sensitivity. The goal of these experiments was to identify a neural pathway by which prolonged stress produces hyperalgesia in awake, behaving rats.

Methods Used: Awake Sprague-Dawley rats were stressed using a period of restraint combined with a low-flow stream of air directed at the face (30 min). Mechanical pain thresholds were measured before and after the stress paradigm. To assess the role of the DMH in this mild stress-induced hyperalgesia, a cannula was stereotactically implanted to allow direct microinjections into the area. To inactivate DMH neurons, the GABA agonist musimol was injected prior to the stress paradigm. To activate DMH neurons in the absence of imposed stress, the GABA antagonist bicuculline was injected. An injection of artificial cerebrospinal fluid was used as a control.

Summary of Results: Mild, prolonged stress lowered mechanical pain thresholds compared to baseline. Inhibiting DMH neural activity attenuated stress-induced hyperalgesia, showing that the DMH mediates this behavior. In unstressed rats DMH activation with bicuculline was sufficient to induce hypersensitivity to pain.

Conclusions: The increased sensitivity to pain resulting from mild, chronic stress is mediated by the DMH. Further studies are needed to map the neurotransmitter-specific projections to and from the DMH to elucidate other neural circuits by which the DMH modulates pain and stress responses. These results further our understanding of the interplay between chronic stress and pain, and highlight how relieving stress may be an important part of treating chronic pain.

Effects of Non-Steroidal Anti-Inflammatory Drugs on the Hypoxic Ventilatory Response and Acclimatization to Chronic Hypoxia in Humans

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Purpose of Study: Recent animal studies show that inflammatory processes contribute to respiratory chemoreflex plasticity during chronic hypoxia. Ibuprofen (a non-steroidal anti-inflammatory drug, NSAID) blocks the time-dependent increase in O2-sensitivity of carotid bodies in chronically hypoxic rats (Am J Physiol Lung Cell Mol Physiol 296:L158-166, 2009). Ibuprofen also blocks the time-dependent increase in the hypoxic ventilatory response to chronic hypoxia in chronically hypoxic rats (Respir Physiol Neurobiol. 178: 381-386, 2011). We hypothesized that similar inflammatory signals contribute to ventilatory acclimatization to hypoxia in humans.

Methods Used: To test this, we measured the isocapnic hypoxic ventilatory response (HVR) in 5 subjects at sea level and during two days at high altitude (3,800 m above sea level) using a randomized, double-blind repeated measures protocol. Ibuprofen (400 mg 3 times/day) or placebo was administered over 48 hours at sea level and over 48 hours at 3,800 m. The HVR was measured after 24 and 48 hours of treatment (e.g. ibuprofen) at sea level and 3,800 m. Subjects returned to sea level for at least one month before repeating the protocol with the other treatment (e.g. placebo).

Summary of Results: Results showed no significant difference in the HVR between placebo and ibuprofen treatments at sea level. With placebo, there was a significant increase in the HVR at altitude indicating normal ventilatory acclimatization. However, ibuprofen blocked the increase in HVR at altitude. Repeated measures ANOVA showed significant effects of drug and location on the HVR and a significant interaction between treatment and altitude.

Conclusions: The precise role of inflammatory signals in acclimatization to chronic hypoxia remains to be determined and the results may have implications for the treatment of acute mountain sickness at high altitude with NSAIDs.

The Effect of Lipid Minimization on Parenteral Nutrition Associated Cholestasis in Pediatric Surgical Patients

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Purpose of Study: Surgical infants who require long-term parenteral nutrition (PN) are at risk for liver disease. PN associated liver disease (PNALD) carries a high morbidity and mortality rate. Recent reports have demonstrated that a lower lipid dosage in PN can reverse PNALD. But there are no published studies assessing the effect of PN lipid minimization on the prevention of PNALD. In 2009, the General Surgery service at Seattle Children's Hospital began using a lipid minimization protocol in surgical infants thought to require long-term PN with a goal of preventing PNALD. The purpose of this study was to evaluate whether lipid minimization is associated with a lower incidence of PNALD when compared to a standard lipid regimen.

Methods Used: Surgical patients with necrotizing enterocolitis, gastrochisis, and jejunouileal atresia admitted to our institution over a 6-year period from 2005 to 2011 were retrospectively reviewed. The control group (132 patients) was admitted between 2005-2008, while the experimental group (83 patients) was admitted between 2009-2011. Weekly liver function tests for each patient were recorded. The primary outcome was PNALD, defined as a conjugated bilirubin of greater than 2 mg/dL for two consecutive blood draws over at least two weeks. Chi-squared tests, the Wilcoxon signed-rank test and t-tests were used to compare control and experimental data. A multivariable logistic regression model was constructed to model the association of lipid minimization with the development of PNALD.

Summary of Results: There was a significant reduction in the incidence of PNALD when the control and experimental groups were compared (43% vs 22%, p = 0.002). There were no differences between groups in respect to gestational age, surgical diagnoses, in-hospital length of stay, duration of PN, days of positive blood culture, and mortality. On multivariable logistic regression, an increased incidence of PNALD was associated with standard lipid dosing (odds ratio = 4.11, p = 0.001) and longer duration of PN (odds ratio = 1.04, p < 0.001).

Conclusions: Lipid minimization in surgical infants on long-term PN is associated with a reduction in the incidence of PNALD. Lipid minimization should be considered in all surgical infants who will require long-term PN administration.
obtained while in the emergency room disclosed a large pericardial effusion. Repeat laboratory evaluation showed persistent decrement in kidney function (serum creatinine 3.95 mg/dl from baseline 2.8 mg/dl). After catheter placement the patient was started on hemodialysis. Transthoracic Echo-cardiography showed severe dilatation of the aortic root (measuring 6.5 cm) with diastolic and trace aortic regurgitation. There was also a moderate-sized pericardial effusion with significant hemodynamic changes. Non-gated contrast-enhanced CT was notable for a right sinus of Valsalva aneurysm with dissection with indeterminate involvement of the right coronary artery ostium. He was subsequently operated on and recovered very well. This case highlights the importance of an extensive differential in PCKD patients where vascular abnormalities are more common than the background population.

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BEADED NECKLACE-LIKE IMAGE OBSERVED BY REAL-TIME THREE-DIMENSIONAL TRANSESOPHAGEAL ECHOCARDIOGRAPHY AS EVIDENCE OF BACTERIAL VEGETATIONS IN A DIALYSIS CATHETER

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Case Report: We present images observed in a patient with MRSA bacteremia from a hemodialysis catheter and demonstrate the superiority of real-time three-dimensional transesophageal echocardiography (RT3D-TEE) over two-dimensional transesophageal echocardiography (2D-TEE) at identifying catheter-associated infected vegetations. Other studies have reported RT3D-TEE as an improved modality to identify and characterize intracardiac structures. However, to the best of our knowledge, there are no reports describing the specific characteristics of bacterial vegetations in a dialysis catheter. As the prevalence of hemodialysis-dependent patients increases, the incidence of catheter-related blood stream infection (CRBSI) will only increase. Considering this, RT3D-TEE could play a central role in the diagnosis of CRBSI.

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ATENOLOL COMPOUNDING AND ATRIOVENTRICULAR BLOCK: A CASE REPORT

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Case Report: Atenolol is a beta antagonist used to control dysrythmias and is often used in liquid form in pediatrics. Compounding medications has inherent risks with the most common being a concentration error at the time the solution is made. We report a case of nearly complete atrioventricular (AV) block in a child taking this medication. Although the concentration was correct at the time of initial production, precipitation resulted in a higher concentration of medication in the bottom of the bottle and led to a gradual overdose with time. An asymptomatic 4 year old male with documented supraventricular tachycardia was prescribed Atenolol for control of his dysrhythmia. He was seen in a pediatric cardiac electrophysiology clinic for a routine follow up examination. Bradycardia was noted and an electrocardiogram demonstrated nearly complete AV block. He was taking approximately 1 mg/kg/day divided twice daily (4.25 ml per dose) of a 2 mg/ml solution. He was admitted to the hospital and observed. Within 12 hours his AV conduction defect resolved and he was discharged on his remaining Atenolol solution and found a high concentration of drug in the liquid with obvious flocculation of the drug in the bottom of the bottle. We surveyed local pharmacies to ascertain the methods used in compounding liquids for children and found significant variations in their methods. A review of the literature did not reveal any reported pediatric cases of AV block by Atenolol or flocculation resulting in overdose. This case demonstrates the potential for serious side effects in medications which are not properly compounded. It is important that families, primary care providers and subspecialists understand the implications of medication compounding errors that may lead to serious side effects.

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FIRST-YEAR BRAIN NATRIURETIC PEPTIDE (BNP) AS A BIOMARKER AFTER HEART TRANSPLANT FOR POOR OUTCOME AND PREDICTION OF THE SEVERITY OF CARDIAC ALLOGRAFT VASCULOPATHY (CAV)

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Purpose of Study: BNP has been reported to be a biomarker for poor outcome after heart transplant. Elevated BNP levels have been associated with reduced survival and an increase in the development of CAV. It has not been established whether high levels of BNP at 1-year post-transplant also correlates to greater severity of CAV as per the new ISHLT CAV nomenclature (Mehra M et al J Heart and Lung Transplant 2010; 29(7): 717-727).

Methods Used: We evaluated 238 heart transplant patients who received a transplant between 2001 and 2007. Patients were separated into three

Conclusions: First-year Cylex score did not correlate to the development of CAV which suggests that T-cell mediated function is most likely not primarily involved in the development of CAV. A higher incidence of first-year AMR in those patients who developed CAV suggests that antibody or humoral factors are important.
groups based on their BNP levels at the first-year: 157 patients with BNP <100 pg/mL, 56 patients with BNP 100-250 pg/mL, and 25 patients with BNP >250 pg/mL. Study patients were followed for 5 years for endpoints of survival, freedom from CAV (stenosis ≥ 30%), and freedom from non-fatal major adverse cardiac events (NF-MACE: MI, congestive heart failure, stroke, percutaneous cardiac intervention, and need for pacemaker or defibrillator). First-year freedom from any-treated rejection was also obtained.

**Summary of Results:** Patients with BNP >250 pg/mL were found to have significantly lower subsequent five-year survival, freedom from CAV compared to the lower groups of BNP. Severity of CAV was higher in the high BNP group compared to the other two groups. Of those patients who developed CAV, the high BNP group had more patients who developed CAV2 compared to patients with BNP 100-250 and BNP <100 pg/mL (24% vs. 4% vs. 7%, respectively). The high BNP group also had less freedom from any-treated rejection than the other two groups.

**Conclusions:** Elevated first-year levels of BNP >250 pg/mL appears to be a biomarker for poor outcome and the subsequent development of more severe CAV. Targeted change in immunosuppression such as switch to proliferation signal inhibitors might be considered for this high risk population.

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**IS HORMONE REPLACEMENT THERAPY IN POSTMENOPAUSAL WOMEN ASSOCIATED WITH POOR OUTCOME AFTER HEART TRANSPLANTATION?**

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**Purpose of Study:** Hormone replacement therapy (HRT) for postmenopausal women has been controversial with regard to cardiac outcomes and adverse effects. Prior work demonstrates that HRT causes increases in heart disease, stroke, and cancer in older women. The use of HRT in heart transplantation has not yet been studied. We review the outcomes of female heart transplant recipients that initiated HRT following cardiac transplantation.

**Methods Used:** Between 1994 and 2011 we reviewed the records of 356 postmenopausal female heart transplant recipients of which we found 19 who were on HRT defined as the use of hormone therapy after age 35. These patients were compared in a 3:1 fashion to a contemporaneous control group matched for age, gender, era, and time after transplantation (paired to the time from transplant to initiation of HRT). We assessed for outcomes including subsequent five-year survival, freedom from cardiac allograft vasculopathy (CAV, stenosis ≥ 30%), freedom from non-fatal major adverse cardiac events (NF-MACE: MI, congestive heart failure, stroke, need for pacemaker or defibrillator), and subsequent 1-year freedom from any-treated rejection. Additionnally, we compared significant adverse effects of HRT between the two groups.

**Summary of Results:** HRT treated patients had similar outcomes to their matched controls. There was no significant difference in subsequent five-year survival, freedom from CAV, and freedom from NF-MACE between the HRT group and the matched control group (table). Likewise, there was no significant difference in subsequent 1-year freedom from any-treated rejection in comparison to the matched controls (other). Table: Adverse effects of HRT including subsequent 5-year incidence of thrombosis (pulmonary embolus), malignancy, and stroke were not significantly different compared to the controls (table).

**Conclusions:** HRT is not associated with poor outcome or adverse effects in postmenopausal female heart transplant patients. However, a larger cohort of patients is necessary to confirm these observations.

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**OBESITY AND PROTECTION FROM CARDIAC ALLOGRAFT VASCULOPATHY: IS THE MYTH TRUE?**

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**Purpose of Study:** Obesity, defined as Body Mass Index (BMI) greater than 33, has been reported to be associated with protective effects for the development of cardiac allograft vasculopathy, but reports have been contentious. Furthermore, it has not yet been established in a large single center using non-induction triple-drug therapy whether obesity at the time of transplant protects against cardiac allograft vasculopathy or leads to greater subsequent morbidity and mortality.

**Methods Used:** Between 1994 and 2011 we reviewed 634 heart transplant recipients receiving non-induction triple drug immunosuppression therapy and stratified these patients into three groups relative to their BMI at time of transplant: 551 patients with BMI <30, 67 patients with BMI between 30 and 33, and 16 patients with BMI >33. The outcomes assessed for all groups were 5-year survival, freedom from cardiac allograft vasculopathy (CAV, stenosis ≥ 30%), freedom from non-fatal major adverse cardiac events (NF-MACE: MI, congestive heart failure, stroke, need for pacemaker or defibrillator, and percutaneous intervention), and 1-year freedom from any-treated rejection. Patients who received subsequent bariatric intervention/surgery were excluded from this analysis.

**Summary of Results:** The patients in the BMI >33 group were found to have significantly lower 5-year survival. However, there was a significantly higher 5-year freedom from CAV compared to the lower weight groups. In addition, 5-year freedom from NF-MACE and 1-year freedom from any-treated rejection were similar in all groups (see table).

**Conclusions:** Obese patients (BMI >33) on non-induction triple-drug immunosuppression at the time of heart transplantation appear to have a significant risk for lower 5-year survival, but a higher freedom from CAV compared to the lower BMI groups. Larger numbers of obese patients are needed to confirm these results and provide a mechanistic rationale.

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**THE POLICY OF PLACING OLDER DONORS INTO OLDER RECIPIENTS: IS IT WORTH IT?**

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**Purpose of Study:** In order to expand the donor pool, many heart transplant programs have been using an alternate list whereby older donors (>50 years) are used for older recipients (>60 years). This policy has been popular among many of the larger heart transplant programs. From the ISHLT registry, it has been noted that older donors have decreased survival after heart transplant. It has not been established whether older patients receiving older donor hearts have acceptable outcome after heart transplantation. Therefore, we reviewed our older patients who received older donor hearts and compared them to similar older patients who received younger donor hearts.

**Methods Used:** Between 2000 and 2011, we evaluated 942 cardiac transplant recipients in which we excluded patients with early donor-transmitted coronary disease. We found 403 patients ≥60 years of age at the time of transplant. This recipient cohort was stratified into two groups divided by age of the donor. 339 recipients with donors <50 years of age were compared to 64 recipients with older donors ≥50 years of age. The following outcomes were compared between the groups: 5-year actuarial survival, freedom from cardiac allograft vasculopathy (CAV, stenosis ≥30%), freedom from non-fatal major adverse cardiac events (NF-MACE: MI, congestive heart failure, percutaneous cardiac intervention, stroke, need for pacemaker or defibrillator), and 1-year freedom from any-treated rejection.

**Summary of Results:** The older donor group compared to the younger donor group demonstrated a significant risk for lower 5-year survival. Furthermore, there was no difference between the two groups in 5-year freedom...
from CAV, freedom from NF-MACE, and 1-year freedom from any-treated rejection (see table).

**Conclusion:** The use of older donors (≥50 years) in older recipients (≥60 years) appears to result in lower 5-year survival. Consideration of utilizing older donors into an older recipient should be viewed with caution. A larger study is warranted to confirm these findings.

171 HAS THE VIRTUAL CROSSMATCH TRULY DECREASED TIME ON THE HEART TRANSPLANT WAITING LIST FOR SENSITIZED PATIENTS?

Merz A, Rafiei M, Stern LK, Hamilton M, Kobashigawa J Cedars-Sinai Heart Institute, Los Angeles, CA.

**Purpose of Study:** Sensitization (presence of circulating antibodies) poses a risk for hyperacute rejection and for poor long-term outcome after heart transplantation. Sensitized patients, defined as having a panel reactive antibody screen (PRA) ≥10%, may have a longer waiting time for heart transplant due to less available compatible donor hearts. These sensitized patients have required a negative prospective donor-specific crossmatch (DSXM) prior to proceeding with heart transplant surgery. This further limits the donor pool for these patients as only local donors are available for this prospective DSXM to occur. Recently, the virtual crossmatch (VC), which involves computerized listing of unacceptable antigens for any one donor, has now enabled many of these sensitized heart transplant patients to find a compatible donor heart. Donors from around the country are now available for these sensitized patients since no prospective DSXM is needed. It has not been established whether the VC has truly impacted heart transplant waiting time for sensitized patients in our program located in a large metropolitan area.

**Methods Used:** Between 2006 and 2011, we reviewed 350 heart failure patients awaiting heart transplantation in the pre-VC era compared to the VC era (beginning October 1, 2009). Time to heart transplantation and death on the waiting list were compared for patients in various PRA groups (0–10%, 11–24%, ≥25%) for both eras.

**Summary of Results:** The time to heart transplantation was similar in the 3 PRA groups within the pre-VC and VC eras. Although, there was a decline in waiting times from the pre-VC era to the VC era, this was similar in all 3 PRA groups. Death on the waiting list was also similar in all groups and did not change from pre-VC to VC era (see table).

**Conclusions:** In our program, sensitized patients have not waited longer for heart transplantation prior to or after the advent of the VC. Therefore, the VC has not impacted heart transplant waiting time for sensitized patients in our program. This may be due to the large number of donor hearts available in our large metropolitan area.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Recipient Age 60-70 Donor Age ≤ 50 (N=395)</th>
<th>Recipient Age 60-70 Donor Age ≥ 50 (N=60)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year Actuarial Survival</td>
<td>84%</td>
<td>81%</td>
<td>0.04</td>
</tr>
<tr>
<td>5-Year Freedom from CAV</td>
<td>95%</td>
<td>86%</td>
<td>0.03</td>
</tr>
<tr>
<td>5-Year Freedom from NF- MACE</td>
<td>90%</td>
<td>85%</td>
<td>0.23</td>
</tr>
<tr>
<td>1-Year Freedom from Any- Treated Rejection</td>
<td>90%</td>
<td>89%</td>
<td>0.38</td>
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</tbody>
</table>

172 THE NATURAL HISTORY OF BIOPSY NEGATIVE REJECTION AFTER HEART TRANSPLANTATION

Tang Z, Rafiei M, Stern LK, Hamilton M, Kobashigawa J Cedars-Sinai Heart Institute, Los Angeles, CA.

**Purpose of Study:** The most recent International Society for Heart and Lung Transplantation (ISHLT) biopsy scale include cellular and antibody-mediated rejections. However, there are cases where there is acute decline in left ventricular ejection fraction (≤45% LVEF), yet the heart biopsy reveals no evidence for cellular or antibody mediated rejection. Therefore, these cases would be called “biopsy-negative rejection (BNR).” It is possible that these cases may represent atypical forms of rejection or sampling error from the biopsy. Characteristics and treatment response of this form of rejection has yet to be elucidated.

**Methods Used:** Between 2002 and 2011, we found 12 cases of BNR in 11 heart transplant patients as previously defined. One of the 11 patients were treated a second time for BNR. Characteristics and response to treatment were noted. Severe infections are also known to cause left ventricular dysfunction, thus patients with a clear clinical picture of sepsis with fever, increase in white blood count, or positive cultures were excluded.

**Summary of Results:** In the 11 patients treated for BNR, the 12 cases presented with an average LVEF of 31% ± 12% and 67% (8 of 12) of the treated episodes occurred during the first-year post-transplant. 4 of 11 patients presented with symptoms of heart failure that required inotropic support. 6 cases without heart failure symptoms were treated with high dose corticosteroids. The remaining cases with heart failure utilizing inotropic support were treated with therapies including IV solumedrol, IV anti-thymocyte globulin, and/or IV immunoglobulin (IVIG). Overall, 42% of these treated BNR episodes favored with return to normal left ventricular function (LVEF > 55% ± 6%) within a mean of 14 ± 12 days from the initial negative biopsy. This includes 8 cases without heart failure symptoms and 4 cases with heart failure symptoms.

**Conclusions:** BNR represents a more severe form of rejection in that there is cardiac dysfunction. Characteristics of these cases of rejection are described above with most cases responding to appropriate rejection therapy. A detailed mechanism of this type of rejection needs to be elucidated.

173 INFECTIOUS COMPLICATIONS OF DESENSITIZATION THERAPY: IS THE CURE WORSE THAN THE DISEASE?

Stern LK, Rafiei M, Patel DP, Hamilton M, Kobashigawa J Cedars-Sinai Heart Institute, Los Angeles, CA.

**Purpose of Study:** Sensitized patients have circulating antibodies that lengthen waiting time for heart transplantation due to incompatible donor hearts. Desensitization therapy for these sensitized patients awaiting heart transplant is believed to be important to decrease waiting time. Desensitization therapy is reported to significantly reduce circulating antibodies, however these therapies such as rituximab, bortezomib, immune globulin (IVIG), and plasmapheresis may also lead to infectious complications. The incidence of infectious complications due to desensitization therapy for elevated circulating antibody has not been established.

**Methods Used:** Between 2007 and 2011, we reviewed 329 patients awaiting heart transplantation and among them found 18 patients who underwent desensitization for elevated circulating antibodies. Patients were divided into those that received IVIG and rituximab, plasmapheresis with bortezomib, and IVIG alone. The incidence of infectious complications within 60 days of the completion of desensitization therapy were recorded. The efficacy of desensitization therapy, defined as a decrease in panel reactive antibody (PRA) values following a course of therapy, was also recorded.

**Summary of Results:** 13/18 (72%) patients experienced 13 infectious complications among all types of desensitization therapy which included: 1 (8%) fungal, 11 (85%) bacterial, and 1 (8%) viral. Specifically, 8 infectious complications were experienced for IVIG and rituximab therapy and 9 infectious complications were observed for bortezomib and plasmapheresis therapy (see table). One patient acquired a bacterial infection following a course of IVIG alone. 12/18 (66%) patients ultimately had significant reduction in circulating antibodies.

**Conclusions:** Desensitization therapy is effective in reducing circulating antibody in sensitized patients awaiting heart transplantation. However, there appears to be significant risk for subsequent infectious complications and therefore this form of therapy must be used with caution.
174 TRICUSPID REGURGITATION IN THE FIRST YEAR AFTER HEART TRANSPLANT: DOES IT MEEK GLOOM AND DOOM?

Lee D, Rafiei M, Stern LK, Hamilton M, Kobashigawa J. Cedars-Sinai Heart Institute, Los Angeles, CA.

Purpose of Study: Tricuspid regurgitation (TR) is usually due to high pulmonary artery or right ventricular pressures (high pressure TR) or due to abnormalities in the tricuspid valve itself (low pressure TR). TR after heart transplant is not uncommon. Some of these TR cases are due to the use of routine heart biopsies where the tricuspid valve is inadvertently damaged. The long-term outcome for these patients who develop moderate-severe TR in the first year after heart transplant has not been established.

Methods Used: Between 2003 and 2010 we reviewed 594 heart transplant patients' echocardiograms in the first year after heart transplant to find moderate-severe TR. These patients were followed for 5-year outcomes including survival, development of transplant coronary artery disease (TCAD), right atrial heart function and the need for tricuspid valve surgery. These patients were divided into those with low pressure TR (n = 9) and those with high pressure TR (n = 27). The remaining patients without moderate-severe TR in the first year served as controls (n = 558). Cases of flail tricuspid valve leaflets were recorded.

Summary of Results: All 3 groups had similar 5-year survival and freedom from TCAD. The 2 TR groups had similar dilated right atriums and ventricles and reduced right ventricular ejection fraction (RVEF) as well as need for tricuspid valve surgery (see table). The low pressure TR group had significantly more flail tricuspid valves (probably due to complications of heart biopsy).

Conclusions: Moderate-severe TR in the first year after heart transplant does not appear to affect 5-year outcome but does result in right ventricular enlargement and dysfunction. Flail tricuspid valves most likely due to heart biopsies occurs in a small number of patients (~2%). Longer term follow-up may reveal increased need for tricuspid valve surgery.

Endocrinology and Metabolism II
Concurrent Session
1:15 PM
Friday, January 27, 2012

177 EFFECTS OF LYSOSOMAL DEGRADATION INDUCERS ON IAPP TOXICITY IN PANCREATIC β-CELLS

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Purpose of Study: Islet pathology in T2DM is characterized by a deficit in β-cells and amyloid derived from islet amyloid polypeptide (IAPP), a 37 aa protein, coexpressed and secreted with insulin. Human-IAPP (hIAPP) has the propensity to form intracellular toxic oligomers and causes β-cell apoptosis. We established that increased rates hIAPP disrupt lysosomal-depndent degradation (autophagy pathway). β-cells from hIAPP transgenic rats (HPR rats), T2DM models, display an accumulation of autophagosomes and p62/sequestosome-1 (Rivera et al., Cell Death Differ. 2010). A high-throughput screen of 480 bioactive compounds indentified 8 compounds (7 of which are FDA approved drugs) with the capacity to sequester autophagy and lysosomal degradation of long-lived and misfolded proteins (Zhang et al., PNAS 2007). In these cases, the GA range was 25–34 wks (average 30 wks) the BW ranged from 725–1950, (average 1298 g). There were 16 patients whose cardiac anatomy was not amenable to surgical correction/palliation, who had multiple anomalies that would have prevented a successful cardiac surgery, or chromosomal abnormalities not compatible with long-term survival. Of those who survived to surgery, 52% were small for gestational age (SGA), compared to those who did not survive to surgery, 5% were SGA. 36% of patients <37 wks GA who survived to surgery were SGA.

Conclusions: It is likely that not only BW, but also maturity of the neonate plays a role in cardiac surgery decision making.
178 ATTENUATION OF ACUTE EXERCISE-INDUCED MITOCHONDRIAL BIOGENESIS AND OXIDANT DEFENSE IN A MODEL OF INSULIN RESISTANT DIABETES

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Purpose of Study: Physical inactivity is associated with an increased risk of cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality. Much is unknown about this link, but early evidence implicates a vascular component. Although diabetes can be treated with physical activity, exercise capacity is impaired in diabetes. The vascular response to exercise is largely unexplored. Previous work in our lab showed that control rats demonstrated vascular mitochondrial biogenesis in response to 8-day exercise training. This adaptation failed in models of hypertension and metabolic syndrome which showed decreased eNOS content and function. We hypothesized that diabetes would inhibit mitochondrial adaptation to exercise resulting from a mal-function in NO production in the vasculature.

Methods Used: In the current study, we examined the effect of short-term exercise training (8 days, 45 min., 15 m/min, 0% grade) on regulators of mitochondrial adaptation, antioxidant enzyme expression, and ETC (electron transport chain) components in the aortas of 18-week-old male control (Wistar) or lean insulin-resistant diabetic (Goto-kakizaki) rats (n = 6 per group). Primary Aortic Vascular Smooth Muscle Cells (VSMC) from Wistar and GK rats were isolated in culture and analyzed following serum starvation.

Summary of Results: Exercised Wistar Rats showed increased signaling to mitochondrial biogenesis (eNOS, SIRT1, SIRT3-5) and showed early trends of mitochondrial biogenesis (increased UCP-3). Exercised GK Rats Lacked this adaptation and showed consistent decreases in two mitochondrial ETC complexes.

Conclusions: Mitochondrial adaptation to exercise is inhibited in diabetes. SIRT1/eNOS appear to play a key role in this maladaptation.

179 SLEEP DISRUPTION IN PRE-OBESE MICE WITH ALTERED BRAIN LIPID METABOLISM PREDISPOSES TO WEIGHT GAIN

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Purpose of Study: To investigate the consequences of sleep disruption in neuron-specific lipoprotein lipase knockout (NEXLPL-KO) mice compared to that of wild type (WT) mice.

Methods Used: 3-month-old male NEXLPL-KO and WT mice were used. Previous experiments have shown that 3-month old NEXLPL-KO mice are pre-obese, developing obesity by 4.5 mo. Four mice were recorded at a time: two NEXLPL-KO and two WT mice, age- and weight-matched, a total of six per genotype. All mice were on a 14-hour light cycle from 6:00 to 20:00. Mice were introduced to individual metabolic chambers with calorimeter, food, and water measurements recorded in 12-minute intervals. The mice acclimated to the chambers during the first day. The second day was a baseline day, and at 14:00 on the third day the mice were removed in order to carry out the sleep deprivation experiment. Mice were sleep deprived for the last 6 hours of the light period on day 3 of the experimental protocol by the “gentle handling” method. This method involved gently touching the mice with a brush, or introducing new objects whenever behavioral signs of sleep were observed. Activity, food intake, and metabolic recordings were resumed beginning after the sleep deprivation period for the next 12 hours, after which mice were weighed and sacrificed.

Summary of Results: NEXLPL-KO mice showed a greater increase in total food intake after the 6-hour sleep deprivation period (NEXLPL-KO mice increased 52.6% from baseline, compared to the WT increase of 28.6%). NEXLPL-KO mice showed a greater decrease in activity than WT mice after the 6-hour sleep deprivation period (NEXLPL-KO mice decreased 50.9% from baseline, compared to the WT decrease of 41.9%). Body weights over this short period of sleep deprivation were unchanged between groups of mice. This bidirectional change in energy balance in NEXLPL-KO mice implies a strong predisposition to weight gain.

Conclusions: These data indicate that a deficiency in neuronal lipoprotein lipid signaling disrupts homeostatic responses to sleep disruption. Sleep disturbance could be a contributing environmental factor precipitating weight gain in genetically predisposed animals, and perhaps humans.

180 CORONIN 2A IS A DOCKING SITE FOR SUMOYLATED PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA

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Purpose of Study: Proper control of inflammation is essential for effective immune responses and normal homeostatic processes. Imbalances in the inflammatory response can contribute to overwhelming infection and chronic inflammatory diseases, such as diabetes and atherosclerosis. Members of the nuclear receptor family negatively regulate inflammation via several distinct mechanisms. We have recently described that upon post-translational modification by Small Ubiquitin-like Modifier (SUMO), these receptors dampen inflammatory gene expressions in “trans” without directly binding to DNA, a mechanism called transrepression. Previously, we found that SUMOylated liver X receptors (LXRs) interact with Coronin 2A (Coro2A) and block the recruitment of actin molecules, an “on-switch” important for activating inflammatory gene expression in macrophages. The purpose of this study is to determine the role of Coro2A in SUMOylated peroxisome proliferator-activated receptor γ (PPARγ) mediated transrepression.

Methods Used: Chromatin immunoprecipitation was performed to determine genomic occupancy of PPARγ and Coro2A. RNA interference against Coro2A was used for loss of function studies. Bioinformatic analysis identified three candidate domains containing canonical SUMO1 interaction motifs (SIM1) on Coro2A. Site-directed mutagenesis was performed to generate Coro2A-SIM1 mutants. Co-immunoprecipitation studies were conducted to evaluate changes in interaction between the Coro2A mutants and PPARγ. Luciferase assays were used to determine the functional significance of these SIM1 motifs in the context of PPARγ transrepression.

Summary of Results: Our studies show that PPARγ residency on inflammatory genes, nos2 and ccl2, were reduced when Coro2A expression is down-regulated. Mutation of Coro2A-SIM1 motifs decreased its interaction with PPARγ. Surprisingly, over-expressing the SIM1 mutants in luciferase assays resulted in statistically insignificant decreases in PPARγ transrepression.

Conclusions: Together, these studies point to an alternative compensating, Coro2A-SIM1-independent, mechanism for PPARγ transrepression. Further understanding of this mechanism is essential for developing new targets for therapeutic intervention against inflammatory diseases.
Summary of Results: IUGR increased DNA methylation of the PPARγ2 promoter 2 in male rat VAT (140 ± 12)%). In contrast, IUGR did not sig- nificantly affect DNA methylation of PPARγ promoter 2 in female adolescent rat VAT (88 ± 17), p < 0.05.

Conclusions: In conclusion, IUGR increases PPARγ2 promoter methyla- tion in VAT of adolescent male rats. Interestingly, we observed increased DNA methylation in association with increased mRNA levels of PPARγ. We speculate that histone modifications along the PPARγ gene are also affected by IUGR and that in combination these changes contribute to the increased PPARγ mRNA observed in IUGR rat VAT.

182 DIFFERENTIAL BRAIN, HORMONE, AND SATIETY RESPONSES TO GLUCOSE AND FRUCTOSE INGESTION
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Purpose of Study: Increases in fructose consumption parallel the rise in obesity. Central administration of fructose provokes feeding in rodents, whereas centrally administered glucose produces satiety. Imaging studies in humans show that food intake results in deactivation of the hypothalamus and striatum, brain regions that regulate appetite and reward. We used functional magnetic resonance imaging (fMRI) to test the hypothesis that fructose and glucose ingestion would produce different responses in brain regions that regulate feeding.

Methods Used: 20 healthy volunteers underwent 2 fMRI sessions with in- gestion of a fructose or glucose drink in a blindsed, random-order crossover design. Subjects had baseline acquisitions including pulsed arterial spin label- ing and BOLD sequences to determine regional cerebral blood flow (CBF), markers of neural activation, and functional connectivity (FC), respectively. Subsequently, they drank 75 g of either sugar followed by a 60-min acquisition and blood sampling period. Participants rated fullness and satiety before and after the scan.

Summary of Results: CBF in the hypothalamus, thalamus, insula and striatum was significantly reduced after glucose ingestion (p < 0.05,FWE whole brain corrected). In contrast, fructose ingestion reduced CBF in the thalamus, hippocampus and visual cortex (p < 0.05). Glucose ingestion in- creased FC between the hypothalamus (the seed region) and the thalamus, nucleus accumbens and striatum, whereas fructose ingestion increased FC between the hypothalamus and thalamus (p < 0.05). Fructose ingestion caused a smaller rise in plasma glucose, insulin and GLP-1 (p < 0.01) than glucose. Ratings of fullness (p = 0.001) and satiety (p < 0.02) were increased only after glucose ingestion.

Conclusions: Our results demonstrate that glucose but not fructose ingestion reduces the activation of the hypothalamus and striatum, brain regions that regulate appetite and reward processing. Moreover, glucose but not fructose ingestion increased functional connections between the hypothalamic-striatal network and increased satiety. These disparate responses to fructose ingestion were associated with reduced levels of insulin and GLP-1 and might play a role in promoting feeding behavior.

183 EFFECTS OF FRUCTOSE ON GLUCOSE CONTRIBUTION TO FATTY ACID SYNTHESIS IN 3T3-L1 ADIPOCYTES
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Purpose of Study: Fructose consumption has been implicated in the de- velopment of obesity and related disorders. While there is growing infor- mation on the effects of fructose in fatty liver disease, very little is known about the effects of fructose on adipose tissue. We hypothesized that adipo- cytes exposed to fructose and glucose would preferentially utilize fructose for fatty acid synthesis. The objective of this study was to determine the effects of fructose exposure on glucose contribution to fatty acid synthesis in 3T3-L1 adipocytes.

Methods Used: 3T3-L1 preadipocytes were established in cell culture. Differ- entiation was induced with methylisobutylxanthine/insulin/dexamethasone for 7 days. During this time, the total sugar content of medium was main- tained at 4.5g/L, but substitutions with isotopes of glucose or fructose were made in the following experimental groups: A) Glucose-only with 25% U13C-glucose as a tracer B) 25% fructose replacement with 25% U13C- glucose tracer, and C) 25% U13C-fructose. Acetyl-CoA enrichment by the labeled sugar was determined. TCA cycle analysis demonstrated an increased ratio of acetyl-CoA production toward acetyl-CoA production were determined by isotopomer analysis of glutamate.

Summary of Results: Acetyl-CoA enrichment in glucose-only treated cells (group A) was lower than that of cells exposed to fructose with labeled glucose (group B) (14.4 ± 1.35% versus 19.8 ± 0.14, p < 0.05). Cells treated with labeled fructose (Group C) exhibited very low enrichment (0.87 ± 0.11%). TCA cycle analysis demonstrated an increased ratio of acetyl-CoA produced via the pyruvate carboxylase versus pyruvate dehydrogenase pathways in group B compared to group A.

Conclusions: 3T3-L1 adipocytes in cell culture utilize very little fructose in fatty acid synthesis. However, partial replacement of medium glucose for fructose leads to an increase in glucose contribution to fatty acid synthesis, mediated by a shift in TCA cycle production of acetyl-CoA toward the pyruvate decarboxylase pathway. Fructose is therefore not a preferred substrate for fatty acid synthesis and its effects on de novo synthesis are mediated by glucose.

184 OBSESE MICE TREATED WITH AGENTS THAT MODIFY THE ADAPTIVE IMMUNE RESPONSE HAVE AN IMPROVED PROFILE OF ADIPOSE TISSUE MACROPHAGES AND T LYMPHOCYTES, BUT DO NOT EXHIBIT IMPROVED INSULIN RESISTANCE
Montes V.1, Ledbetter J.1, Turner M.2, Subramanian S.1, Elkon K.2, Chait A.1
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Purpose of Study: Adipose tissue inflammation is believed to result in insulin resistance (IR) in obesity in humans and animal models. Emphasis has been on the role of pro-inflammatory macrophages as the driving force be- hind the IR. Recent studies also have invoked the adaptive immune system, including T and B cells, in the recruitment of pro-inflammatory macrophages and the development of IR. To test the role of the adaptive immune response in IR, we used two agents that modify the adaptive immune response to in- duce a decreased inflammatory response in the adipose tissue of mice fed a diet high in carbohydrate, fat and cholesterol.

Methods Used: The agents used were CTLA-4 Ig and anti-CD40L anti- body. Both are able to block the co-stimulation essential for activation of the adaptive immune response. C57BL/6 mice were fed an obesogenic diet for 16 weeks, and were treated with CTLA-4 Ig or anti-CD40L antibody (300 mcg/week), or left untreated. IR was measured with GTT and fasting insulin levels at 13 weeks. Flow cytometry analysis of whole epididymal adipose tissue was performed after sacrifice at 16 weeks.

Summary of Results: These agents did alter the immune cell components of adipose tissue in mice fed the obesogenic diet. Most notably, treated mice demonstrated a marked reduction in pro-inflammatory adipose tissue macrophages (as compared to untreated, CTLA-4 Ig = 47% reduction, p<.001, n=9; MR1 = 76% reduction, p<.001, n=9). They also exhibited a significant decrease in activated adipose tissue CD8+ T cells (as compared to untreated, CTLA-4 Ig = 83% Reduction, p<.01, n=6; MR1= 76% reduction, p<.01, n=6). There was not a significant corresponding improvement in IR in CTLA-4 Ig treated mice, and IR only showed a mild trend to improvement in the anti-CD40L antibody treated mice.

Conclusions: These data suggest that the presence of pro-inflammatory im- mune cells, especially pro-inflammatory macrophages, in obese mouse adipose tissue does not appear to be a significant contributor to the whole body IR phenotype.

185 EFFECTIVENESS OF STANDARDIZATION OF COMMUNITY HEALTHCARE WORKERS WITH TRAINING PROGRAMS
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Purpose of Study: Community Healthcare Workers (CHWs) have emerged with great potential to address the impending health crisis associated with the diabetes epidemic and stretched healthcare system. CHWs act as educators and advocates in communities, working with underserved culturally diverse...
populations. Ideally, CHWs in this role receive rigorous training, ongoing support, and become members of the care team. We hypothesize that a multimodal teaching/training program will be an effective mechanism to train and support CHWs as members of the care team.

Methods Used: Twenty CHWs from rural and underserved areas of New Mexico were recruited to participate in collaboration with the Extension Community Health Outcomes (ECHO) project. Participants completed five baseline skills testing: depression assessment, vital signs assessment, medication assessment, diabetes foot examinations, and blood glucose monitoring and interpretation. Each skill set was evaluated by a trained expert using a standardized check list. Participants then completed face-to-face training on these skills followed by a six-month participation in weekly video conference sessions with the Multidisciplinary ECHO Diabetes team focusing on didactic presentations, case-based learning and problem solving. At the end of 6 months, participants repeated the skills testing.

Summary of Results: Participants demonstrated significant improvement in assessment for depression (p = 0.0013), measuring and interpreting vital signs (p < 0.0001), medication assessment (p = 0.0001), and conducting foot examinations (p = 0.0007). (Table 1)

Conclusions: We demonstrated that our robust CHW multidimensional training program improved specific diabetes clinical skills. Future steps include determining the cost effective benefit of having CHWs use these skills in the clinical setting.

**187 VITAMIN D ENHANCES MYOGENIC CELL DIFFERENTIATION OF C2C12 SKELETAL MYOBLAST CELLS BY MODULATING THE EXPRESSION OF KEY ANGIOGENIC GROWTH FACTORS AND ANGIOGENIC GROWTH FACTORS INHIBITORS**

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Purpose of Study: Vitamin D is most recognized for its regulation of calcium homeostasis in relation to the intestine, kidney, and bone. Although clinical studies have linked vitamin D to increased muscle function and strength, little is known of its molecular mechanistic action. We recently demonstrated that 1,25D—the active form of vitamin D—exerts an anti-proliferative and a direct and indirect pro-myogenic effect on skeletal muscle cells; this has provoked our investigation of 1,25D's effect on angiogenesis. Angiogenesis is a vital process for new capillary development and tissue repair. Our aim is to examine the mechanism by which 1,25D enhances myogenesis and capillary growth through modulating key angiogenic factors and angiogenic inhibitors.

Methods Used: Mouse C2C12 myoblasts were incubated with 100nM 1,25D or placebo for 1, 4 and 10 days. At the end of the respective incubation time, total RNA was isolated for PCR angiogenesis and angiogenesis inhibitors arrays and for qPCR. Total proteins were isolated for western blots and proteome profiler angiogenesis arrays.

Summary of Results: We identified significant changes in several key angiogenic growth factors and angiogenic inhibitors upon incubation with 1,25D. 1,25D increased VEGFa and FGF-1 and decreased FGF-2 and TIMP-3. VEGFa and FGF-1 are two thoroughly described pro-angiogenic growth factors that promote neo-vascularization and tissue regeneration. FGF-2 and TIMP-3 are angiogenic inhibitors. They have been described to accomplish inhibition through FGF-2's interaction with IGFs and TIMP-3's indirect inhibition of VEGFa. Our previous study showed that 1,25D alters IGF-I/II expression, supporting the rational for the changes in VEGFa and FGF-2 expression.

Conclusions: These results reinforce our previous findings and contribute to a more comprehensive description of the mechanism by which 1,25D promotes myogenesis and angiogenesis. This study provides the therapeutic rationale for administering vitamin D and/or vitamin D analogues to treat muscle disorders and provides an alternative solution for therapies that directly manipulate VEGF and FGF's to promote angiogenesis.

**188 ASSESSING PHYSICIANS ATITUDES TOWARD COMMUNITY HEALTH CARE WORKERS AS MEMBERS OF THE DIABETES CARE TEAM**

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Purpose of Study: Diabetes is a potentially devastating disease that affects millions of Americans every year. A large proportion of these diabetic patients have a significant educational barrier in understanding their disease and the treatment thereof. Many programs have been developed in an effort to alleviate patient non-compliance with the use of a Community Health Worker (CHW) who acts as an advocate/educator to those considered ‘health illiterate’. However, healthcare providers have not unanimously adapted these types of programs. The goal of this study is to gain insight into physician attitudes toward CHWs and diabetes education.

Methods Used: We designed and distributed a survey to evaluate Primary Care Physician (PCP) perceptions of the role of CHWs as diabetes patient educators. Demographic information was collected to assess for differences among physician, location, age, years in practice. All PCPs in New Mexico were considered eligible for the study and participation was voluntary. The
survey was distributed via email list serves from various medical associations and organizations and by direct contact at regional conferences.

Summary of Results: One hundred and forty two surveys were collected. RedCap online database was used to collect and analyze data. Preliminary review demonstrated that 91% of PCPs who have had experience working with CHWs found them to be an important part of diabetes patient education team. However 60% of physicians feel there are significant barriers to CHW use. Complete statistical analysis is currently in progress.

Conclusions: CHWs are highly valued by PCPs as ancillary members of the diabetes team but significant barriers to increasing their utilization as members of the team exist. Efforts to overcome those barriers are needed.

189 EVIDENCE OF DEFECT IN THE RELEASE OF TESTOSTERONE FROM XXY MOUSE TESTIS

Purpose of Study: Klindenfelter syndrome (KS) is characterized hypergonadotropic hypogonadism as evidenced by elevated FSH and LH and low testosterone (T) in the circulation. In an experimental XXY mouse model of KS, we have previously demonstrated that there is hyperplasia and hypertrophy of Leydig cells in XXY testes. Isolated leydig cells produce significantly higher amount of T in XXY compared to XY controls, although circulating T level in serum was lower in XXY animals. The aim of the study was to further characterize T production in XXY testes and to find direct evidence of a defect in the release of T to circulation in XXY mice.

Methods Used: XXY mice were generated in our laboratory through a 4 generation breeding scheme as published previously. Testes of 4 XXY mice and their 4 XY littermates ranging between 5-11 months of age were used in the experiments. Testicular venous system was ligated and blood collected from the venous effluent. Testis was dissected out, decapsulated and incubated in the serum free medium in the presence or absence of 10 ng/ml of luteinizing hormone (LH) for 3 hrs. T was measured in the incubation medium, testicular homogenate and testicular venous effluent using LC/MS/MS.

Summary of Results: Incubation of decapsulated whole testis in culture medium resulted in higher testicular content of T in XXY mice in comparison to XY (mean 19.3 ng vs 12.3 ng, P<0.05). Addition of LH in the culture medium further increased T content in XXY mice (mean 24.5 ng vs 15.1 ng, P<0.05). However, in XXY tests the increase was not statistically significant (P=0.3). There was no difference in the amount of T released in the medium from XY vs. XXY tests. When we measured T concentration in the testicular venous effluent, there was 2-fold lower concentration of T in the venous effluent from XXY tests compared to XY tests (mean 6.3 ng/ml vs 13.0 ng/ml, P<0.05).

Conclusions: Our data provides further evidence that synthesis of T is not impaired in the XXY tests. Additionally, T production is actually higher in XXY tests compared to XY control. Although the amount of T is higher in the testis of XXY mice, there is a defect in the release of T from testis to venous circulation which is supported by lower concentration of T in testicular venous effluent. Studies are underway to understand the exact nature of this defect.

Gastroenterology and Hepatology

1:30 PM

Concurrent Session

Friday, January 27, 2012

190 OROGASTRIC ZINC DECREASES INTESTINAL INFLAMMATION IN SHIGA TOXIN PRODUCING E. COLI INFECTION
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Purpose of Study: There is no safe and effective therapy for Shiga Toxin Producing E.Coli (STEC) infections, such as the recent German outbreak of hemolytic uremic syndrome caused by an O104 strain expressing shiga toxin 2 (Stx2). Antibiotic treatment causes increased Stx production and more severe disease. We previously showed that Zinc (Zn) inhibits the in vitro expression of STEC virulence factors. Our aim was to determine if orogastric Zn could favorably influence the clinical outcome, and intestinal inflammatory response, in STEC infection in vivo.

Methods Used: 2 groups of 10 rabbits were infected with STEC E22-Stx2, an enteropathogenic strain containing a bacteriophage encoding Stx2 which causes hemorrhagic colitis. One group was treated by gavage with elemental Zn for 7 days beginning at time of infection. Rabbits were observed for evidence of infection (wt. loss, diarrhea), then euthanized to obtain intestinal tissue for histologic analysis of inflammation, and quantitation of mucosal pro- (IL-1β, IL-6, TNF-α, IFN-γ) and anti-(IL-10) inflammatory cytokine production, using quantitative polymerase chain reaction based on rabbit specific primers.

Summary of Results: Only 10% of the rabbits which received Zn developed clinical evidence of infection (vs. 80% of controls). Zn treated animals had a 10% wt. gain, vs. a 5% weight loss in controls. Significantly lower pro-inflammatory cytokine responses were evoked in the ceca (the primary site of infection) in the Zn-treated group (IL-1β, 126 fold; IL-6, 126 fold; IFN-γ, 10 fold; TNF-α, 77 fold) as compared to untreated controls. The IL-10 response was not changed by Zn. Similar responses were observed in ileum and colon for all the cytokines tested. Histologic evidence of inflammation paralleled the cytokine responses.

Conclusions: Orogastrically administered Zn was safe, and favorably influenced the clinical course and intestinal inflammatory responses induced by infection of rabbits with an STEC strain producing Stx2. Since antibiotic therapy must be withheld for STEC infections in humans because of increased morbidity with antibiotics, oral Zn therapy may provide an important approach to treatment of these infections for which only supportive care can now be recommended.

191 WILSON DISEASE: ABNORMAL METHIONINE METABOLISM AND THE ROLE OF INFLAMMATION AND STEATOSIS IN EARLY STAGES OF LIVER DISEASE
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Purpose of Study: Wilson disease (WD) is a rare autosomal recessive disorder of copper transport featuring hepatic copper accumulation and development of hepatic steatosis. Copper has been shown to inhibit the enzyme S-adenosylhomocysteine hydrolase (SAHH), central in methionine metabolism and in regulating S-adenosylhomocysteine (SAH) and S-adenosylhomocysteine (SAM) levels. The SAM/SAH ratio is an indicator of methylation capacity and regulates gene expression. This study examines the effects of copper induced SAHH inhibition and treatment with copper chelator penicillamine (PCA) in the pathogenesis of inflammation and steatosis in an animal model of WD in order to establish a link between methionine metabolism and gene expression regulation.

Methods Used: Livers and blood were collected from 7 toxic mice (tx-j) and 7 C3H control mice in each age group at 12 and 24 weeks, and 7 PCA treated tx-j mice at 24 weeks. We measured methionine metabolism metabolites SAM and SAH (HPLC) and SAHH activity. Lipid metabolism genes glutamine synthetase glutamate dehydrogenase (Gdh) and perilipin A (plin5) were measured via Real Time-PCR. Hepatic copper levels in tx-j mice were 35-40 times greater than controls (p<0.0001) while PCA tx-j mice accumulated half as much copper as untreated tx-j mice (p=0.0001). At 24 weeks, SAHH activity was reduced in tx-j mice (p=0.01) but re-established similar to controls in PCA tx-j mice. The SAM/SAH ratio was lower in PCA and untreated tx-j mice (p<0.05). GRP78, SREBP1c, CPT1α and PPARα expressions were reduced in untreated tx-j mice at both ages and further reduced in PCA tx-j mice. TNFα expression was higher in untreated tx-j mice but reduced in PCA tx-j mice.

Conclusions: Copper accumulation is associated with SAHH activity inhibition in tx-j mice that was restored in PCA tx-j mice. The SAM/SAH ratio was reduced in PCA and untreated tx-j mice with changes in the inflammation and steatosis gene expression. These findings indicate that copper induced abnormal methionine metabolism and subsequent inflammation and steatosis play an important role in the pathogenesis of early liver disease in WD.
AUTONOMIC DYSREGULATION IN RESPONSE TO A VISCERAL STRESSOR IN IRRITABLE BOWEL SYNDROME

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Purpose of Study: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by intermittent abdominal pain with diarrhea and/or constipation. Recent studies suggest that autonomic dysregulation may play a pathophysiological role in IBS. In this study we examine autonomic nervous system (ANS) responses at rest and during a visceral stressor in IBS patients and healthy controls to explore autonomic dysregulation in IBS. Furthermore we examine the effects of sex, anxiety, depression, and perception of the visceral stressor on ANS function.

Methods Used: Male and female IBS patients and controls aged 18–55 underwent a structured psychiatric interview (MINI) and completed the Hospital Anxiety and Depression Scale and Verbal Descriptor Visual Analog Scale. Echocardiogram and skin conductance were measured at rest and during a visceral stressor for heart rate variability autoregression spectral analysis. Linear mixed models using the SAS v9.2 Mixed procedure were performed to assess group differences. Significant group differences were identified by race/ethnicity including African American, Caucasian, and Hispanic. All patients had significant higher cardiosympathetic tone than females (p = 0.002) but no group differences were found within each sex. As anxiety symptoms increased, controls had lower cardiovagal tone (p = 0.04) while the IBS patients remained unchanged. Sympathetic tone positively correlated with perception of unpleasantness during the visceral stressor in IBS (r = 0.592, p < 0.001) but not in controls.

Conclusions: IBS is associated with autonomic dysregulation with IBS patients having a lower cardiovagal tone at rest but a lack of response to visceral stressor and to the effect of anxiety. In IBS patients, autonomic arousal during the visceral stressor was associated with their perceived unpleasantness during the procedure, suggesting that sympathetic nervous system activity may be a biomarker for visceral hypersensitivity in IBS.

ETHNIC DIFFERENCES IN HEALTHCARE UTILIZATION FOR PEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Purpose of Study: Ethnic differences have been observed in previous studies looking at healthcare utilization in pediatric patients with gastroesophageal reflux disease. We looked at patients who have been diagnosed with inflammatory bowel disease (IBD) in a southwestern city in the United States and hypothesized that ethnic differences also exist in access to healthcare for these pediatric patients. The aim of this study was to evaluate healthcare utilization patterns among ethnicities in a southwestern pediatric IBD patient population.

Methods Used: Hospital and clinic databases were analyzed for patient visits of pediatric IBD patients at the Emergency Department of the Children’s Hospital of Nevada and the University of Nevada School of Medicine gastroenterology clinic in Las Vegas during the years 2004–2011. All patients seen were identified by race/ethnicity including African American, Caucasian, Hispanic, or Asian/other. The number of patient encounters was compared among groups by ANOVA. A p value of < 0.05 was considered statistically significant.

Summary of Results: Amongst the 38 pediatric IBD patients included in the study, the race/ethnicity distribution was 18.4% AA, 63.2% Caucasian, and 18.4% Hispanic. The average number of clinic visits per year was similar among groups (p>0.614). However, African-American patients were more than twice as likely to seek care in the emergency department setting compared to other ethnic groups (p=0.004). The data shown in the table are patient encounters per year expressed as mean ± SD.

Conclusions: Compared to Caucasians and Hispanics, African Americans have increased access to care in the emergency department setting among pediatric IBD patients. Cultural, economic, and medical factors may contribute to these differences.

SIGNIFICANCE OF CANDIDA ESOPHAGITIS IN INFANTS WITH GASTROESOPHAGEAL REFLUX DISEASE PRESENTING WITH FEEDING REFUSAL

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Purpose of Study: Candida esophagitis is typically thought to be associated with immune deficiency. However, Candida esophagitis can be seen in infants with normal immune systems who present with severe gastroesophageal reflux disease (GERD).

Methods Used: We queried a clinical database and selected infants with a final diagnosis of candida esophagitis and GERD from 1999–2008. Patients who met the following criteria were included in the study: diagnosis of GERD and Candida esophagitis underwent an esophagogastroduodenoscopy (EGD) with biopsy +/- esophageal brushings and had normal immune system. Data regarding symptoms at time of presentation, formula and medication history and overall growth throughout the treatment course and outcome of care were noted and compared.

Summary of Results: Fifteen infants aged 1 week to 9 months of age (average age 4.6 +/- 3.3 mo. x +/- SD met the inclusion criteria. Patient demographics were 80% males, 40% Caucasian, 33.3% African American, 26.6% Hispanic. All patients had emesis and were below the mean for weight for age (z-score with WD). Additionally, 80% presented with feeding intolerance, 47% had diareea and 33% oral candidiasis. All infants failed to resolve the above symptoms despite the following therapy/interventions: formula change, ranitidine, metoclopramide and proton pump inhibitors. They underwent EGD and were diagnosed with Candida esophagitis. They were treated with fluconazole. After treatment all patients showed improvement of symptoms.

Conclusions: Children who fail multiple approaches to GERD treatment should be evaluated for Candida esophagitis. We have found that infants with normal immune systems who present with severe GERD refractory to treatment may have Candida esophagitis and proper treatment resolves their symptoms.
numerous mitotic figures, amphophilic cytoplasm, round nuclei with salt and pepper chromatin, in a trabecular growth pattern. Conclusions: Although GNET rarely metastasize to the neck, metastatic disease should be part of the differential for patients with a prior history of GNET.

196 UNUSUAL COMPLICATION AFTER PERCUTANEOUS ENDOSCOPIC GASTROSTOMY TUBE PLACEMENT: A CASE REPORT
Rutter RP1, Herman M2 1LECOM, Bradenton, FL and 2Borland-Groover Clinic, Orange Park, FL. Case Report: Complications for percutaneous endoscopic gastrostomy (PEG) tube placement are rare. Specific risk factors include patients who are malnourished, have underlying malignancy and with patients in whom the PEG procedure is performed in an outpatient setting. We present the case of a 65 year-old female who presented with a colocutaneous fistula four weeks after PEG tube placement for malnourishment. The procedure was uneventful with no complications and adequate placement of the tube. The patient developed diarrhea, weight loss, and stool appearing from the PEG tube three weeks after placement. Radiological studies confirmed migration of the PEG tube from the gastrum and into the transverse colon forming a colocutaneous fistula. Successful endoscopic removal was performed. We discuss the potential complications associated with PEG tube placement and review the approach to management as highlighted by this case.

197 CROHN’S DISEASE AND ULCERATIVE COLITIS PATIENT EDUCATION AT A SUPPORT GROUP IN PLAINS, MONTANA
Blaskovich T University of Washington School of Medicine, Seattle, WA. Purpose of Study: The relapsing and remitting course of Crohn's disease and ulcerative colitis results in a significant reduction in the quality of life during exacerbations of the diseases. There is an incidence rate of 2-7/100,000 in the United States and COMPdata from the Clark Fork Valley Hospital in Plains, Montana, suggests that there is a higher incident of these diseases in Sanders County, Montana. The goal of this project was to provide an informative presentation to a Crohn’s and colitis support group to educate and promote more active participation in care. Methods Used: A literature search was conducted to find the latest inflammatory bowel disease related statistics and research. Support group participants and providers were contacted to determine what information should be discussed during the presentation. An interactive presentation was prepared and presented to the support group. The presentation addressed the clinical features of the diseases, current research, and ways to be an active participant in care. Summary of Results: Group members were very receptive of the pre-presentation and actively participated in discussions. They expressed confusion about disease courses and treatment options, and stated that they felt reassured after the wide clinical spectrum of both diseases was explained. The group leader asked to distribute the presentation materials to non-attending group members and two attendees asked for copies to show their families. Conclusions: The Crohn’s and colitis support group, “True Guts,” had their first meeting in June 2011. The patients and their families and caregivers have already benefited from expressing emotion and learning coping methods from one another; but they had not addressed their need to obtain information about their diseases, which is an important aspect of support groups. During the presentation, attendees discovered new ways to participate in their own care as well as assistance and reassurance from other group members.

198 WILDERNESS MEDICINE CAREER DAY FOR TEENS IN RED LODGE, MONTANA
Gallagher C University Of Washington School of Medicine, Seattle, WA. Purpose of Study: Red Lodge, Montana is a town of 2,483 people that sits at the base of the Beartooth Mountain Range. Outdoor recreation is a major pastime here and a significant contributor to the Emergency Room visits at Beartooth Billings Clinic in Red Lodge. As of 2011, Montana has a total of 97 Designated Health Profession Shortage Areas. The purpose of this project was to build interest in healthcare careers in Red Lodge, MT among the community’s high school students through hands on exposure to the exciting careers available in Wilderness Medicine. Methods Used: A previously scheduled community event was used as the basis of this project. 18 high school students from Red Lodge and the surrounding communities were selected by the Area Health Education Center (AHEC) office in Billings, MT to participate in a 5-day camp for building interest in health care careers. The students were invited to Red Lodge, MT for one day to explore careers in Wilderness Medicine. A literature review was conducted to determine the most effective way to generate interest in pursuing healthcare careers in high school aged students. Presentations and activities were developed which included guest speakers and hands-on activities. Media included paper handouts for students, powerpoint presentations, and many interactive projects. Summary of Results: Basic education followed by immediate hands-on application in the field was determined to be the most effective method of generating interest in a Wilderness Medicine career. Doctors and Search and Rescue personnel presented career opportunities and students were given resources to continue to pursue these options independently. Didactic information on problems encountered in Wilderness Medicine was followed by an interactive mock-rescue in the backcountry, where recently learned skills were applied. Two EMTs, a physician, and a scent dog led the mock-rescue. Conclusions: Activities for high school students interested in healthcare careers are most effective when they are interactive and hands-on. The team effort of local physicians, EMTs, and rescue personnel in making a successful and exciting Wilderness Medicine Careers Day was a testament to the ongoing effort to educate and generate interest in young Montanans for healthcare careers. Students reported increased interest in Wilderness Medicine after finishing the day.

199 PREVENTION OF DIARRHEA AND INTESTINAL PARASITOSIS THROUGH COMMUNITY EDUCATION IN BELÉN, PERU
Smith IT University of Washington School of Medicine, Seattle, WA. Purpose of Study: Diarrhea and intestinal infections such as ascariasis and giardiasis are among the top five causes of morbidity in Belén, an
impoverished region in the Peruvian Amazon. Based upon a community assessment it was found that while the community understood the importance of diarrheal disease, knowledge about causes, prevention, consequences, and treatment of was low. Therefore, a community-based education project was implemented with the goal of decreasing the prevalence of diarrheal diseases and intestinal infections in Belén.

Methods Used: This project was conducted in partnership with 3 local primary schools and the non-profit organization Selva Amazonica. Based upon a literature review and with the guidance of local teachers, culturally relevant educational materials were developed in Spanish. The focus of the material was prevention of diarrhea and intestinal parasitosis through better hygiene, vaccination and prevention of dehydration through use of oral rehydration solutions. Interactive education sessions were given to primary school-age children and structured discussions were held with parents to collectively identify inexpensive ways to prevent and treat diarrhea and intestinal parasitosis. Eight teachers were recruited to participate in the presentations and a training session was held to discuss how to sustain the educational sessions.

Summary of Results: 735 children from three different primary schools participated in the educational sessions, and a total of 124 parents were involved in the discussion sessions. The majority of children were able to identify causes and prevention of diarrhea and parasitosis after the session. Parents’ knowledge was measured by asking them to collectively work on solutions to the issues presented. The intervention was well received by the community. The children were participative and behavioral changes such as increased hand washing and shoe wearing was observed by the teachers. Parents felt empowered to prevent and treat diarrhea and parasitosis in their homes and communities.

Conclusions: The project increased collective knowledge about diarrhea and other parasitic infections. Sustainability will depend on ongoing cooperation between educators, parents and children. Continued adult and child health education is needed to decrease the burden of these infections in Belén.

200 COMBATING MALNUTRITION IN AT-RISK CHILDREN UNDER FIVE IN RURAL UGANDA THROUGH NUTRITION EDUCATION

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Purpose of Study: Under-nutrition contributes to over 1/3 of all child deaths worldwide. The effects of childhood malnutrition are seen throughout life and contribute to low school performance, decreased productivity, and impaired social and intellectual development. In Uganda, 38% of children under five are stunted, 16% are underweight, and 72% of children aged 6–23 months do not receive an adequate quality of food. This project aimed to combat malnutrition in children under five in the Kiboga District by improving the nutrition habits of families with at-risk children through the creation of culturally appropriate educational tools.

Methods Used: Strengthening complimentary foods which are given at 6 months of age and improving hygiene practices have been shown to be effective strategies to reduce childhood malnutrition. Therefore, a poster and a hand-held teaching aid were created that focused on proper hygiene, balanced diet, ways to encourage children to eat, and complimentary foods. These materials were distributed to the pediatric nurses, nutrition specialist, and the immunization clinic nurses at the Kiboga District Hospital. These health professionals received training to utilize these tools for future use. Presentations were held in both the pediatric ward and the immunization clinic. The nutrition specialist also received an electronic copy of these materials and plans to distribute them to the village health workers to strengthen their existing programs.

Summary of Results: 3 health professionals were trained to conduct education sessions about proper hygiene and nutrition. 4 presentations were held, 2 in the pediatric ward and 2 in the immunization clinic. 92 families participated, of which 13 had undernourished children. Families were engaged in the discussions and understood many of the key concepts. During the presentations, proper child spacing was often brought up, and participants wanted more information on this topic.

Conclusions: This project increased the awareness of proper nutrition and hygiene practices of families with children at-risk for malnutrition. Further analysis is needed to determine if this intervention leads to changes in behavior, dietary practices, or decreases the rate of malnutrition in children under five. Future efforts should include discussions of proper child spacing and family planning.
Summary of Results: Major thematic constructs identified were: (1) AYA survivors believe that survivorship discussions affect their self-esteem and are not healthy conversations because conversations regarding future late effects are too negative, (2) AYA survivors want to move on from their cancer experience, (3) AYAs fear going to new physicians alone, (4) both AYAs and parents believe a survivorship care plan would be helpful, (5) lack of health insurance is a source of stress and barriers for parents and AYAs to access long-term survivorship care, and (6) language barriers and lack of health insurance literacy impedes health insurance knowledge.

Conclusions: These themes that were identified will be used to guide the development of a culturally-tailored educational intervention in the form of a photonovela. The aim of the photonovela will be to improve families’ survivorship care discussions by decreasing cancer stigma and improving their knowledge about the importance of survivorship care planning for AYA childhood cancer survivors.

203 OVERCOMING BARRIERS OF PRESCRIPTION ADHERENCE: A MULTIFACETED APPROACH

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Purpose of Study: Prescription adherence is something that many patients struggle with. Non-adherence leads to worse health outcomes and increased ER visits. Harborview Family Medicine Clinic is being piloted as a Medical Home. This collaboration allows for a multi-disciplinary approach to combating non-adherence in a vulnerable clinic population. The purpose of this project is to improve patient adherence. One method is individualized, identifying personal barriers and then applying a patient specific intervention. The other method, community-based, is aimed at increasing medication understanding among an immigrant population with limited cultural and language experience.

Methods Used: Adherence was identified as a major concern for the clinic through discussion and observation. Baseline data was collected and the following emerged as the major barriers: memory, regimen complication, cultural beliefs and health literacy. A literature review was performed to validate the barriers and need for intervention. It also identified effective tools for improving adherence. A multifaceted approach was developed to first identify and then address the differing needs of individual patients and immigrant populations.

Summary of Results: Interactive tools were created and utilized to address identified barriers. Tools included: prescription bottle education, calendar handout of weekly medicines, medset education, workshops on major concepts in Western health care, including prescription medicine. The immigrant community approach is comprised of curriculum aimed at increasing adherence through interactive education about the Western healthcare system and management of medications. Each session utilized a variety of created tools. Forty-seven patients participated in the clinical approach, a personalized two-step process. First patient knowledge, adherence, and major barriers through survey and discussion were identified. Second, intervention was based upon the major barrier they faced utilizing tools created.

Conclusions: HFMC is uniquely positioned, with medication adherence as a goal of the medical home, to collaborate on overcoming patient barriers. The tools created for this project provide a framework in which to address adherence in a multifaceted way, designed for patients with low cultural, language and health literacy.

204 FREQUENCY AND PREDICTORS OF PATIENT ATTITUDES TOWARDS FULL BODY SKIN EXAMINATIONS

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Purpose of Study: Skin cancer is the most common cancer in the United States, accounting for about half of all incidences of malignancy. Screening is an essential aspect of preventative care and early intervention. However, previous studies have shown a low incidence of screening exams among the general population. Our research aims to explore the attitudes of patients towards general skin exams, how often patients undergo full body skin exams, and potential risk factors for skin cancer.

Methods Used: Study protocol was approved by the UCLA IRB. Questionnaires were collected from 1041 patients recruited at the UCLA General Dermatology clinics. Data analysis was done with frequency tables and linear regressions using the SAS System for Windows 9.0.

Summary of Results: Ninety-seven percent of the patient population surveyed was willing to undergo FBSEs, while only 3% was not (p < 0.001). Sixty-eight percent of patients have ever undergone a FBSE, whereas 32% never have (p < 0.001). A linear regression was run to determine which of the variables surveyed had a statistically significant influence on patient willingness to undergo exams, yielding: perceived necessity, gender concordance, presence of a same-gendered assistant, exams from a dermatologist, and exams from a family medicine practitioner (p < 0.001, < 0.025, 0.020, 0.010, 0.030, respectively).

Conclusions: Skin exams are important preventative tools against skin cancer, the implementation of which should be advanced as much as possible. Further data analysis will be needed to examine the unwilling population as well as the willing population that has never undergone exams in hopes of uncovering obstacles regarding access to exams in these patients.

205 ASSESSMENT AND IMPROVEMENT OF PRE-DEPARTURE TRAINING FOR MEDICAL STUDENTS AND RESIDENTS ON GLOBAL HEALTH PROJECTS


Purpose of Study: Increasing numbers of medical students are participating in global health projects and international electives. In response to this trend, the 2007 report by the AFMC Resources Group on Global Health recommended that Canadian medical schools develop strategies to integrate global health into curricula and ensure student safety and ethical conduct. In 2008, the AFMC and CFMS released a template for the conduct of pre-departure training (PDT) for all students preparing for electives in low-resource settings.

This study was undertaken in order to evaluate the effectiveness of PDT provided by UBC’s Global Health Initiative (GHI), in the form of workshops focused on the core competencies identified by the AFMC and a full day devoted to topics around personal safety and ethical issues. Before departing overseas, students completed evaluations of the quality and comprehensiveness of PDT. Based on these results, GHI has produced a series of online modules to further improve and standardize PDT following the AFMC/CFMS guidelines.

Methods Used: A literature review and survey of existing PDT programs at other Canadian medical schools was conducted in Jul–Aug 2012. Qualitative evaluation surveys and post-deployment debriefings were used to evaluate the effectiveness of the existing GHI PDT program.

Respondents indicated dissatisfaction with the lack of flexibility in scheduling necessitated by live workshops and seminars. Offering online learning modules will increase flexibility in delivering content which can be easily updated and peer reviewed.

Conclusions: PDT should be structured around the core competencies identified by the AFMC. PDT was useful for students working abroad in global health areas. Improvements to GHI’s PDT program should focus on improving flexibility and relevance in order to maximize the efficiency of time spent in PDT.

206 AM I MAKING MYSELF CLEAR? BARRIERS TO PATIENT-DOCTOR COMMUNICATION WHILE USING PHONE INTERPRETERS IN A MEDICAL HOME FOR AT-RISK CHILDREN

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Purpose of Study: The Children’s Health Center (CHC) is a primary care Health Professional Shortage Area facility in Fresno County that serves economically disadvantaged children from diverse cultural & linguistic
backgrounds who are at high-risk for developmental, behavioral, and psychosocial problems. The purpose of this study is to test the hypothesis that caregivers and health care providers in the Newborn Follow-up (NB) and Continuity Clinics (CC) will report increased communication difficulties with phone interpretation when compared to caregivers and providers in the Urgent Care (UC) Clinic.

Methods Used: This is a descriptive study of a convenience sample of caregivers and providers in the NB Follow-up, CC, and UC Clinics at CHC who agreed to participate during a 3 month study period. Study participants were asked to complete a questionaire after each encounter to rate the quality of communication during the encounter. General demographic information and open-ended questions about the encounter were also obtained. Surveys were validated in English for providers and Spanish for caregivers.

Summary of Results: 29 providers (48% Caucasian, 48% Asian, 4% Other) completed 94 surveys. Caregivers (95% Spanish speakers, 91% were patient’s mother) completed surveys from 103 encounters. There were no significant differences in mean ratings by caregivers or providers regarding the quality of communication during the encounter when comparing NB, CC, or UC clinics. However, overall mean ratings revealed provider & parent difficulties with phone interpreters not noticing problems with understanding of one another, providers not feeling they have enough time with patients, and caregivers not feeling at ease talking with interpreters.

Conclusions: Literature shows that using trained medical interpreters is crucial in providing family-centered, culturally competent health care. Our preliminary findings reveal barriers to clear communication between provider and parent that should be considered when using phone interpretation. Future research is planned to understand communication barriers related to phone interpretation faced by pediatric providers and parents in difficult primary care situations, such as when dealing with psycho-socio-behavioral concerns.

IS THE 2002 FRENCH ADOPTION OF A NO-FAULT MEDICAL MALPRACTICE MODEL CONSISTENT WITH EVERETT ROGERS DIFFUSION OF INNOVATIONS THEORY?

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Purpose of Study: This study was done to determine how the fundamental realization of different health care models took hold in the French population and governing bodies and to determine what was the driving force behind the subsequent reform movement. We address how the Rogers’ Diffusion of Innovation model conforms with and deviates from the public policy processes associated with health care reform in France. Subsequently, we can make comparisons to the current United States health care reform process.

Methods Used: An extensive literature review of the Newborn Follow-up, review of French legal documents was performed. These documents helped elucidate the public health law currently in force and the changes that were made to the French medical malpractice system - most notably in the reforms approved by French Parliament in March of 2002. Other publications were used to fill in knowledge and background information.

Summary of Results: The medical malpractice system in France was until recently very similar to the United States. Under a tort malpractice system, patients were able to bring cases directly to the courts and present a case of medical negligence and patient harm. The French government implemented a no-fault compensation system as part of a broad health care reform in 2002. In this, patients are required to bring complaints before a government-appointed claims handler who determines if the claim fits the medical injury review board’s standards for compensation based not on provider negligence, but rather on the patient’s real or perceived loss. Everett Rogers’ Diffusion of Innovations theory tries to account for the adoption of new knowledge by existing entities through a multi-step diffusion process. The theory describes how an innovation is identified, discussed, adopted or rejected, and retrospective reviews of effectiveness. This theory is well suited to apply to health policy reforms.

Conclusions: There are many facets of the diffusion theory that apply to the French health care reform process. Also, there are correlations between the examined factors of the French reforms and the current discontent within the United States for their current health care delivery system that allows discussion and some prediction regarding the future direction of American health care reform.

SIMULATION OF SICKLE CELL DISEASE IS A NOVEL METHOD FOR TEACHING & ASSESSMENT

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Purpose of Study: Sickle cell disease (SCD) is a rare disorder marked by acute exacerbations that lead to frequent hospitalizations, devastating morbidity, and premature death. Because prevalence is low, some pediatrics residents finish training having little to no clinical experience managing acute complications. Infrequent clinical encounters coupled with the inherently complicated nature of SCD have contributed to knowledge and training gaps. Pediatrics residents need opportunities for clinical experience managing acute complications of SCD. The purpose of this study was to develop simulation exercises and associated scoring methods and determine whether these scenarios could be used to evaluate acute SCD exacerbation care skills.

Methods Used: Scenarios were created from actual patient cases and followed the American Board of Pediatrics and ACGME content outlines. Participants individually managed seven simulation scenarios: Vaso-Occlusive Pain Crisis, Acute Chest Syndrome, Ceftriaxone-induced Hemolytic Anemia (CHIA), Asthma Exacerbation, Posterior Reversible Encephalopathy Syndrome (PRES), Acute Splenic Sequestration Crisis, and Wrist Pain. Participants were required to make diagnostic and treatment interventions within a 5-minute period. Two raters scored recorded performances using a checklist of key diagnostic & therapeutic actions and global evaluations (1-poor to 9-superior).

Summary of Results: The assessment cohort included 16 interns, 5 PGY-2, 2 PGY-3, 2 chief residents, and 3 Hem/Onc fellows. Asthma exacerbation was the scenario most proficiently managed (mean checklist score= 77%, SD 12.9); PRES proved most challenging (mean checklist score= 46.1%, SD 12.8). Mean global scores ranged from 4.1 on CHIA and PRES to 6.4 for asthma exacerbation. Checklist scoring had strong interrater reliability (0.73 – 0.93); global evaluations varied widely (0.46 - 0.84).

Conclusions: This is the first study using mannequin-based simulation to teach and assess pediatric residents skills in the acute management of a single disease process. The model proved valid for differentiating skills of more experienced pediatrics trainees from those early in training. It provided a reliable evaluation of a participant’s ability to recognize and respond to simulated acute exacerbations of SCD.

A PROFILE OF DEPRESSED MEDICAL STUDENTS

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Purpose of Study: The aims of the study are: (1) To determine the prevalence of depressive symptoms in a national sample of medical students; (2) to identify correlates of depressive symptoms, and; (3) to test the buffering role of social support in reducing depression symptoms.

Methods Used: This cross-sectional study, used data from 2,682 medical students from 36 U.S. accredited medical schools who completed a 10-minute, web-based Health and Lifestyle Questionnaire in 2005. The measures in the questionnaire included: a 43-item Readjustment Rating Scale (SRRS), a 10-item Alcohol Use Disorder Identification Test (AUDIT), a 15-item social support index, and a 10-item Center for Epidemiologic Studies Depression Scale (CES-D).

Summary of Results: The sample consists of 40.0% male, 59.9% female. The average CES-D score was 12.6 (SD = 10.3). Of the sample, 18.4% had mild depressive symptoms (CES-D scored 16-26), and 11.3% had severe depressive symptoms (CES-D scored ≥27). With the exception of illicit drug use and social support, none of the independent variables showed significant relationship with severity of depressive symptoms among the students who scored ≥16 on the CES-D. Results of stepwise multiple regression analysis show that among students who scored ≥16 on the CES-D and controlling for the confounding effect of age, gender, year in medical school, smoking, drinking, illicit drug use; stressful life events continued to be associated with severe depressive symptoms (β = 0.69, p < 0.01). None of the covariates predicted CES-D scores except for illicit drug use (β = 1.33, p < 0.05). In addition, students who had more social support showed lower relationship between stress and severity of depressive symptoms (β = −0.37, p < 0.05).
Conclusions: Symptoms of severe depression are prevalent in medical students and are significantly associated with the number of stressful life events. In addition, the presence of social support is a protective factor that buffers the negative psychological impact of stressful events on medical students. Our next step is to identify source(s) of stress and support, to develop effective interventions and coping skills.

210  MUSCULOSKELETAL EDUCATION: AN ASSESSMENT OF THE CLINICAL CONFIDENCE AND KNOWLEDGE BASE OF MEDICAL STUDENTS AT UC IRVINE

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Purpose of Study: With the aging population, the prevalence of musculoskeletal (MSK) conditions is increasing and will continue to increase over time. MSK complaints are the primary reason that individuals seek medical attention in the US, comprising 15%-30% of all primary care encounters. Many current studies have shown recently graduated medical students and residents lack the clinical knowledge and confidence necessary to care for such patients. As a result, patients with MSK complaints receive less than optimal care, delayed diagnosis, and inappropriate referrals. It is reasonable to confer that medical students in the US are not receiving the instruction in MSK medicine that they need. To assess how more MSK related education in medical students’ curriculum will impact students’ knowledge and confidence.

Methods Used: We established a multidisciplinary team of musculoskeletal educators including family medicine, orthopedic surgeons, and scientists from UC Irvine involved in musculoskeletal research. We developed a lecture series based on input from the multidisciplinary team. We plan to integrate the new education into the UC Irvine School of Medicine basic science curriculum. A survey was created to assess medical students’ knowledge and subjective confidence in musculoskeletal related topics.

Summary of Results: We plan to assess students’ perception on amount of curriculum time spent on MSK education, subjective importance of MSK education, confidence in performing a MSK physical exam, and objective scores on MSK knowledge-based written exam. We will survey students before and after course completion. Secondary endpoints will assess students’ feedback on timing of the course presentation of material. We also plan to look at which topics require more time spent on based on the results of the knowledge exam and subjective perceptions.

Conclusions: We hope that the results from this study will support the growing body of evidence suggesting that medical students benefit from early exposure to musculoskeletal education. We hope to supplement our current curriculum at UC Irvine SOM as well as advocate other institutions to implement similar programs across the country.

211  DO HEALTHCARE WORKERS HAVE BETTER LIPOPROTEINS?

Raymond LW1,2, Pankowski J 2, Sensenbrenner K 1 Univ of North Carolina, Chapel Hill, Charlotte, NC and 2Carolinas HealthCare System, Charlotte, NC.

Purpose of Study: We tested the hypothesis that healthcare workers (HCW) have more healthful lipoprotein levels (LPL) than non-HCW, because of education, training and familiarity with medical care.

Methods Used: Non-fasting serum concentrations of total cholesterol (TChol, mg/dL), high-density lipoprotein (HDL), triglycerides (TG), low-density lipoprotein (LDL) and non-HDL by autoanalyzer were compared in 221 HCW vs. 991 non-HCW from 10 diverse worksites. Both sets of analytes represented baseline values prior to start-up of wellness programs or other interventions. The majority of participants found existing curriculum to be disease-focused, separating the patient and physician experiences, thus limiting their understanding of the patient’s situation as real, acknowledging current and future commitment to the patient, involving the patient in treatment options, and exploring the patient’s story. Ineffective language included terminating involvement and not recognizing the patient’s story.

Data collection is ongoing and will be included in the final report.

Conclusions: The majority of participants found existing curriculum to be positive and beneficial for their communication skills in difficult conversations. Effective language addressed the many facets of a patient’s experience. Such language built an empathic relationship where the physician recognized and supported the patient’s unique illness narrative. Ineffective language was disease-focused, separating the patient and physician experiences, thus limiting emotional involvement.

Health Care Research II
Concurrent Session
1:30 PM
Friday, January 27, 2012

212  LEARNING THE RIGHT WORDS: EVALUATING COMMUNICATION TRAINING IN DIFFICULT CONVERSATIONS

Vu T, Farber S University of Washington, School of Medicine, Seattle, WA.

Purpose of Study: Although research exists to aid physicians in determining the best ways to approach emotional topics in difficult conversations, there is room to explore how best to teach these skills to medical students during their clinical years. Communication is critical to the doctor-patient relationship, contributing to the empathy, trust, and understanding between the two. Evaluating student impressions of education within a clerkship that teaches skills in sharing poor prognosis can help refine curriculum around difficult conversations.

Methods Used: The study recruited fourth-year medical students enrolled in a chronic care clerkship, a required course that emphasizes communication training as a primary educational objective. An online qualitative approach was used to collect anonymous responses to questions about experiences in the clerkship, with serious illness and death, and with effective and ineffective communication in difficult conversations. Data were analyzed using grounded theory techniques.

Summary of Results: Preliminary results demonstrated that 67% of participants felt their communication was better after the clerkship while 33% felt no change; no students felt a decrease in their communication skills. 92% of participants identified the communication training within the clerkship as good or excellent, and 8% as satisfactory. Effective language included recognizing a patient’s complex situation and lack of resolution, recognizing the patient’s situation as real, acknowledging current and future commitment to the patient, involving the patient in treatment options, and exploring the patient’s story. Ineffective language included terminating involvement and not recognizing the patient’s story.

Conclusions: The majority of participants found existing curriculum to be positive and beneficial for their communication skills in difficult conversations. Effective language addressed the many facets of a patient’s experience. Such language built an empathic relationship where the physician recognized and supported the patient’s unique illness narrative. Ineffective language was disease-focused, separating the patient and physician experiences, thus limiting emotional involvement.

Table

<table>
<thead>
<tr>
<th>Serum lipoproteins in healthcare workers (HCW) and non-HCW</th>
<th>Total Cholesterol</th>
<th>HDL</th>
<th>TG</th>
<th>LDL</th>
<th>Non-HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCW (n = 221)</td>
<td>183 ± 57</td>
<td>47 ± 12</td>
<td>100 ± 44</td>
<td>115 ± 31</td>
<td>155 ± 36</td>
</tr>
<tr>
<td>Non-HCW (n = 991)</td>
<td>184 ± 57</td>
<td>45 ± 12</td>
<td>122 ± 87</td>
<td>118 ± 50</td>
<td>178 ± 54</td>
</tr>
<tr>
<td>p values</td>
<td>0.07</td>
<td>0.06</td>
<td>0.002</td>
<td>0.19</td>
<td>0.24</td>
</tr>
</tbody>
</table>

213  TDAP VACCINATION RATES IN POSTPARTUM WOMEN FOLLOWING IMPLEMENTATION OF TDAP IMMUNIZATION HISTORY REMINDER IN ELECTRONIC MECIAL RECORDS

Aziz N1, Yeaton-Massey A1, Balise R2, Norton M3, Brodzinsky L1 1Stanford University School of Medicine/Lucile Packard Children’s Hospital, Stanford, CA and 2Stanford University School of Medicine, Stanford, CA.

Purpose of Study: Following ACIP and ACOG Tdap vaccination recommendations for postpartum (PP) women due to increasing pertussis infection in infants, various strategies for implementing these guidelines have been reported. However, with subsequent pregnancies, determination of Tdap vaccination eligibility may be challenging. We evaluated how the implementation of a Tdap immunization history reminder in EMR affected subsequent vaccination rates in PP women.

Methods Used: We conducted a retrospective study at a university medical center with a preexisting Tdap vaccine policy since June 2007. We evaluated before-intervention period (BIP) and after-intervention period (AIP) Tdap
vaccine order and administration rates in PP patients during 6 months surrounding the implementation of Tdap vaccination history in EMR. This information was entered into EMR using prenatal records, patient record, and electronic pharmacy records and was viewable by provider in PP notes. We compared rates of Tdap vaccination BIP (10/20/09-1/19/10) with AIP (1/20/10-4/20/10) and evaluated patient characteristics associated with order and administration of vaccine. MMR vaccination rates were assessed in BIP and AIP as proxy for immunization trends. We performed univariate and multivariate analyses.

**Summary of Results:** 2211 women delivered during this time period, (1099 BIP, 1123 AIP). Tdap vaccine was less likely to be ordered and administered for PP women delivering during AIP compared with those in BIP, respectively (53.4% vs. 57.8%, p=0.035; 25.1% vs. 31.9%, p<0.001). MMR vaccination rates did not differ during BIP and AIP. In multivariable analysis, delivery during AIP was associated with decreased Tdap order and administration rates, (aOR 0.80, 95%CI 0.65-0.99) and (aOR 0.77, 95% CI 0.60-0.97).

**Conclusions:** Our results demonstrate that implementation of a computer-based Tdap vaccination history reminder system for PP women in EMR resulted in decreased Tdap vaccination in our patient population. This EMR intervention may have better informed providers and thus decreased unnecessary Tdap immunization in women who may have previously received vaccine.

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**214 INVESTIGATION OF COMPETING CRITERIA FOR CATHETER-ASSOCIATED URINARY TRACT INFECTIONS USING A NOVEL ELECTRONIC SURVEILLANCE TOOL**


**Purpose of Study:** Catheter-associated urinary tract infection (CA-UTI) is the most common hospital-acquired infection (HAI) in the US, yet the definition is controversial. Hospitals are required to report CA-UTI using the CDC definition, yet the Infectious Diseases Society of America (IDSA) definition may be more clinically relevant. We developed a tool to compare the performance characteristics of these definitions by querying the medical records of a cohort of catheterized patients.

**Methods Used:** Novel surveillance tool, from Feb 2010 to July 2011, collected medical record data: demographics, diagnoses, catheter history, fever, urinalysis, urine cultures (UCx), and subjective symptoms found in notes via natural language processing.

**Summary of Results:** 2460 candidate cases (criteria: UCx ordered while catheterized) were identified from 1519 admissions. Controls were candidate cases with negative UCx. See table and figure below.

**Conclusions:** We developed and applied an electronic surveillance tool to compare clinical features of CA-UTI using CDC vs. IDSA criteria. The definitions overlap in only 46% of cases, suggesting discordance between "reportable" CDC and "clinically relevant" IDSA CA-UTI. For both definitions, CA-UTI was associated with increased length of stay, cost of stay, catheter dwell time, fever, and female gender. We estimate that this tool could save 100 worker hours/year while improving real-time detection of CA-UTI. Further efforts should determine whether these findings may be generalized to other settings, the impact of both definitions on care, and how to adapt the tool to other HAIs.

**215 INCIDENCE OF ACRAL SURFACE INSPECTION FOR DETECTION OF ACRAL LENTIGINOUS MELANOMA IN ETHNIC AND CAUCASIAN POPULATIONS**

Tsai M, Chiu M, Young L David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Acral lentiginous melanoma (ALM) is a rare subtype of melanoma that predominantly affects the palms and soles of the feet, and has a predisposition for darker skin types. Compared to Caucasians, ethnic minorities are more likely to have thicker lesions and more advanced disease at the time of diagnosis. Early detection of cancerous lesions is key for improving survival; however, the feet are often not inspected during skin examinations. This study compared the incidence of acral surface inspection during skin examinations in ethnic and Caucasian populations.

**Methods Used:** Written surveys regarding previous experiences with skin exams were collected from 1,040 UCLA dermatology clinic patients. Data were analyzed using Wilcoxon tests and logistic regression in R software.

**Summary of Results:** More Caucasian patients have performed a self skin exam from a health care provider, with rates of 85.7% for Caucasians and 63.8% for ethnic patients (p<0.01, odds ratio=2.37, 95% confidence interval=1.65-3.40). Of those who performed self skin exams, there were no significant differences in the rates of foot or hand foot inspection between Caucasian and ethnic patients. More Caucasian than ethnic patients have undergone a skin exam from a health care provider, with rates of 77.5% for Caucasians and 38.9% for ethnic patients (p<0.01, OR=3.65, CI=2.62-5.10). During skin exams by a health care provider, more Caucasians than ethnic patients had their hands (p<0.01, OR=2.09, CI=1.16-3.77) and feet (p<0.03, OR=1.78, CI=1.05-3.02) inspected.

**Conclusions:** The differences in the frequencies of skin exams and the incidences of hand and foot inspection may be contributors to the current disparities in survival for ethnic patients. Increased awareness of skin cancer and ALM for both patients and health care providers will be important in addressing the present inequalities between Caucasian and ethnic patients.

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**216 CAN TOOLS FROM BEHAVIORAL ECONOMICS AND SOCIAL PSYCHOLOGY HELP TO CONTROL CHRONIC DISEASES?**

Mogler B1,2, Shapiro M1, Shu S1, Fox C1, Goldstein N1 1UCLA, Los Angeles, CA and 2Charles Drew University, Los Angeles, CA.

**Purpose of Study:** In spite of a revolution in therapeutics, the ability to control chronic diseases remains elusive. Even among people in whom diseases such as hypertension have been diagnosed, many still do not achieve satisfactory control. We undertook a study to develop and implement in a randomized trial an intervention to promote better control of blood pressure, using tools from behavioral economics. As a part of this effort, we analyzed literature pertaining to behavioral change that may have relevance to interventions in chronic disease. We present here a conceptual model of chronic disease control and the use of behavioral tools in that effort.

**Methods Used:** Clinicians typically accept the assumption derived from neoclassical economic theory of “boundedly rational” behavior, in which a person is expected to act in a way that maximizes their self-interest. In such a framework, it would be expected that a patient would adhere to an evidence-based treatment if they had appropriate knowledge, felt competent to pursue the treatment, and were not deterred by direct and indirect costs associated with the treatment. However, patients may not always be the rational actors we imagine. Barriers to optimal behavior include an “ostrich effect,” ambi-guity aversion, myopic loss aversion, and a negative effect of incentives upon the intrinsic motivation to control the disease.

**Summary of Results:** We conceptualize disease management as being on a continuum from diagnosis to long-term control. Knowledge, self-efficacy, attention, intrinsic motivation and cost all are relevant to achieving and maintaining control. Potential behavioral tools include financial incentives, which are useful for discrete activities but may not be effective for chronic disease care unless combined with other strategies like trait labeling and efforts to increase intrinsic motivation. Other potential strategies include leveraging of social norms, overcoming present bias, a “goals as reference
points” strategy that breaks down a task like weight loss into more manageable stages, elicitation of implementation intentions, intelligent defaults, and reminders with a twist. Most of these strategies have not been tested in medical settings.

**Conclusions:** The effectiveness of these approaches merit serious consideration as tools for the clinician.

### 217 EFFECT OF PHYSICIAN FOLLOW-UP AND SPECIALTY DIFFERENCES ON 30-DAY READMISSION FOR HEART FAILURE PATIENTS

Jang D, Xu H, Escarec J, Ong M David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA.

**Purpose of Study:** To determine whether heart failure patients who have an outpatient physician visit within 30 days after discharge have a lower rate of 30-day readmission than patients without such a visit. The study also examines whether the medical specialty of the physician seen at the first outpatient visit has an effect on the rate of 30-day readmission.

**Methods Used:** The study examined 1265 Medicare Advantage patients discharged with a principal diagnosis of heart failure from an academic medical center between June 2005 and July 2010. Only those hospitalizations not preceded by another hospitalization within 30 days were included. Inpatient and outpatient records were examined to determine if a rehospitalization occurred within 30 days and if an outpatient visit occurred within 30 days of these index hospitalizations. Outpatient visits occurring after a rehospitalization were not included. Medical staff rosters were used to determine the identity and specialty of physicians who provided the initial post-discharge outpatient care. The study examined the relationship between 30-day readmissions and outpatient visits within 30 days using bi-variable and multi-variable analyses.

**Summary of Results:** Of heart failure patients who saw a physician within 30 days after discharge, 17.0% had a 30-day readmission, compared to 29.8% of patients who did not see a physician. Compared to a reference group of patients who had no outpatient visit, the adjusted odds ratio for 30-day readmission for patients who first saw a cardiologist was 0.33. The odd ratios for patients seen by primary care and other specialty physicians were 0.48 and 0.49, respectively.

**Conclusions:** The study suggests that patients discharged for heart failure should have physician follow-up within 30 days after discharge to reduce the risk of 30-day readmission. The follow-up should be with a cardiologist for the greatest reduction in readmission risk.

### 218 CHRONIC DISEASE EDUCATION NEEDS OF DISCHARGED EMERGENCY DEPARTMENT PATIENTS

Bautista E1, Jobe K2 University of Washington, Seattle, WA and 3University of Washington, Seattle, WA.

**Purpose of Study:** With 15.3% of all emergency department (ED) patients nationwide lacking health insurance, the ED may be the only encounter underserved patients have with healthcare. This study hypothesized that a higher proportion of underserved ED patients with acute attacks of a chronic disease had less understanding of their chronic diseases than those with regular healthcare access. These patients could possibly benefit from further education in the ED beyond their acute complaint, leading to better disease management and decreased ED re-visits.

**Methods Used:** Discharged ED patients received surveys with questions directed at 3 goals: 1) Measuring discrepancies in understanding and managing chronic diseases between different groups using a scale of 0 (Not at all), 3 (Somewhat), and 5 (Very well); 2) determining post-ED behavior such as ED education in the ED beyond their acute complaint, leading to better disease management and decreased ED re-visits.

**Summary of Results:** Of 136 eligible participants, 82 took part in the study. Those without PCPs rated their understanding of their diagnosis and treatments less at 3.67 and 2.20 respectively, compared to those with PCPs with respective ratings of 4.56 and 4.71 (p<0.05). They also felt less confident in managing their chronic diseases with a score of 3.20 compared to 4.22 for those with PCPs (p<0.05). 30% of all tested subjects indicated a preference for receiving further resources in the ED, with 47% of this group requesting information sheets.

**Conclusions:** Partially supporting the hypothesis, the results suggest that discharged ED patients without a PCP feel less confident in managing and understanding their chronic diseases regardless of primary complaint. With 30% of patients requesting more chronic disease education in the ED, providing additional resources about their conditions or risk factors along with ED clinic info could potentially benefit underserved patients in maintaining their health. Further studies could evaluate the efficacy of educational interventions and if it leads to decreased ED utilization among this population.

### 219 METHODS AND DESIGN OF THE BLOOD PRESSURE IN DIALYSIS (BID) STUDY: A RANDOMIZED CONTROLLED TRIAL OF INTENSIVE CONTROL OF SYSTOLIC BLOOD PRESSURE IN HEMODIALYSIS PATIENTS

Gul A1, Miskulin D2, Gassman J3, Horowitz B4, Harford A1, Zager P1,4

1University of New Mexico, Albuquerque, NM; 2Tufts Medical Center, Boston, MA; 3Cleveland Clinic, Cleveland, OH and 4Dialysis Clinic, Inc., Albuquerque, NM.

**Purpose of Study:** Current KDOQI-US, CARI-Australia, UK and K-DIGO guidelines call for a pre-dialysis SBP ≤140 mm Hg. However, the evidence supporting these guidelines was graded as weak since it was largely extrapolated from the general population. Observational studies suggest that mortality may be increased among hemodialysis (HD) patients who meet these guidelines. However, a meta-analysis suggested that treatment with antihypertensive drugs decreased mortality. Thus, identifying the optimal pre-dialysis SBP requires a large RCT. The BID Study is a pilot, multi-center RCT, funded by the NIH and DCI, which will inform the design of a full-scale study to determine the effects of tight control of SBP on all-cause and cardiovascular-mortality in HD patients.

**Methods Used:** Participants (n=120) include patients ≥18 years who have been maintained on thrice weekly HD for ≥90 days. Pre-dialysis SBP measured in accord with American Heart Association recommendations, guides therapy in BID. Participants are randomized to a pre-dialysis SBP of 110-140 mm Hg or 155-165 mm Hg, which is maintained for 1 year. Cardiac structure and function and aortic pulse wave velocity are assessed by MRI at baseline and study end. Primary outcomes are the feasibility and safety of achieving and maintaining the assigned SBP targets during the one-year intervention. Secondary outcomes include mortality, cardiovascular events, vascular access thrombosis, adverse events and differences in the rates of change in left ventricular mass and health related quality of life.

**Summary of Results:** Results pending completion.

**Conclusions:** The BID Study is a pilot, multi-center RCT to assess the safety and feasibility of two different SBP goals in HD patients that will inform the design of a full-scale RCT to examine the effects of tight BP control on all-cause and cardiovascular-mortality in HD patients.

### 220 THE ABCS OF HOSPITALIZED PATIENTS: A MULTIDISCIPLINARY CHECKLIST TO IMPROVE QUALITY OF INPATIENT CARE

Perkins C, Afsar-manesh N UCLA, Los Angeles, CA.

**Purpose of Study:** The societal and financial burden of hospital-acquired conditions (HACs) is significant. Due to the complexity of inpatient care, simple, evidence-based interventions that reduce the incidence of HACs are often overlooked. In 2009, a pilot of the ABCs of Hospitalized Patients in Ronald Reagan Medical Center found that a checklist for physicians reduces HAC risk factors. The objective of this study is to obtain longitudinal data on the effectiveness of checklists in reducing risks factors for HACs.

**Methods Used:** The existing checklist from the 2009 pilot was updated and included the measures listed in the table below. Training sessions for nurses, residents, and interns on how to complete and utilize the checklist were conducted. For the 7 East unit of Ronald Reagan UCLA Medical Center, checklists were completed by the night nurses, placed in the orders section of the chart, and reviewed by the provider team on the following day.

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Summary of Results: Although data collection efforts are still ongoing, we have seen a slight decrease in the use of Foley catheters (15 to 13%), and telemetry use has decreased significantly from 74 to 59%.

Conclusions: The initial data is not entirely consistent with that obtained during the 2009 pilot, as DVT prophylaxis levels have not increased and blood glucose levels have not been impacted. However, it is important to note that a few more weeks of data collection are needed to gain statistically significant results. A few other factors could also explain this disparity, including implementation timing (i.e., time of year with respect to start of new residents).

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### Summary of Results:

- **Risk for HbA1c Improvement with Awareness**
  - A: Ambulation: A high patient's risk score can lead to falls with trauma B. Preventive fall prevention by the primary team.
  - B: Blood Glucose ≥100 mg/dl: A. Elevated blood sugars over 24 hours can lead to increased infections rate B. Better blood sugar control and decreased infections.
  - C: Central Venous Catheters (CVC): A. Increase in number of days the catheter has been in place can lead to infections B. Removal of catheters to prevent bloodstream infections.
  - D: Deep Venous Thrombosis (DVT) Prophylaxis: A. Patient is not on appropriate prophylaxis can develop DVT/thrombotic embolism (PE). B. Prevention of DVT/PE.
  - E: Emissions of the Skin/Tissue Ulcers: A. Risk of developing pressure ulcers with high risk scores B. Prevention of skin breakdown.
  - F: Foley Catheter: A. Increase number of days Foley catheters lead to a primary tract infection (UTI) B. Removal of catheters to prevent catheter-associated UTI.
  - G: Glucose Communication: A. Any information that the nurse would like to communicate to the provider team.

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### Methods Used:

- Purpose of Study: The Loma Linda Veterans Administration Medical Center, Loma Linda, CA.
- Methods Used: The Loma Linda University School of Medicine, Loma Linda, CA.
- Purpose of Study: The Loma Linda University School of Medicine, Loma Linda, CA.
- Methods Used: The Loma Linda Veterans Administration Medical Center, Loma Linda, CA.

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### Purpose of Study: Increasing literature suggests that psoriasis patients with severe disease appear to have increased frequency of cardiovascular (CV) diseases. The National Psoriasis Foundation recommends screening for CV risk factors as early as age 20. The extent to which these screening guidelines are implemented in practice is unclear. We aimed to assess whether primary care physicians (PCPs) and cardiologists are aware of the increased CV outcomes in psoriasis patients and whether they screen for CV risk factors in psoriasis patients.

### Methods Used: We distributed 1200 questionnaires to PCPs and cardiologists between October 1, 2010 and April 15, 2011. A representative national sample of physicians was obtained by random selection from professional medical societies.

### Summary of Results: A total of 251 PCPs and cardiologists responded to the questionnaire. Fewer than half of physicians reported screening for CV risk factors: 108 (43%) screened for hypertension; 27 (11%) screened for dyslipidemia; 75 (30%) screened for obesity, and 67 (27%) screened for diabetes. Physicians who cared for a greater number of psoriasis patients were significantly more likely to screen for CV risk factors (hypertension p=0.0041, dyslipidemia p=0.0143, and diabetes p=0.0065). Compared to PCPs, cardiologists were 1.85 times more likely to be aware of worse CV outcomes among psoriasis patients (95% CI 1.03–3.33, p=0.039) and 2.46 times more likely to screen for dyslipidemia compared to PCPs (95% CI 1.07–5.63, p=0.034). Overall, 113 (45%) of physicians were aware that psoriasis is associated with worse CV outcomes.

### Conclusions: Most PCPs and cardiologists did not routinely screen psoriasis patients for CV risk factors. Educating physicians regarding potentially increased CV risk in psoriasis and adopting a multidisciplinary approach in the care of psoriasis patients will likely lead to improved patient outcomes.

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### Purpose of Study: Comparing the effectiveness of open and closed-ended questioning models in patients presenting to the emergency department with the chief complaint of chest pain.

### Methods Used: In the Emergency Department environment, time is one of the scarcest commodities. Emergency medicine physicians must be skilful at quickly obtaining a history of present illness without overlooking any potentially life-saving details. There are few chief complaints where the diagnosis is more contingent on rapidly gathering correct information than chest pain. Chest pain is an exceedingly non-specific complaint, originating from a diverse array of underlying conditions including: myocardial infarction, cardiac ischemia, pulmonary embolism, costochondritis, chest well well

### Conclusions: By performing a direct comparison of the open and closed-ended question models, the results of this study will provide a quantification of each technique’s respective effectiveness.

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### Summary of Results:

- **222 ARE PSORIASIS PATIENTS BEING SCREENED FOR CARDIOVASCULAR RISK FACTORS? A STUDY OF AWARENESS AND SCREENING PRACTICES AMONG PRIMARY CARE PHYSICIANS AND CARDIOLOGISTS**
  - Brezinski EA,1,2 Parni KC,2,3 Lin T,1 Li C, Armstrong AW2 University of California Davis, School of Medicine, Sacramento, CA. 1University of California Davis, Sacramento, CA. 2AT Still University-School of Osteopathic Medicine in Arizona, Mesa, AZ. 3University of California Davis, Sacramento, CA. 4University of California Davis, Sacramento, CA.
  - Purpose of Study: Increasing literature suggests that psoriasis patients with severe disease appear to have increased frequency of cardiovascular (CV) diseases. The National Psoriasis Foundation recommends screening for CV risk factors as early as age 20. The extent to which these screening guidelines are implemented in practice is unclear. We aimed to assess whether primary care physicians (PCPs) and cardiologists are aware of the increased CV outcomes in psoriasis patients and whether they screen for CV risk factors in psoriasis patients.
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  - Conclusions: Most PCPs and cardiologists did not routinely screen psoriasis patients for CV risk factors. Educating physicians regarding potentially increased CV risk in psoriasis and adopting a multidisciplinary approach in the care of psoriasis patients will likely lead to improved patient outcomes.

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### Summary of Results:

- **223 TWO-YEAR ABSTINENCE OF CIGARETTE SMOKERS ENROLLED IN AN OUT-PATIENT TOBACCO DEPENDENCE TREATMENT PROGRAM**
  - Chung SJ1, Debay M1, Wos D1. Ferry L1,2 1Loma Linda University School of Medicine, Loma Linda, CA. 2Loma Linda Veterans Administration Medical Center, Loma Linda, CA.
  - Purpose of Study: The Loma Linda Veterans Administration Medical Center (LLU-VAMC) tobacco dependence treatment (TDT) program has enrolled nearly 9,000 patients since 1997. Enrolled smokers are offered four weekly education classes and physician treatment and follow-up in the Preventive Medicine Clinic (PMC). The TDT program collects patient data at each visit from their enrollment to their last follow-up visit, after which the smoking status documented in CPRS clinical notes at the closest date beyond the 3, 6, 12 and 24-month time points after the quit date. We then calculated the abstinence period prevalence-APP (between two time points) and the prolonged abstinence prevalence-APP at 3 months, decreases dramatically to

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224 CHIEF COMPLAINTS OF FREQUENT EMERGENCY DEPARTMENT UTILIZERS AND PREVALENCE OF SUBSTANCE ABUSE AND PSYCHIATRIC DISORDERS

Dang M1, Layton M1,2, Neven D3, Howell D2, Roll J1
1University of Washington, Seattle, WA; 2Washington State University, Spokane, WA and 3Providence Sacred Heart, Spokane, WA.

Purpose of Study: Overcrowding of the emergency department (ED) has been an ongoing issue for hospitals across the nation. A city-wide ED care coordination program has been established in Spokane, WA to coordinate care for individuals that over utilize the ED with chronic or recurrent pain complaints. A high frequency of substance abuse (SA) and psychiatric illness in this population has been shown to contribute to excessive ED utilization. The goal of this retrospective study was to describe the characteristics of patients enrolled in this ED care coordination program that frequent the ED with pain complaints.

Methods Used: This study was a retrospective electronic medical record review. Records were reviewed six months before and after program enrollment for age, gender, history of substance abuse and/or psychiatric disorders and the types of presenting pain complaints. 278 patients aged ≥18 years enrolled in a city-wide ED care coordination program between February 1, 2006 and November 1, 2010 were included in this study.

Summary of Results: 56% (156) of patients reported a history of substance abuse and 29.5% (82) had a documented psychiatric diagnosis. 24% (67) had a history of co-occurring substance abuse and psychiatric diagnosis. The most common substances abused were opioids and the most common psychiatric diagnoses were personality disorders. Pain complaints accounted for 58.3% of all chief complaints prior to enrollment. The top three presenting chief complaints were abdominal pain, headache, and back and neck pain.

Conclusions: Patients who frequently visit EDs with pain complaints commonly have substance abuse and psychiatric histories. In addition to care coordination needs, these patients also need substance abuse and mental health treatment.

225 MCI TRIAGE: ASSESSMENT OF PROVIDER PERFORMANCE IN KING COUNTY, WA

Kenningham K1, King M1,2,3 1University of Washington, Seattle, WA; 2Harborview Medical Center, Seattle, WA and 3Seattle Children’s Hospital, Seattle, WA.

Purpose of Study: Following 9/11 and Hurricane Katrina, there has been a surge in disaster planning and training. Though children comprise a quarter of the US population, there are distinct needs during mass casualty incidents (MCI), and are at increased vulnerability during such events, disaster preparedness protocols and training programs lack sufficient inclusion of pediatric focus. There has been recently rising interest in addressing this shortfall in and developing curricula to incorporate pediatric focus in disaster preparedness training. Currently, there is much debate over which providers should be prioritized for such training. This study aims to evaluate which factors reflect the greatest shortfall in pediatric triage skills in a varied population of medical providers in King County, WA.

Methods Used: Eighty-eight employees of several hospitals and pre-hospital agencies throughout King County, WA, attended a pediatric disaster preparedness conference and workshop on September 20, 2011. Attendees included administrators, physicians, nurses, respiratory therapists, and EMTs. Following didactic introduction to pediatric triage algorithms, attendees participated in three educational workshops, including a simulated pediatric MCI requiring triage of 30 mannequin mock patients. Provider characteristics were surveyed and relationship with triage assessment was evaluated via median tests.

Summary of Results: Of 88 participants, 60 worked at a facility with pediatric patients, 32 reported regular pediatric exposure (>50% of patient encounters), 54 worked in an ED or ICU, 53 were PALS-certified, 18 had actual MCI experience, 9 were EMS providers, and 6 had military experience. Providers with regular pediatric exposure performed more accurate pediatric MCI triage compared to those without (Wilcoxon ranksum test, p = 0.027). There was no significant relationship between triage score and level or type of provider, years of experience, workshop group, workplace, or PALS certification.

Conclusions: In King County, WA, the primary predictor of better pediatric MCI triage performance following a brief tutorial is regular exposure to pediatric patients. If prioritizing providers for educational intervention, we should consider targeting those without regular pediatric patient exposure.

Hematology Oncology and Surgery

Concurrent Session

1:30 PM

Friday, January 27, 2012

226 FACTORS ASSOCIATED WITH LOCAL-REGIONAL FAILURE AFTER DEFINITIVE CHEMORADIATION FOR LOCALLY ADVANCED ESOPHAGEAL CANCER

Amin A1,2, Welsh JW1, Allen PK1, Xiao L2, Suzuki A1, Hayashi Y1, Blum M1, Hofstetter W4, Komaki R1, Liao ZJ, Lee JH, Bhutani MS3, Ajani JA1
1University of Texas MD Anderson Cancer Center, Houston, TX; 2The University of Texas MD Anderson Cancer Center, Houston, TX; 3The University of Texas MD Anderson Cancer Center, Houston, TX; 4The University of Texas MD Anderson Cancer Center, Houston, TX and 5UC Irvine School of Medicine, Irvine, CA.

Purpose of Study: Esophageal cancer is often treated with a trimodality approach (chemoradiation followed by surgery). However a proportion of such patients achieve a clinical complete response (cCR) following chemoradiation alone. We retrospectively analyzed patients who reached cCR after definitive chemoradiation for locally advanced esophageal cancer to identify clinical predictors of local disease recurrence.

Methods Used: We identified 141 patients who obtained initial cCR after definitive chemoradiation for esophageal cancer from January 2002 through January 2009. The initial response to treatment was assessed by endoscopic evaluation and biopsy results, with cCR defined as having no evidence of disease present. Patterns of failure were categorized as in-field (within the planned treatment volume [PTV]), outside the radiation treatment field, or both.

Summary of Results: At a median follow-up of 22 months (range 6-87 months), 77 patients (55%) had experienced disease recurrence. Most first failures (32, or 23%) were outside the radiation field, followed by 30 (21%) within the field and 15 (11%) were both. In multivariate analysis, in-field failure after cCR was associated with a post-treatment standardized uptake value (SU V) on positron emission tomography of >3.5 (odds ratio [OR] 4.93, p = 0.022), squamous histology (OR 0.07, p = 0.010), and borderline for T3/T4 disease (OR 10.25, p = 0.055). All failures, in-field and out-of-field, correlated with T3/T4 disease (OR 11.61, p = 0.015), N1 disease (OR 5.07, p = 0.010), pretreatment SUV >10 (OR 4.00, p = 0.048), and post-treatment SUV >3.5 (OR 3.59, p = 0.052).

Conclusions: Clinical characteristics can be used to predict failure patterns after definitive chemoradiation. Such risk-assessment strategies can help individualize therapy.

227 THE NOISE POWER SPECTRUM OF AN EXPERIMENTAL PROTON CT SCANNER

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Purpose of Study: Protons are increasingly used in radiation therapy because they have a finite depth, sparing distal tissue, and deliver the highest dose near the end of their range (Bragg peak), sparing proximal tissue. Proton therapy requires tomographic images for accurate planning of beam delivery.
Proton computed tomography (pCT) is likely to be more accurate in this respect than current x-ray CT because the Hounsfield values obtained from x-ray CT need to be converted to relative proton stopping power (RSP), whereas proton CT would provide this directly. The purpose of this study was to evaluate the noise power spectrum (NPS) of an experimental pCT scanner at Loma Linda University Medical Center.

Methods Used: The uniformity module of the Catphan CT performance phantom (The Phantom Laboratory, NY) underwent a pCT scan with 200 MeV protons. The pCT scanner recorded entrance and exit vectors of individual protons with silicon strip detectors and measured proton energy with a CsI crystal calorimeter (read out by photodiodes). The phantom was rotated by a precision stage to generate the many projections. The signal of the calorimeter was converted to the integral of proton stopping relative to water along the path of each proton. A 3D map of the RSP was then reconstructed using an initial filtered backprojection (FBP) method followed by an iterative projection method combined with a total variation super-iorization (TVS) scheme, developed previously by Penfold et al. The NPS analysis was performed with Matlab (MathSoft Inc.). The final NPS was obtained by averaging the individual spectra of all analyzed images.

Summary of Results: An appropriate NPS was obtained from the Catphan module scan. With a slice thickness of 2.5 mm and 1.7 million protons used for reconstruction per slice, the root mean square (RMS) noise was 0.0243 RSP for the final FBP image and 0.0128 RSP for the final iterative reconstruction. The NPS of the initial FBP reconstruction showed a larger high-frequency noise content than the iterative reconstruction, whereas the NPS of the iterative reconstruction showed a maximum at low frequencies.

Conclusions: FBP-reconstructed pCT images showed a different NPS than those reconstructed with an iterative method and TVS. This study shows that the noise power spectrum is a useful measure for comparing current and future reconstruction techniques in pCT.

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EXPERIENCE WITH A NEW INTEGRATED NEGATIVE PRESSURE WOUND THERAPY SYSTEM WITH VOLUMETRIC AUTOMATED FLUID INSTILLATION IN AT-RISK WOUNDS

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Purpose of Study: Studies have reported favorable outcomes with the combined use of negative pressure wound therapy (NPWT) and instillation of topical solutions in at-risk wounds. Until recently, commercially available NPWT-installation systems (i.e., continuous or gravity-fed) have been limited in their ability to regulate solution volume delivery. We report initial experience using a new integrated NPWT system with volumetric automated instillation (NPWTi) using a less hydrophobic reticulated open-cell foam dressing on at-risk wounds.

Methods Used: Therapy goals included infection clearance and wound coverage. Patients received systemic antibiotics and wound debridement. Before NPWTi, punch-wound biopsy cultures showed bacterial contamination. Patient 1, an 86-year-old female diabetic with peripheral vascular disease (PVD), presented with a left foot abscess. The abscess was drained and the wound debrided. NPWTi consisted of 12 cycles/day for 3 days with 3-minute saline soaks at negative one hundred and twenty five mmHg negative pressure (NP) for 2 hours. Patient 2, a 43-year-old female, presented with an infected, radiated chest wound. NPWTi consisted of 24 cycles/day for 3 days with 3-minute polyhexamidine soaks at negative one hundred and twenty five mmHg NP applied for one hour. Patient 3, a 64-year-old diabetic male with PVD, presented with an infected amputation. NPWTi consisted of 12 cycles/day for 6 days with 3-minute polyhexamidine soaks at negative one hundred and twenty five mmHg NP for 2 hours.

Summary of Results: NPWTi appeared to assist in wound cleansing and exudate removal. All patients were followed to wound closure with 3-month follow up with no recurrence or wound infection. Clinical findings included granulation tissue formation was present with negative cultures for patients at time of coverage with a flap or graft. All wounds healed and patients were discharged.

Conclusions: NPWTi may play an important role in the initial management of highly contaminated or infected wounds following surgical debridement.

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ANTERIOR LUMBAR INTERBODY FUSION L5/S1 HAS NO EFFECT ON SPINOPELVIC PARAMETERS IN THE SETTING OF ADULT DEGENERATIVE SCLEROSIS

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Purpose of Study: This radiographic study evaluates the spinopelvic parameters of adult scoliosis patients in order to assess the benefit of correction with anterior interbody fusion at L5/S1. Radiographic parameters known to effect quality of life were measured for both pre and post-operative patients who underwent anterior release with L5/S1 interbody graft (n=20) and those who did not (n=18).

Methods Used: Parameters were measured using a standard PACS imaging system and data was summarized through means and standard deviations (continuous covariates) and frequencies and percentages (categorical covariates). Patterns in change were then observed using spaghetti and box plots, and differences in change between pre and the post-operative measures were investigated through t-tests and Wilcox signed-rank tests.

Summary of Results: Sagittal vertical axis (SVA), pelvic tilt (PT), sacral slope (LL), lumbar lordosis (L1), thoracic kyphosis (TK), lumbar-sacral (L5/S1) angle, and pelvic incidence (PI) were all measured, with changes in SVA, PT, SS, and LL serving as the focus of analysis, as these most closely reflect patient outcome. The degree of change of SVA in the L5/S1 graft group (mean = 37.9, SD = 61.7) was less than that of the non-graft group (mean = 49.1, SD = 47.8). There was little difference in change of PT between groups, although the L5/S1 graft group (mean = 3.3, SD = 8.5) experienced a larger change than the non-graft group (mean = 1.7, SD = 13.0). While SS shows an upward trend in the L5/S1 graft group and a downward trend in the non-graft group, the average and median SS change is close to zero. Lastly, LL increased in both groups. None of the above differences were
shown to be significant at the 0.05 level, so regression models were not investigated.

Conclusions: This study suggests that there may not be a difference in ALIF at L5/S1 to affect final spinopelvic parameters. Limitations include small sample size, which failed to show significance. This data questions the justification for L5/S1 grafting and emphasizes the need for further research, given the increased operative risk inherent to this procedure.

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OCULAR BIOMICOMPATIBILITY OF NITINOL
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Purpose of Study: Nitinol is a nickel-titanium shape memory alloy that is widely used in implantable surgical devices. The alloy is an increasingly popular material for use in surgical instruments because of its shape-retaining characteristics, tensile strength and record of good biocompatibility. The main concern in the use of nitinol is its nickel component. Although nickel has been found to have multiple adverse effects, many studies have demonstrated good biocompatibility of nitinol in various human tissues. However, there have been no studies to assess nitinol biocompatibility in ocular tissues. The results of this study will be important in establishing the safety of a new minimally invasive nitinol suture developed for use in the eye.

Methods Used: Cultures of human retinal pigment epithelium (ARPE-19) and human corneal endothelium (HCN E6/E7) were used. First, to establish the levels at which nickel is toxic to these ocular cells, different concentrations of nickel chloride were added to confluent cells and incubated for 3 days. Cell viability was then measured. To test for leaching effects of nitinol, nitinol wire was incubated in media, which was aspirated and frozen down at different time points within an 8 week period. Both cell lines were then exposed to the different batches of media for 2 days and cell viability was measured. Cell viability for the above experiments was determined with MTT assay. In order to observe cell growth in the presence of nitinol, cells were seeded onto culture plates containing pieces of nitinol wire and allowed to grow to confluency.

Summary of Results: There is a statistically significant decrease in cell viability for ARPE-19 cells at 2.5 mM nickel chloride and for HCN E6/E7 cells at 0.5 mM. The leaching experiments showed no statistically significant decrease in cell viability for both cell lines. Cell growth experiments demonstrated that the cells were able to grow to confluency in the presence of and in contact with the nitinol.

Conclusions: The nitinol showed minimal leaching effects and did not affect cell proliferation. Therefore, these results support the safety of ocular nitinol sutures for use in the eye. Further experimentation needs to be done to determine absolute levels of nickel that may be released from the nitinol wire.

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AUTOMATED BRIGHTNESS CONTROL FLUOROSCOPY SETTINGS WITH SHIELDING INCREASES RADIATION EXPOSURE TO SURROUNDING UNSHELDED TISSUES

Purpose of Study: Radiation exposure to the uterus was significantly reduced by 2.5 and 5.5-fold (p<0.05) in ABC and fixed settings, respectively, with shielding. However, there was an approximate 2-fold increase in radiation exposure to the ureter and ipsilateral kidney (p<0.05) when shielding of the uterus was performed with ABC. Under fixed settings, there was no significant difference (p>0.05) in radiation levels at these locations regardless of shielding status.

Conclusions: Utilization of ABC with shielding of the uterus almost doubled radiation exposure to surrounding unshielded tissue. Radiation can be reduced and image quality improved using fixed settings when shielding is indicated.

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RASSF1C DECREASES MST1/2 ACTIVATION
Palma AE, Poh C, Alkakhouri M, Amaar Y, Reeves M.

Purpose of Study: Recently, RASSF1A has been shown to mediate the apoptotic effects of TNF-α by interacting with the mammalian sterile 20-like kinase 1 and 2 (MST1/2) through the Salvador/Rassf/Hippo (SARAH) domain, leading to MST1/2 phosphorylation and activation of apoptosis. In contrast, we have previously shown that RASSF1C promotes cell proliferation and attenuates apoptosis in cancer cells. Since both RASSF1A and RASSF1C contain the SARAH domain located in their identical C-termini, RASSF1C should be capable of interacting with SARAH domain-containing proteins, and could potentially attenuate MST1/2-mediated apoptosis. Thus, in this study we have investigated the impact of RASSF1C on MST1/2 activation in presence of TNF-α, including whether RASSF1C modulates MST1/2 pro-apoptotic pathways differently from RASSF1A.

Methods Used: Breast and lung cancer cells over-expressing RASSF1A and RASSF1C were used in this study. Cells were cultured in the proper media and treated with TNF-α for 24 hr. Cells were collected and used for Western blot analysis utilizing antibodies that detect MST and p-MST forms.

Summary of Results: Our preliminary data suggest that RASSF1C over-expression decreases the phosphorylation levels of MST1/2 in TNF-α-treated lung cancer cells compared to those cells over-expressing RASSF1A. In breast cancer cells, RASSF1C expression does not seem to affect MST phosphorylation.

Conclusions: Our findings suggest that over-expression of RASSF1C in lung cancer cells may attenuate the MST1/2 apoptotic pathway by sequestering of MST1/2 proteins and inhibiting their activation by phosphorylation. The findings also further support our hypothesis, at least in lung cancer cells, that RASSF1C has antagonistic effect on MST1/2 activation compared to that of RASSF1A.

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ASSESSMENT OF GLUTAREDOXIN 5 GENE EXPRESSION IN HUMAN BREAST AND LUNG CANCER CELLS
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Purpose of Study: Glutaredoxin 5 (GLRX5), a gene that encodes a mitochondrial protein involved in the biogenesis of iron-sulfur (Fe-S) clusters and in the maintenance of mitochondrial homeostasis, protects cells from apoptosis. Little is known about the expression profile of this important gene in human cancer cells. Therefore, we compared the expression of GLRX5 in breast and lung cancer cells to that of corresponding primary epithelial cells.

Methods Used: Primary mammmary epithelial cell, MCF-10A, lung primary epithelial cell, CRL-9482, breast cancer cell lines, T47D, MDA-MB-231 and HS578T, and lung cancer cell lines, NCI-H1299 and A549, were used for the study. Cells were cultured in the proper media, grown to 70% confluency, and collected for total RNA isolation. Total RNA was isolated using an RNA extraction kit and 1 μg of RNA was used for RT-PCR analysis in triplicates. GLRX5 gene specific primers were used to quantify GLRX5 expression. Cyclophilin gene specific primers were used to quantify Cyclophilin gene expression as an internal load control.

Summary of Results: RT-PCR analysis showed that GLRX5 expression was up-regulated by 3 to 11 fold in breast cancer cell lines, T47D and MDA-MB-231, and was down-regulated by approximately 7 to 8 fold in breast cancer cell line, HS578T, compared to its expression in primary mammary...
epithelial cell, MCF-10A. GLRX5 expression in lung cancer cell lines, NCI-H1299 and A549, was down-regulated by 2 to 3 fold, compared to its expression in lung epithelial cell. 2012.

Conclusions: Elevated GLRX5 gene expression may protect cancer cells from apoptotic effects and enhance survival of breast cancer cell lines, T47D and MDA-MB231, but not HeS78T. In contrast, GLRX5 gene expression may have negative effects on lung cancer cell survival.

235 DEVELOPMENT OF A PATIENT-SPECIFIC TWO-COMPARTMENT ANTHROPOMORPHIC BREAST PHANTOM
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Purpose of Study: To develop a technique for the construction of a two-compartment anthropomorphic breast phantom specific to an individual patient’s pendant breast anatomy.

Methods Used: Three-dimensional breast images were acquired on a prototype dedicated breast computed tomography (bCT) scanner as a part of an ongoing IRB-approved clinical trial of bCT. The images from the breast of a patient with average diameter (14.3 cm) and glandularity (25%) were segmented into adipose and glandular tissue regions and combined into 1.59 mm thick breast sections. Corresponding phantom breast slices were machined from polyethylene using the adipose tissue edge as an outer contour and by cutting out the internal glandular tissue features. The stack of polyethylene breast slices was encased in thermoplastic to create a “skin” enclosure and filled with water. Water-filled spaces modeled glandular tissue structures and the surrounding polyethylene modeled the adipose tissue compartment. Utility of the phantom was demonstrated by inserting 200 μm microcalcifications as well as measuring point dose deposition during bCT scanning.

Summary of Results: The breast phantom closely resembled the patient’s anatomy with a diameter of 13.9 cm and 18.5% glandularity. Rigid registration of the original patient images with bCT images of the phantom showed similar tissue distribution. The mean coefficient of determination comparing linear profiles through coronal slices of the original and phantom image sets was 0.87. Phantom scans demonstrated visualization of microcalcifications and the ability to perform real-time dosimetry during bCT scanning.

Conclusions: Our study demonstrates a technique to generate a two-compartment anthropomorphic breast phantom from bCT images. The phantom is the first, to our knowledge, to accurately model the uncompressed pendant breast and the underlying distribution of glandular tissue for a specific patient. The modular design of the phantom allows for studies of a single breast segment and the entire breast volume. Insertion of other devices, materials, and tissues of interest into the phantom provide a robust platform for future bCT studies.

236 STEREOTACTIC RADIATION FOR THE TREATMENT OF VESTIBULAR SCHWANNOMA: TUMOR CONTROL AND HEARING PRESERVATION
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Purpose of Study: Vestibular schwannoma (VS) is a benign tumor derived from Schwann cells. Hearing loss commonly occurs in varying degrees as a result of VS and has a substantial impact on quality of life. Treatment options include observation, surgical resection, stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT). In this study, we assess the outcomes of patients with VS treated with either SRS or SRT.

Methods Used: Patients receiving SRS or SRT for VS between 1996 and 2010 were reviewed. Inclusion criteria: 1) histopathologically confirmed VS, 2) SRS or SRT performed at UCLA Ronald Reagan Medical Center, 3) functional hearing and/or tumor size assessed pre- and post-SRS or SRT. Functional hearing was defined as ability to use a phone with the affected ear.

Summary of Results: 66 patients met all of the inclusion criteria and had information readily available. 21 received SRS while 45 received SRT. 34 were male and 32 were female. The average age at completion of SRS or SRT was 55 years old (range: 23-83). The median dose for SRS was 1200cGy, and the average dose for SRT was 180cGy to the 90% IDL over 30 fractions. Patients had an average radiological and clinical follow-up of 41 and 35 months, respectively. 91% of patients had either stable or decreased tumor size on final radiologic follow-up; 95% had stable or improved functional hearing on final clinical follow-up. SRT was associated with a lower rate of tumor size increase following treatment relative to SRS (5% vs. 25%, respectively, P=0.067). Similarly, in patients with functional hearing prior to treatment, SRT was associated with a lower risk of functional hearing loss relative to SRS (3% vs. 40%, respectively, P=0.04).

Conclusions: Patients with VS often seek SRS or SRT to control the growth of their tumor and/or preserve their hearing. Our data show good tumor control over time with SRS and SRT. Furthermore, SRT was associated with improved tumor control and functional hearing results relative to SRS. Further research is needed to determine optimal use of SRS and SRT for treatment of VS.

237 CHANGES IN APPARENT DIFFUSION COEFFICIENT, LATERAL VENTRICULAR VOLUME, AND EXTENT OF T2 PERIVENTRICULAR HYPERINTENSITY AFTER ENDOSCOPIC THIRD VENTRICULOSTOMY IN CHILDREN
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Purpose of Study: Endoscopic third ventriculostomy (ETV) is a treatment option for intraventricular obstructive hydrocephalus (IVOH). After successful ETV and resolution of symptoms, ventriculomegaly may persist, making it difficult for surgeons to judge whether further treatments are needed. A rise in periventricular apparent diffusion coefficient (ADC) values with periventricular T2 hyperintensity has been associated with increased ventricular pressure and ventriculomegaly in infants and thought to be due to transpseudynmal CSF flow. The relationship between periventricular ADC values, lateral ventricular sizes, and the extent of T2 hyperintensity in hydrocephalic children treated with ETV has not been studied.

Methods Used: Hydrocephalic children treated with ETV between December 1993 and June 2011 at BC Children’s Hospital with pre- and postoperative T2-weighted and diffusion-weighted MR images were reviewed. ADC values were measured in 5 different regions of interest (ROI) pre- and postoperatively and were compared to age matched normal values. Lateral ventricle volume and distance of T2 hyperintensity beyond the ventricular wall was measured from T2-weighted images.

Summary of Results: Periventricular ADC values increased prior to ETV and returned to normal range postoperatively. Other ROIs did not change with treatment. Periventricular T2 hyperintensity also dissipated postoperatively. Lateral ventricle volume decreased but remained elevated at the time of last imaging. There was a strong correlation between mean periventricular ADC values and T2 hyperintensity distance. No statistically significant correlation was found between mean ADC values in the periventricular white matter and lateral ventricular volume.

Conclusions: Periventricular ADC values are elevated during acute phases of IVOH and return to normal following treatment. This change parallels the loss of T2 hyperintensity in the same regions. These changes precede substantial decreases in lateral ventricular volumes. ADC values were never below normal suggesting periventricular ischemia, if present cannot be demonstrated by this method.

Immunology and Rheumatology I

Concurrent Session
1:30 PM
Friday, January 27, 2012

238 LUNG IMAGING ABNORMALITIES IN HEALTHY SUBJECTS SUGGESTING THE LUNG MAY BE AN INITIATING SITE OF INFLAMMATION IN RHEUMATOID ARTHRITIS
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Purpose of Study: Rheumatoid arthritis (RA)-related autoantibodies (Abs) are elevated prior to joint symptoms in RA suggesting RA autoimmunity may be initiated outside of the joints. To test a hypothesis that the site of initiation of RA may be the lung, we compared lung findings in RA-related Ab+ subjects at risk for future RA but without current inflammatory arthritis (IA) to Ab- controls and patients with established early RA.

Methods Used: 42 Ab+ cases without IA were identified from the Studies of the Etiology of RA (SERA) project, a prospective study of preclinical RA. Cases were positive for Abs >96% specific for future RA: anti-CCP and/or ≤2 rheumatoid factor (RF) isotypes (IgA, M, G). Additionally, 15 Ab- sera controls (frequency matched to Ab+ cases on age, sex and smoking) and 12 patients with early RF/CCP+ RA (<1 year) were selected. All subjects underwent high-resolution computed tomography (HRCT) of the lungs, interpreted in a blinded fashion by 2 radiologists.

Summary of Results: Ab+ cases were a mean age of 54, 52% female and 38% smokers (no significant differences from Ab- controls or early RA subjects). 32/42 (76%) of Ab+ cases had airborne diseases on HRCT including bronchial wall thickening, bronchiectasis, centrilobular opacities and air trapping, compared to 31% of Ab- controls (p<0.01). One Ab+ subject with airborne diseases developed RA by 1987 criteria ~13 mos. after lung study. Finally, 11/12 (92%) of early RA subjects had airways abnormalities that were similar to the Ab+ cases (p=0.5).

Conclusions: Airways abnormalities are present in a high proportion of RA-related Ab+ cases without IA, and are similar to those seen in early RA. This suggests a continuum of lung injury during RA development and suggests that the lungs may be a site of initiation of RA-related autoimmunity. Studies are underway to examine further the role of the lung in the early pathogenesis of RA.

239 TLR9 EXPRESSION ON B CELL SUBSETS IN NORMAL AND AUTOIMMUNE PERIPHERAL BLOOD

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Purpose of Study: Toll-like-Receptor-9 (TLR9) is a part of the pattern recognition receptor which recognizes hypomethylated DNA (Cytosin-Phosphate-Guanine). TLR9 has recently been shown to play a specific role in autoantibody production and the pathogenesis of systemic lupus erythematous (SLE) in both animal models and humans. Studies show that the level of TLR9 is elevated in SLE B cells and this elevation correlates with increased SLE disease activity. Activation of TLR9 by hypomethylated DNA (CPG rich) leads to increased level of anti-dsDNA antibody production in SLE B cells compared to RA and normal B cells. Blocking TLR9 along with TLR7 has been shown to ameliorate lupus nephritis in mice models. Recent reports suggest that the activation of different subsets of B cells may cause varied production of memory B cells and plasma cells. The aim of this study is to determine the level of intracellular TLR9 expression in developmental subsets of B cells identified in normal and autoimmune human peripheral blood. Identification of the B cell subsets affected by TLR9-mediated activation has the potential to aid in the development of targeted therapeutics against RA and SLE.

Methods Used: Human adult peripheral blood samples from lupus and RA patients and normal controls were stained for seven-color flow cytometry to assess co-expression of CD19, CD24, CD21, IgM, CD38, CD27 and intracellular TLR9 (CD289). TLR9 levels in gated B cell subsets were determined by the mean fluorescence intensity (MFI).

Summary of Results: Previous reports of increased TLR9 expression in total B cells from SLE patients were validated using intracellular flow cytometry. A comparison of intracellular TLR9 expression in memory (CD27+) and non-memory (CD27-) B cells showed higher TLR9 expression in CD27+ cells in normal, RA and SLE patient samples. Ongoing studies will assess the level of TLR9 in transitional B cells subsets in normal and autoimmune (SLE and RA) peripheral blood.

Conclusions: Intracellular expression of TLR9 is higher in SLE B cells compared with RA and normal, also memory B cells have higher levels of TLR9 than non-memory B cells in both normal and autoimmune peripheral blood.

240 RHEUMATOID ARTHRITIS-ASSOCIATED LUNG DISEASE WITHOUT CLINICAL ARTHRITIS?

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Purpose of Study: The lung may play a role in the pathogenesis of rheumatoid arthritis (RA) perhaps acting as the initial site of autoimmunity prior to inflammatory arthritis (IA); therefore, studying patients with lung disease and RA-related autoantibodies (Abs) without IA may improve treatment of such patients and help to understand the etiology of RA.

Methods Used: We describe a patient with lung disease and elevated RA-related Abs without IA, discuss the treatment of lung disease in this setting, and the potential role of the lung in RA pathogenesis.

Summary of Results: A 61 year old male, former smoker presented with cough and shortness of breath. Spirometry noted restrictive disease and imaging showed ground-glass opacities, airways thickening and minimal peripheral fibrosis consistent with fibrotic non-specific interstitial pneumonia. Abs tested to identify connective tissue disease (CTD) had the following abnormalities: rheumatoid factor (RF) (358 IU/mL [>14]), anti-cyclic citrullinated peptide-2 (aCCP) (53 U/mL [<20]) and anti-nuclear antibodies (1:12000 spotted [≤1:160]), he had no signs or symptoms supporting this show similar lung histology and generation of RA-related Abs in the lungs of patients with RA (Rangel-Moreno 2006). Based in part on findings from this patient, studies are planned to examine the role of the lung in the early pathogenesis of RA.

241 THE ROLE OF BAX INHIBITION IN THE DEVELOPMENT OF POSTTRAUMATIC OSTEONECROSIS OF THE KNEE IN MICE

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Purpose of Study: Bcl-2-associated X protein, or Bax is a pro-apoptotic protein that is a member of the Bcl-2 gene family. The purpose of our study is to investigate the effect of BAX inhibition in osteoarthrisis. Our hypothesis is that inhibition of BAX will diminish the development of osteoarthrisis.

Methods Used: In the first part of our study, we used wild type and BAX knockout mice. We injected the left knee with collagenase and sacrificed the mice at different time intervals and compared the wild type and BAX knockout mice. In the second part of our study we are again comparing wild type mice to BAX knockout however we wanted to create a more realistic osteoarthritis model. We anesthetized the mice and used an instron to deliver a force large enough to create a tibial plateau fracture in the right knee. After the force is delivered, we take an x-ray of the knee to verify that the appropriate amount of damage was created to cause the mice to naturally develop a post-traumatic osteoarthrisis. The mice are then sacrificed at different time intervals and the normal (left) knee is compared to the traumatic knee (right) in both the wild-type and BAX knockout mice using a modified Mankin score.

Summary of Results: In the first part of our study, we discovered that there was a significant decrease in the amount of cartilage damage in the BAX knockout mice that received collagenase when compared to the BAX wild-type mice. Interestingly, these changes were not observed at the 3 week and 8 week time periods.

Conclusions: BAX inhibition seems to diminish the development of articular cartilage damage of the knee in mice injected with collagenase at 5 weeks.
post injection, however the damage appears to be temporary and there is no clear histologic difference by week 8. A post-traumatic osteoarthritis model is a better reflection of the natural course of osteoarthritis. We hope to show that there is a reduction in the articular cartilage damage of the post-traumatic knee in BAX knockout mice and our data will be available before the conference.

242 PNEUMOCYSTIS JIROVECI PNEUMONIA IN A PATIENT WITH NEWLY DIAGNOSED SYSTEMIC LUPUS ERYTHEMATOSIS
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Case Report: In non-HIV individuals including patients with rheumatologic diseases, Pneumocystis jirovecii Pneumonia (PCP) has been associated with the use of high dose corticosteroids and carries a high mortality rate (60%). There are currently no established guidelines for prophylaxis in these patients. We present a 38 y/o female with newly diagnosed Systemic Lupus Erythematosis (SLE) who acquired PCP after 5 weeks of corticosteroid use. We reviewed the literature for PCP in SLE, corticosteroid use, and other rheumatologic disease.

Pt. was a 38 y/o female diagnosed with SLE (ANA+, anti-SSA+, arthritis, myositis, pneumonitis, and lymphopenia with lymphocyte count of 600) 38 days prior and initiated on 1 mg/kg daily of prednisone admitted with fever, tachycardia, tachypnea, and hypoxia. Lung imaging including CT scan was unchanged from 5 weeks prior with bilateral predominant interstitial lung disease. Workup for infection including bronchoscopy with bronchoalveolar lavage was positive for PCP and she was started on trimethoprim/sulfamethoxazole (TMP-SMZ). She subsequently developed respiratory failure requiring mechanical ventilation and died of diffuse alveolar damage secondary to PCP.

This case highlights that patients with SLE on immunosuppression are at risk for PCP, with particular risks including underlying lung disease, lymphopenia, and use of high dose steroids. The literature suggests that patients with rheumatic disease on average develop PCP after 12-16 weeks of greater than 40 mg/day of prednisone equivalent; however, as in our case, this may occur sooner. This case also demonstrates the high mortality associated with PCP in non-HIV patients and the need for prophylaxis, although there are no established guidelines in rheumatic diseases. Additionally, there are many difficulties with prophylaxis in SLE including increased risk of symptom flare with TMP-SMX, hemolytic anemia with dapsone, decreased efficacy with pentamidine, and prohibitive cost with atovaquone. Based on available literature, we will suggest potential guidelines for prevention of PCP in patients with SLE and other rheumatic diseases that may serve as a basis for further studies.

243 ALCOHOL URticaria SYNDROME
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Case Report: A 30-year-old East Asian-American nurse reports sensitivity to alcohol-based hand sanitizers. 20 minutes to 4 hours after applying hand-sanitizing gel she develops redness, pruritus, and swelling for 1-2 days. She develops similar symptoms with application of perfume. She avoids drinking alcoholic beverages secondary to developing hives.

Standard expanded patch testing with 85 potential allergens were performed. Additionally, we patch tested the patient to isopropyl alcohol cleaning wipe, 4 hand sanitizers she had used and her 2 perfumes. At 48 hours, she had a 1+ positive reaction to Balsam of Peru, propylene glycol, 1 of her perfumes, a commercial ethyl alcohol-based hand gel, isopropyl alcohol-based cleansing pad, and 2+ reactions to gold sodium thiosulfate. 3 additional ethyl alcohol-based hand gels, and her other perfume. At 96 hours, she continued to have 1+ reactions to Balsam of Peru and propylene glycol and 1+ reactions to the 4 alcohol-based hand sanitizers, her 2 perfumes, and gold sodium thiosulfate. Prick testing revealed positive wheal reactions to alcohol-based hand gels, perfumes, isopropyl alcohol, 100% ethanol, 100% and 10% acetaldehyde, and a positive histamine control. She had negative prick test results to Balsam of Peru, cinnamonaldehyde, 10% ethanol, 10% and 1% acetic acid, and a negative control.

Based on our patient’s history of urticarial reactions and prick test findings with positive reactions to ethanol-containing products, we determined she had contact urticaria provoked by both topical application and systemic ingestion of ethyl-alcohol - alcohol urticaria syndrome (AUS). AUS is a rarely reported and poorly understood entity. Patients present with urticaria and/or generalized erythema with contact or ingestion of alcohol. It may be more common in people of East Asian descent with aldehyde dehydrogenase deficiency. Our patient’s descent and marked reaction to acetaldehyde suggest she may have this deficiency.

Infectious Diseases
Concurrent Session
1:30 PM
Friday, January 27, 2012

244 NOVEL LENSFREE MICROSCOPE TECHNOLOGY BASED ON SHADOW IMAGING FOR THE DETECTION OF GIARDIA LAMBLIA OOCYSTS IN STOOL
Nadiparam SM1, Mudanyali O2, Ozcan A2, Nielsen K1 1David Geffen School of Medicine at UCLA, Los Angeles, CA and 2UCLA, Los Angeles, CA.

Purpose of Study: A lensfree on-chip microscope based on digital in-line holography with sub-cellular resolution (~1.5μm) over a large field of view (FOV) was developed at UCLA. Light emitting diodes generate holograms of images which are recorded by digital sensor array and subsequently transferred to image recognition software using cell phone technology. This platform, also known as shadow imaging, offers a compact, cost-effective high-throughput diagnostic tool for rapid recognition of cells or microbes in resource-limited settings. In the present study we evaluated the ability of shadow imaging to identify Giardia lamblia oocysts in stool and differentiate organisms from stool sediment.

Methods Used: Stool specimens were collected from patients submitting samples for suspected giardiasis at UCLA. Specimens found to be negative were pooled. A 0.5 mL aliquot of stool was seeded with 500,000 formalin-fixed Giardia lamblia oocysts. Serial dilutions were performed on stool for clear visualization of oocysts via brightfield microscopy as well as field-portable lensfree on-chip shadow imaging. Samples were prepared on a drop of water sandwiched between 2 coverslips.

Summary of Results: Following dilution of stool specimens to a 13:1 ratio, (point of maximum visualization following dispersion) Giardia oocysts were clearly identified, and differentiated from sediment using lensfree on-chip microscopy. Imaging resolution demonstrated that morphology and size of Giardia were identical across lensfree and conventional microscopy.

Conclusions: Lensfree on-chip microscopy can identify Giardia oocysts in stool, and distinguish organisms from stool sediment over an imaging FOV that is more than an order-of-magnitude larger than conventional microscopy. Lensfree microscope images can be further improved using a super-resolution technique, which provides ~1μm resolution over the same imaging area. Future experiments in field settings will assess the sensitivity and specificity of lensfree on-chip microscopy (shadow imaging) in comparison to conventional microscopy and enable its use in the rapid diagnosis of giardiasis and other parasites in resource-poor settings.

245 IMAGING OF MALARIA PARASITES USING PORTABLE LENSFREE MICROSCOPES
Mudanyali O1, Bishara W1, Nadiparam S1, Sikora U1, Su T1, Yaglidere O1, Ramasawmy R1, Nielsen K1, Ozcan A1,2,3 1UCLA, Los Angeles, CA; 2UCLA, Los Angeles, CA; 3UCLA, Los Angeles, CA and 4Foundation for Tropical Medicine of Amazonas, Manaus, Brazil.

Purpose of Study: In order to develop point-of-care, automated, cost-effective and field-deployable malaria screening platforms, we developed a portable lensfree super-resolution microscope that weighs less than 100 grams and provides submicron resolution over a field of view (FOV) of 24 mm2 that is >100 folds larger than the imaging area of an objective lens with comparable resolution. In order to evaluate the efficacy of this lensfree microscope for malaria diagnostics, we conducted initial field trials in the Foundation for Tropical Medicine of Amazonas (Manaus, Brazil).
Methods Used: Lensfree super-resolution microscopy relies on the acquisition of lensfree in-line holograms of individual particles (e.g., cells) within a sample (e.g., blood) which are digitally processed through image reconstruction algorithms to yield both phase and amplitude images of the specimens at the sub-micron level. This on-chip imaging modality does not require the use of bulky/costly components (e.g., lenses or scanning stages), instead it utilizes partially coherent light sources (i.e., simple light emitting diodes - LEDs) to illuminate the specimen and an opto-electronic sensor (i.e., CMOS) to digitally record lensfree holograms over a wide imaging area (e.g., 24 mm²). During our initial field trials in the Foundation for Tropical Medicine of Amazonas, we imaged more than 50 positive malaria specimens using lensfree microscopes which were previously examined via traditional bright-field microscopy.

Summary of Results: Lensfree imaging results of Giemsa-stained blood smears of malaria infected specimen show promising agreement with the corresponding images obtained using bright-field microscopy. Portable lensfree microscopes can digitally distinguish infected red blood cells from healthy ones, which might enable rapid examination of specimens even in resource poor settings of remote endemic regions.

Conclusions: Our initial lensfree imaging results are rather encouraging toward the use of field-portable, cost-effective and high-throughput automated microscopic analysis platforms for malaria diagnostics in resource limited settings.

Purpose of Study: Antiretroviral therapy (ART) has become more widely available in resource-limited countries. Expansion of treatment, however, has engendered drug resistance, which needs to be characterized as it is a measure of treatment efficacy and will influence future treatment strategies.

Methods Used: The online databases PubMed and Google Scholar were searched for articles using the terms “drug resistance” or “drug resistant” and “HIV” or “AIDS” and “resource limited” or “Africa” or “Asia.” Abstracts from recent conferences were also searched. All patients were naïve to ART before initiation of treatment. Analysis was restricted to data that were collected either in 2007 and later or in 2005 or 2006 if the country had implemented a national scale up of ART at least one year before data collection. 17 studies met these criteria.

Summary of Results: The overall prevalence of transmitted HIVDR in Africa was found to be 5.6% (217/3863). 2.4% of patients were resistant to reverse transcriptase inhibitors (NRTIs), 3.2% to non-nucleoside reverse transcriptase inhibitors (NNRTIs), 1.2% to protease inhibitors (PIs), and 1.1% to multiple drug classes. Prevalence varied among sub-regions: 7.1% (26/368) in Middle Africa, 6.7% (157/2337) in East Africa, 3.0% (21/708) in Southern Africa, and 2.6% (13/450) in West Africa. NRTI, NNRTI, PI, and multi-class resistance rates, respectively, were found to be: 3.0%, 3.3%, 1.9%, and 1.6% in Middle Africa; 2.9%, 3.9%, 1.5%, and 1.5% in East Africa; 0.4%, 1.8%, 0.8%, and 0% in Southern Africa; 2.2%, 1.3%, 0.2%, and 0% in West Africa. In Asia, transmitted HIVDR was identified in 7.6% (160/2094) of patients. 4.3% were resistant to NRTIs, 3.8% to NNRTIs, 0.3% to PIs, and 0.7% to multiple drug classes.

Conclusions: In resource-limited settings, HIVDR has historically been low according to the WHO classification system (<5%). The data presented here, however, suggest that transmitted HIVDR has escalated to an intermediate prevalence (5-15%). The rates of transmitted HIVDR increased over time and correlated with the timing of the rollout in different regions. The increase is not surprising with the large scale-up of ART, but it does indicate a need for baseline drug resistance mutation testing and increased availability and affordability of second-line ART.
Conclusions: The prevalence of chronic HBV in this cohort was similar to recent studies from other African populations. Given our long-term follow-up, lamivudine resistance was lower than expected for co-infected patients on HBV mono-therapy. Future studies will be important to determine the relative risks, benefits, and costs of combination versus mono-therapy for HBV in this setting.

249 VIRAL GASTROENTERITIS IN CHILDREN IN COLORADO: A STOOL STORY
Osborne CM1, Robinson C2, Schultz-Cherry S3, Dominguez SR3
1University of Colorado School of Medicine, Aurora, CO; 2Children’s Hospital Colorado, Aurora, CO; 3St. Jude Children’s Research Hospital, Memphis, TN.

Purpose of Study: Diarrhea associated with gastroenteritis is the second leading cause of death in children under age 5 outside the neonatal period and remains a significant cause of morbidity throughout the world. While bacterial and parasitic gastroenteritis has declined in prevalence due to cleaner drinking water and proper sewage disposal, the prevalence of viral gastroenteritis has not. To date, few large scale studies on the epidemiology of viral gastroenteritis in children have been done in the United States using sensitive PCR diagnostic assays.

Methods Used: A total of 1,182 stool samples were collected from children with gastrointestinal symptoms, which were submitted to the viral clinical virology laboratory at Children’s Hospital Colorado from 2006 to 2008. Stool specimens were extracted using viral RNA kits on a BioRobot EZ1 extractor and tested for the presence of norovirus, astrovirus, rotavirus, sapovirus, and coronavirus using several multiplex qRT-PCR assays. All samples were pooled and analyzed in sets of six. Any positive pooled samples were tested individually for the specific virus. Influenza RNA was spiked into all samples to test for presence of PCR inhibitors. Retrospective chart review of positive samples was conducted to determine clinical and epidemiological patterns and characteristics of infection associated with each viral agent. A subset of RNA from samples negative by qRT-PCR will be pooled and submitted for next generation sequencing aimed at novel virus detection.

Summary of Results: Of pooled samples, 192/197 (97%) were positive for spiked influenza RNA; 19/197 (9%) and 97/197 (49%) of pooled samples were positive for Norovirus GI and GII respectively. Of pooled samples, 29/100 (29%) were positive for adenovirus and 29/100 (29%) were positive for rotavirus; whereas, 21/100 (21%) and 6/100 (6%) were positive for astrovirus and sapovirus respectively. Analysis of individual samples from positive pools, retrospective chart review, and sequencing are currently ongoing.

Conclusions: A significant number of stool samples are positive for RNA from various viral agents.

250 CONFIDENTIALITY AND ACCESS TO SERVICES: PATIENT SATISFACTION AND SERVICE STRENGTHENING: AT DESMOND TUTU HIV FOUNDATION YOUTH CENTRE CLINIC, MASIPHUMELELE TOWNSHIP, CAPE TOWN, SOUTH AFRICA
Young S1, Aquino L2, Hoffman R1, Dyani W2, Coates T1, Bekker L21 David Geffen School of Medicine at UCLA, Los Angeles, CA; 2Desmond Tutu HIV Foundation, Cape Town, South Africa and 3UCLA, Los Angeles, CA.

Purpose of Study: South African youth are at high risk for HIV infection and among the fastest growing newly infected groups, yet lack youth-specific services. Additionally, Masiphumelele Clinic faces overcrowding and perceived compromised confidentiality. In order to provide youth-specific HIV, STI, and pregnancy services, the Desmond Tutu HIV Foundation (DTHF) opened the Youth Centre Clinic. This study determines patient satisfaction with services and areas for services strengthening at DTHF Youth Centre Clinic.

Methods Used: Youth between ages 12 and 24 were recruited through paper-based advertisements, text message, phone call, and snowball sampling. Prior clinic attendance was required. Participants completed a one-page, self-administered, paper-based survey with one open and nine closed-ended questions in English or Xhosa. Questions evaluated demographics and services. Quantitative data was tabulated in Excel. Qualitative data was organized into themes. Each participant received R10 ($1.50).

Summary of Results: Twenty-four of 160 patients completed the survey. Compared to the clinic’s 17% male and 82% female composition, participant gender was 29% male and 71% female. Mean male age was 17.3 and female age was 19.2. 52% requested HIV test, 24% pregnancy test, 8% STI test, and 16% “family planning” or “TB”. 84% received their desired service. 96% felt safe and comfortable; 92% felt their visit was confidential. 92% reported the clinic “very easy” or “easy” to visit, yet 63% reported “earlier morning” or “later afternoon” hours would ease clinic visitation. 92% recommended the clinic.

Conclusions: The DTHF Youth Centre Clinic provides confidential, accessible services, yet extended hours and family planning would strengthen clinic services.

251 DECREASED T-HELPER 1 AND T-HELPER 2 CYTOKINE PRODUCTION BY CORD BLOOD MONONUCLEAR CELLS MAY CONTRIBUTE TO NEONATAL INFECTIONS
Caron JE1, La Pine TR2, Augustine NH3, Martins TB3, Wilson A3, Hill HR1,2,3
1University of Utah, Salt Lake City, UT; 2University of Utah, Salt Lake City, UT; 3ARUP Institute, Salt Lake City, UT.

Purpose of Study: Human neonates are uniquely susceptible to severe and overwhelming bacterial and fungal infections. Deficiencies in both innate and adaptive neonatal immune responses contribute to this increased susceptibility. T-helper 1 (Th1) and T-helper 2 (Th2) cells produce cytokines that regulate these immune responses. We have demonstrated that polymorphonuclear leukocytes from human neonates exhibit deficiencies in activation and movement. Here we examine neonatal Th1 and Th2 cell cytokine production using the T-cell mitogen phytohemagglutinin (PHA). Specifically, we examined cord blood mixed mononuclear cell (MCCs) production of the Th-1 cytokines IFN-γ and IL-2, and the Th-2 cytokines IL-4, IL-5, IL-10, and IL-13, and compared these to adults.

Methods Used: Cord blood was collected from healthy term deliveries and whole blood from healthy adult volunteers. MCCs were isolated on Ficoll-Paque and stimulated with phytohemagglutinin (PHA), and incubated for 24 hours in tissue culture medium. Cytokine production was measured with our in-house developed multianalyte Luminox technology.

Summary of Results: In response to PHA stimulation: Th1 cytokine production was significantly diminished in cord blood (n=10) compared to adults (n=12) (CORD: IFN-γ: 12.7 pg/mL; IL-2: 470.6 pg/mL; ADULT: IFN-γ: 174.9 pg/mL; IL-2: 2315.2 pg/mL) (p<0.05 all values). Th2 cytokine production was also significantly diminished in cord blood (n=10) compared to adults (n=12) (CORD: IL-4: 6.7 pg/mL; IL-5: 4.8 pg/mL; IL-10: 160.4 pg/mL; ADULT: IL-4: 1534.4 pg/mL; IL-5: 666 pg/mL; IL-10: 1706.8 pg/mL) (p<0.05 all values). IL-13: no significant difference (CORD: n=10, mean: 709 pg/mL; ADULT: n=12: 697.2 pg/mL).

Conclusions: Here we demonstrate diminished cord blood mixed mononuclear cell Th1 and Th2 cytokine responses to the T-cell mitogen phytohemagglutinin compared to adults. These diminished T cell responses may contribute to the decreased innate and adaptive immune responses observed in human neonates, leading to their increased susceptibility to bacterial and fungal infections.

252 PEDIATRIC COCCIDIOIDOMYCOSIS IN CENTRAL CALIFORNIA: A RETROSPECTIVE CASE SERIES
Demetral L, Bowser AM, McCarty J U C S F Fresno, Fresno, CA.

Purpose of Study: To describe the clinical manifestations, natural history, diagnosis, treatment, and outcomes of pediatric patients hospitalized at Children’s Hospital Central California with coccidioidomycosis.

Methods Used: We reviewed the medical records of all children admitted to Children’s Hospital Central California with coccidioidomycosis from 1/1/10 to 9/1/11. Descriptive analyses were conducted for variables including age at diagnosis, gender, race/ethnicity, co-morbid conditions, clinical and radiographic findings, diagnostic methods, treatment and outcomes. Correlational analyses were conducted to determine variables predictive of disease severity and outcome. The study was approved by the hospital’s Institutional Review Board.

Summary of Results: 33 children, 6 month to 18 years of age, were admitted during the study period, with hospitalizations ranging in length from 3-241 days (mean 70 days). These included patients with pneumonia (19),
253 ATYPICAL PRESENTATION OF REACTIVE ARTHRITIS FOLLOWING AN OUTBREAK OF SALMONELLA ENTERICA

Umeyaro E, Sutamnetawugel G, Phisetikul S TTUHSC, Lubbock, TX.

Case Report: Introduction: Reactive arthritis is a non-purulent joint inflammation triggered by bacterial infections in the gastrointestinal or urogenital tracts. Among them are different serotypes of Salmonella enterica.

Case report: A 54 years old female presented with generalized pain, spiking fever, sharp pain in elbows, lumbar spine, knees and hips, associated with morning stiffness. Physical examination revealed tenderness to palpation in both lower extremities and lumbar spine. Routine blood tests showed elevated ESR. Blood, urine cultures, peripheral smear, wet mount were negative, as well as the imaging tests of the chest, abdomen and pelvis.

Three days later our patient developed diarrhea. Fecal cultures were negative for ova, parasites and Clostridium difficile toxin but revealed Salmonella enterica serotype Bredeney. Patient was started on ceftriaxone and indometacin. Considering the clinical picture and the following symptomatic enteritis, the diagnosis of enteric reactive arthritis was made.

Discussion: Reactive arthritis following Salmonella gastroenteritis affects approximately 18% of the patients. Early diagnosis is pivotal since appropriate treatment of gastroenteritis may prevent development of musculoskeletal manifestations. Our patient had symptoms of reactive arthritis several days before gastroenteritis and initially presented with non-specific body aches, muscle and joint pain without evidence of arthritis. Moreover, an extensive workup failed to identify the source of possible infection. Such an unusual presentation highlights the importance of atypical symptoms in cases of reactive arthritis that contribute to late diagnosis and substantial morbidity. Appropriate history taking, attentive physical examination may eventually lead to the increased diagnosis at earlier stage.

Conclusion: Reactive arthritis associated with enteric infection should be considered in the differential diagnosis of any patient with an undifferentiated oligo-arthritis because the enteric infection may have been very mild as to be overlooked by the patient.

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254 DEPRESSION IS COMMON IN TB PATIENTS AND IS ASSOCIATED WITH TREATMENT ABANDONMENT

Karlin DM,1,4, Evans C,2,4, Loisele C,4, Zevallos K,2,6, Fernandez P1,4, Allen N,7, Montoya Tuba,2, Boccia D,8,1, UCLA David Geffen School of Medicine, Los Angeles, CA; 2Imperial College, London, United Kingdom; 3Innovation for health and development, London, United Kingdom; 4Asociacion Benefica PRISMA, Lima, Peru; 5Universidad Peruana Cayetano Heredia Faculty of Sciences and Philosophy, Lima, Peru and 6London School of Hygiene and Tropical Medicine, London, United Kingdom.

Purpose of Study: Tuberculosis (TB) is associated with poverty, stigma and marginalization, which are risk factors for psycho-morbidity, but little is known about the mental health of TB patients. We therefore studied interactions between TB, depression, socio-demographic factors and TB treatment adherence among the urban poor.

Methods Used: Over 7 years, patients with newly diagnosed or recurrent TB and randomly selected healthy controls from shantytowns in Lima were evaluated in a case control study and the patients were then followed-up to determine their treatment outcome. Each participant provided demographic and socio-economic data and completed a Beck Depression Inventory (BDI). Depression scores were adjusted for overlap with the physical symptoms of TB. Poverty was assessed with a composite socio-economic index. Data were analyzed with linear and logistic regressions.

Summary of Results: TB patients (n=1,734) had frequent depression (53%), severe depression (15%) and suicidal ideation (4.7%). Depression was more common and depression scores were higher than in randomly selected healthy members of the same community (n=470; both P<0.005), independently of poverty, education and other cofactors. For TB patients, higher depression scores were independently associated with female gender, poverty, incomplete schooling, illicit drug use, perceived discrimination and longer delay in seeking medical care for TB symptoms (all P<0.01). Furthermore, a prior history or current episode of treatment abandonment was significantly related to current depressive state (OR 1.8, P<0.001)

Conclusions: Depression was highly prevalent among newly diagnosed TB patients and especially associated with prior treatment abandonment. TB programs may optimize disease control, treatment adherence and quality of life by diagnosing and addressing the mental health issues that affect TB patients.

International and Immigrant Health Issues
Concurrent Session
1:30 PM
Friday, January 27, 2012

255 A COMMUNITY-BASED DIABETES EDUCATION EVENT FOR THE HISPANIC POPULATION OF WEISER, IDAHO

Connell J University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Type II diabetes mellitus (T2DM) is endemic among Hispanic populations in the US. The purpose of this project was to create an educational event with two goals: 1. To provide culturally competent diabetes education for members of the Hispanic population in Weiser, ID that would empower participants, and 2. To promote collaboration between major stakeholders in the community involved in diabetes prevention and care.

Methods Used: Interviews were conducted with clinicians, health educators, and members of the Hispanic community to identify and locate the diabetic Hispanic population as target population. A literature review identified two key components for developing a diabetes education event for this population: 1. Cultural appropriateness in terms of language; messages about diet, and family involvement and 2. Collaboration with local organizations with similar goals to promote sustainable interest in the issue. Working in close collaboration with the Idaho Partnership for Hispanic Health (IPHH), the Two Rivers Clinic (TRC) and the Hispanic community, a diabetes education event was planned and implemented. Participants were recruited in clinic, in IPHH classes and with circulating pamphlets. The 3 hour program consisted of diabetes-friendly dinner provided by a local restaurant, nutritional education, musical performances, group discussions about controlling and preventing diabetes, and a Q&A session with a local physician.

Summary of Results: There were 28 participants, including six Hispanic families, 3 health educators, and a local physician. 50% of participants had T2DM. There was active engagement of all participants during the event. In addition to providing a culturally appropriate educational environment in which information could be shared, the event initiated collaborative relationships between health care providers, health educators and the Hispanic community. There was positive post-two-week participant feedback in telephonic evaluations about the program’s effectiveness in achieving its goals.

Conclusions: T2DM is a serious biocultural disease that effects the Hispanic population in Weiser, ID. Providing culturally competent education and fostering collaboration between major stakeholders empowers the community as a whole to improve diabetes health outcomes.

256 A CULTURALLY-APPROPRIATE NUTRITIONAL GUIDE FOR THE DIABETIC HISPANIC COMMUNITY IN BREWSTER, WA

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Purpose of Study: Brewster is located in Eastern WA with a population of 2,300, of which 70% are Hispanics from Mexico. T2DM is endemic among the Hispanic population in Brewster. One simple measure that has been shown to be effective in the control of diabetes among Hispanics is providing culturally sensitive education about foods of low glycemic index. This project sought to provide Mexicans with diabetes in Brewster with culturally relevant information on diet to help them better control their condition.

Methods Used: Interviews were conducted with Mexican patients at the Family Health Center Clinic (FHC) and at the Brewster Market to identify diet in diabetes as a focus for a community project. Further interviews investigated common dietary habits. A literature review was done to identify measures to address diet in diabetes in the US Hispanic population. Two handouts were created that illustrated foods of high glycemic index that should be avoided and those of low glycemic index that would be health-promoting. The handouts were written in Spanish and included food items commonly consumed by the Hispanic population of Brewster. These were placed at the lobby and offices at FHC, the markets’ bulletin board, the library and the laundry mat. One 6-12min educational session was held for each diabetic patient who presented to FHC. Final pamphlets incorporated dietary habits disclosed by patients during educational sessions.

Summary of Results: Twenty patients at the FHC clinic were educated on small dietary changes and ten final pamphlets were distributed to patients at FCH. Electronic copies of the posters were left at FHC for distribution upon patient request. Following this project, physicians at FHC reported greater interest in diet among diabetic patients and patients at-risk for diabetes.

Conclusions: Diabetes is a serious problem in the Hispanic population, but culturally sensitive educational methods about the disease have potential to improve health outcomes and reduce incidence. By creating a simple, culturally sensitive poster that provides information concerning low glycemic food choices, participants were empowered to take control of their illness and encouraged to have further discussion with their doctors.

257 AN APPROACH TO PRIMARY CARE IN UNDER-SERVED RURAL KENYA

Evans J, Mueller K. University of British Columbia, Vancouver, BC, Canada.

Purpose of Study: Our aim was to demonstrate that the quality of primary care in an under-served rural Western Kenyan community, Kanyawegi, could be improved through the implementation of Community Strategy (CS), a Community Health Worker (CHW) program. CS is a Kenyan Government initiative meant to de-centralize health care to the household level. Using CHWs improves accessibility to health education and provides community members with a direct link to the local health centre, Ober Kamoth (OK).

Methods Used: We measured the success of CS by tracking CHW activity and health indicators of individual households over time. We worked with the government and a local Community Based Organization to train 54 CHWs on pertinent health topics, data collection and reporting. CHWs were elected by their local community and work on a volunteer basis. Each CHW is responsible for carrying out monthly visits to 20-30 households, providing education, recognizing disease and referring to OK, and collecting health indicator data to be reported to OK.

Summary of Results: Implemented in August 2010, the Kanyawegi Community Unit (KCU) has since effectively tracked local health trends. We identified significant improvements in several health indicators, such as increases in the usage of insecticide-treated mosquito nets and pit latrines, and in the number of people who know their HIV status. Most CHWs have shown commitment to CS with 69% maintaining high reporting rates and attending monthly meetings and training sessions. The local government recently awarded the KCU for being the top CU in their district. The KCU was also used as a community access point by the government for distributing mosquito nets, and has attracted the interest of two NGOs, now conducting research with the CHWs and providing support to OK.

Conclusions: While preliminary results of community health indicators demonstrate improvement, we have identified the need to maintain CHW motivation and accountability. We recognize this limits our data collection method and are working with the KCU to improve data reliability for the future. Importantly, the presence and support of the government and other NGOs at OK has undeniably enhanced health care delivery in Kanyawegi in an unprecedented manner. Within one year of CS implementation, we have seen tangible improvements to the quality of primary health care delivery in Kanyawegi.

258 CHALLENGES OF BICYCLE DISTRIBUTION IN RURAL WESTERN KENYA: A LOOK AT SUSTAINABILITY


Purpose of Study: Access to health care is an existing problem for rural communities in Western Kenya due to a lack of proper transportation infrastructure. Bicycle distribution helps to address this issue but many of these projects have been restricted due to a lack of sustainability. Bicycle distribution, while beneficial to the community, represents a simple handout of capital. The burden of maintenance costs lies with the community. For this capital distribution to be more effective, methods of community integration need to be examined.

Methods Used: A pilot project was established in June of 2010 distributing bicycles to 16 peer-selected community health workers (CHWs) in the Kit Mikayi and Kaila sublocations of rural Western Kenya. Baseline and follow-up data (N=70), those given and not given bikes, was collected at 6 and 12 months to assess bicycle use, the benefit of the bicycles, maintenance difficulties, and cost of maintenance.

Summary of Results: A total of 100% of CHWs with bicycles reported increased home visits and community health work. The 6 and 12 months follow-up surveys both showed that those with bicycles were able to make on average 3 more home visits per week than those without bicycles. Maintenance problems were reported at 100% during the first 6 months and 92% for the remainder of the year. In terms of maintenance costs an average of 1375 KES per bicycle was reported over the first 6 months, which is comparable to the average of 293 KES/month reported over the final 6 month period. Flat tires accounted for 42% of maintenance issues.

Conclusions: While the distribution of bicycles has been beneficial to the work of CHWs and development of community health programs, it is clear that maintenance issues present a significant challenge. However, within this challenge exists an excellent opportunity to channel their support. One way to bridge bicycle distribution with improved sustainability is to offer workshops in conjunction with tools and supplies. This enables community members to take responsibility for an initial investment of bicycles and ensure that this capital is utilized effectively. In response to this, a pilot workshop teaching basic bicycle maintenance was initiated in June of 2011 for the Kit Mikayi and Kaila sublocations.

259 FEET IN TRANSLATION: IMPROVING QUALITY OF CARE THROUGH BILINGUAL PATIENT EDUCATION

Foss J University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Jackson, WV, has a large population of seasonal and undocumented workers to support its tourism industry, many of whom are from Mexico and lack health insurance or any way to pay for health care. The Teton Free Clinic, with the help of El Puente medical translators, provides a valuable service for this population. The clinic is only open three hours per week and the majority of the patients speak Spanish, while most health providers speak English. Language barriers have a negative impact on health, and multilingual educational materials are cited as one strategy to provide improved language access. The goal of this project was to improve quality of care for patients of the Teton Free Clinic, an underserved population in the Jackson Hole community.

Methods Used: An assessment through discussions with community health leaders and key Hispanic health advocates identified the patients of the Free Clinic as the population in Jackson with the greatest health needs. A survey of the clinic patients indicated their belief that written information about their health conditions would be helpful for them. A literature review was performed to examine if patient education materials could be used to improve health outcomes. The literature review also informed the nature of the educational improvement, keeping in mind the issue of health literacy.

Summary of Results: Written patient education materials were identified by the patients as their greatest priority for improving the quality of care at the Teton Free Clinic. A portable library with materials in English and Spanish on hypertension, diabetes, arthritis, low back pain, colds/flue, hay fever, and urinary tract infections was created and made available to the providers at the clinic. The materials selected on diabetes and hypertension were basic enough so that members of the community with low health literacy
levels could understand, as they included several illustrations and simple language.

Conclusions: In order to help bridge the gap between patients and providers when they don’t speak the same language, patient education materials can improve language access, patient satisfaction, and quality of care. Appropriate educational materials with respect to health literacy should be selected to optimize patient outcomes.

260 PREVENTING COGNITIVE DECLINE AND SOCIAL ISOLATION IN ASIAN/PACIFIC ISLANDER ELDERLY IN SEATTLE, WA

Lin S UW School of Medicine, Seattle, WA.

Purpose of Study: The elderly Asian/Pacific Islander population in the U.S. is at risk for isolation due to language and cultural barriers. Cognitive decline and other health problems can lead to further isolation, depression and suicide. These problems are common to elderly patients in the International District of Seattle, WA. The purpose of this project is to prevent these outcomes by creating a toolkit for use in a future cognitive training program which will help preserve cognition and strengthen social networks in a culturally-sensitive and language-appropriate way.

Methods Used: Interviews were conducted with patients, healthcare providers and staff at an assisted living facility serving mainly Asians and Pacific Islanders to identify top health concerns for elderly patients. A meeting was held with the Adult Day Health program staff to provide education about cognitive training. Input was gathered to prepare a toolkit and determine potential needs and challenges in program design and delivery. A search was conducted using PubMed to find articles on effective cognitive training techniques and impacts on cognition.

Summary of Results: Interviewees identified cognitive decline and social isolation as two important and related issues for older clients. A cognitive training toolkit was assembled after gathering input from PubMed articles and staff. Activities were selected based on appropriate level of play, intellectual stimulation, potential to maintain and build cognitive skills, and to encourage interaction between residents, families and volunteers. A presentation was given to staff and volunteers on the toolkit’s purpose, contents and suggested usage. Volunteers were taught how to engage clients.

Conclusions: Patients and providers of the International District expressed a desire for a program to help maintain cognition through stimulating activities. Providers also voiced a need to encourage social activity especially among clients who self-isolate or have depression or suicide ideation. While language and cultural barriers are challenges to implementing a formal cognitive training program, the greatest challenge is finding the staff and time to carry out these activities on a consistent basis. Until a program can be established, volunteers can utilize the toolkit as often as they are able to.

261 TREATING MEN WHO HAVE SEX WITH MEN (MSM) IN URBAN PERU: A COMPARISON OF HEALTHCARE ACCESS, DELIVERY AND PERCEPTION IN 3 UNIQUE CLINICAL SETTINGS

Redgate C 1,3, Clark J 2,3, Perez-Brumer A 3

UNIQUE CLINICAL SETTINGS

Conclusions: In order to help bridge the gap between patients and providers when they don’t speak the same language, patient education materials can improve language access, patient satisfaction, and quality of care. Appropriate educational materials with respect to health literacy should be selected to optimize patient outcomes.

Methods Used: During July 2011, data was collected during multiple days of doctor shadowing, patient interviews, and an on-site visit with the mobile unit to compare MSM healthcare delivery in 3 distinct settings using three different criteria: access to care, delivery of care, and patient perception.

Summary of Results: We found that access to care was best when it was free, geographically convenient, and recruitment was lead by MSM community members. When providers worked together to optimize the patient’s health education and counseling, delivery of care was observed as the most effective. Sites that the patients believed were the best included those with supportive, respectful staff members who took time to explain their diagnosis.

Conclusions: A group of healthcare providers well versed with the MSM community working together to provide care is the best way to insure optimal treatment, follow-up, and patient satisfaction. Also, development of mobile clinics staffed by counselors and physicians could open healthcare access to groups of MSM individuals who currently have few clinical resources.

262 LOW-COST CLOUD-BASED REMOTE AUSCULTATION

Sarma K 1, Xia P 1, Lin J 2, Tan A 2, Bunn J 2, Chandy KM 2, David Geffen School of Medicine at UCLA, Los Angeles, CA; 2California Institute of Technology, Pasadena, CA; and 3Carnegie Mellon University, Pittsburgh, PA.

Purpose of Study: The delivery of primary care is a major challenge in the developing world due to a combination of factors that include an insufficient number of health workers per capita and poor infrastructure. This project aims to determine whether remote screening for cardiac abnormalities using a low-cost electronic stethoscope and existing mobile phone infrastructure is feasible in order to partially address this problem.

Methods Used: A low-cost ($30) electronic stethoscope was developed using off-the-shelf electronic components and commercially available bell units. Java software was developed both for Android mobile phones and for laptop computers. Recorded stethoscope signals collected using the software was relayed to a Cloud-based database, which was developed using the Google App Engine. The devices were tested for usability by a team of medical students who evaluated them at several primary, secondary and tertiary field sites in India. Recordings were made on site and later uploaded to the Cloud database. On-site examinations were also performed of all patients including conventional auscultation, and abnormal findings were included in the database.

Summary of Results: Recordings were made of 26 patients with abnormal findings (including patients with rheumatic heart disease, atrial septal defects, ventricular septal defects, and mitral regurgitation). In these patients, the abnormality was detectable by auscultation with a conventional stethoscope, and remotely by listening to the electronic recording made by the prototype. However, precise categorization of abnormal sounds was not always possible using the recordings.

Conclusions: The initial field tests demonstrate that a low-cost electronic stethoscope may be effective for remote screening in the developing world, with the proviso that complete remote diagnosis may not be possible in some cases. The electronic stethoscopes can be deployed in areas where direct primary care is not available; this would allow patients to make more informed decisions about the urgency of obtaining medical advice in person. Further trials are required to determine the sensitivity and reliability of this remote screening technique in order to fully validate its application for this purpose.

263 IMPROVING HIV SERVICES IN A RURAL KENYAN SETTING

Yang R, Mai A University of British Columbia, Vancouver, BC, Canada.

Purpose of Study: The HIV epidemic in Kenya is particularly dire in the Kisumu district, due to widespread poverty and a prevailing sex trade. Anomukul et al. (2009) reported a 15.4% HIV prevalence compared to the national average of 7.4%. Since 2007, the Global Initiative for Village Em- powerment (GIVE) has been addressing this problem in a rural community near Kisumu. We present an evaluation of this project’s progress.

Methods Used: GIVE set up a voluntary counselling and testing (VCT) center in 2007, and has since been working with the community clinic to build capacity for a full-time HIV Care Center and an antiretroviral (ARV) dispen- sary. In collaboration with the provincial government and Aphiia Plus (USAID-funded NGO), GIVE has been helping the clinic meet the requirements for ARV distribution; these include CD4 monitoring, proper documentation of
patients, and prophylaxis for opportunistic infections. Furthermore, GIVE has worked to promote HIV awareness in the community, including HIV workshops at primary and secondary schools and the establishment of a community unit (a group of volunteers who visit village households to provide basic health education and referrals).

**Summary of Results:** Since June 2008, 624 people have been tested through VCT, with 20.4% testing positive. The VCT set up the foundation for other NGOs to implement HIV services such as support group meetings and nutritional supplements. Testing rates have gone up since these services were implemented. With support from GIVE, the local staff completed the final requirements for a dispensary in July 2011, and the clinic received its first ARV supply in September. Household data collected by the community unit has shown that GIVE’s efforts to raise HIV awareness and reduce the number of people unaware of their HIV status have been successful.

**Conclusions:** Our multifaceted approach to HIV has so far been effective. Starting initially with a VCT and establishing a community unit and HIV education, we now have a community with realistic access to CD4 counts and ARV services. This was accomplished with a grassroots and collaborative effort with community members, health clinic staff, other NGOs and the government. Future goals include assessing the function and sustainability of the recently implemented CD4 count and ARV therapy services. We will review statistics on HIV services and make modifications accordingly.

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**264**

**DISSEMINATION THROUGH COMMUNITY HEALTH CENTERS SERVING DIVERSE POPULATIONS - A PILOT STUDY**

Christopher M, Edelson J, Tu S

**University of Washington, Seattle, WA.**

**Purpose of Study:** To pre-test a survey designed to assess community health centers’ (CHCs) capacity to implement a research-tested health education program. Pre-testing focused on completion time, reading level and an outcome measure to capture intent to participate in the program. The revised survey will be used in a future study with the aim of understanding how to improve the translation of evidence-based programs into clinical practice.

**Methods Used:** Our survey consists of 70 questions that asked participants to rate different components of their clinic’s organizational capacity for change (core structure, adaptive reserve) using a five-point scale and a research-tested health education program shown to improve colorectal cancer screening rates. Following this section, we tested binary and scaled versions of the outcome measures (i.e. staff intention to participate in the program). We recruited nine medical assistants (MAs) and five medical students; twelve completed the survey online and two completed the paper version. Follow-up interviews assessed survey clarity and intent to participate in the program. Two weeks later, participants completed a revised survey.

**Summary of Results:** On average, participants completed the survey in 14.7 minutes and reported that questions were at an appropriate reading level for them. Thirty participants responded, “yes” when asked if they would participate in the program. Seven explained they were “somewhat likely” to participate, two were “very likely,” four were “definitely likely,” and one was “not at all likely.” Three MAs explained they assumed participation would be mandatory. Ten participants reported uncertainty about the clinic’s capacity to provide adequate time and staff support, but they intended to participate.

**Conclusions:** To increase the sensitivity of the survey’s outcome measures, we changed these from a dichotomous response to a five-point Likert scale. The refined survey will be used in a larger study involving staff from CHCs to provide adequate time and staff support, but they intended to participate.

**Summary of Results:** On average, participants completed the survey in 14.7 minutes and reported that questions were at an appropriate reading level for them. Thirty participants responded, “yes” when asked if they would participate in the program. Seven explained they were “somewhat likely” to participate, two were “very likely,” four were “definitely likely,” and one was “not at all likely.” Three MAs explained they assumed participation would be mandatory. Ten participants reported uncertainty about the clinic’s capacity to provide adequate time and staff support, but they intended to participate.

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**Conclusions:** To increase the sensitivity of the survey’s outcome measures, we changed these from a dichotomous response to a five-point Likert scale. The refined survey will be used in a larger study involving staff from CHCs to provide adequate time and staff support, but they intended to participate.

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**CHANGES IN MEDICAL EDUCATION IN UGANDA SINCE 2005**

Gayman A1, Kamulegeya J2, Nakibuka M2, Hagopian A1, Luboga S1 \*UW School of Medicine, Seattle, WA and 2Makerere University School of Medicine, Kampala, Uganda.

**Purpose of Study:** The purpose of this study is to document changes in medical school education in Uganda since 2005.

**Methods Used:** We conducted a cross-sectional retrospective study of Uganda’s four medical schools, collecting qualitative and quantitative data about changes in curriculum, structure, staffing, students and pedagogy since 2005. All medical schools accredited by the Uganda National Council for Higher Education for the Bachelor of Medicine and Bachelor of Surgery were included (three public and one private). We held structured qualitative interviews with lecturers and administrators and focus groups with medical students. Interviews were also conducted at the National Council for Higher Education. Quantitative data on the number of enrolled students and graduates was obtained from the registrar at each school.

**Summary of Results:** Coding of interviews identified 7 themes: 1. Faculty shortages: Each respondent recognized inadequate numbers of teachers for the growing population of students. 2. Faculty distraction by second jobs: Shortages in faculty are compounded by an increasing pattern of lecturers taking second-jobs as a means of meeting their financial needs. 3. Expanded Research Activity: Research is a priority at all three of Uganda’s public medical schools, but the agenda is set by external funding sources. Conducting research deemed by faculty to be relevant to the community remains a challenge. 4. Evolving community exposure and leadership training: Training is adapting to prepare students for the Ministry of Health positions physicians take after graduation. 5. Stagnant Admissions Process: Government sponsored admissions are done centrally, based purely on quantitative measures. 6. Government Accreditation: In 2005 the Council on Higher Education began accreditation and mandatory curriculum review to ensure accountability and minimum standards for curriculum content. 7. Teaching methods dependence on local environment: Problem-based learning has been introduced at one university but lack of library, internet and staff resources, prohibits expansion to other schools.

**Conclusions:** With the addition of 2 new medical schools, Uganda has increased the output of MBChB students since 2005. To make this expansion successful, it will be critical to address faculty shortages and their need to have a second job.

**Morphogenesis and Malformations**

Concurrent Session

1:30 PM

Friday, January 27, 2012

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**PERIPHERAL MUSCLE WEAKNESS IN RASOPATHIES**

Stevenson D1, Allen S1, Tiddyman W2, Carey J1, Viskochil D1, Stevens A1, Hanson H1, Sheng X1, Thompson B2, Okumura M2, Reinker K3, Johnson Bo, Rauen K21University of Utah, Salt Lake City, UT; 2University of California San Francisco, San Francisco, CA; 3University of Texas Health Sciences Center, San Antonio, TX and 4Shriners Hospital for Children Salt Lake City, Salt Lake City, UT.

**Purpose of Study:** Musculoskeletal abnormalities are part of an overlapping phenotype of the Rasopathies. The objective of this study was to evaluate handgrip strength in different syndromes of the Ras/MAPK pathway compared to healthy controls.

**Methods Used:** Two methods of hand grip strength were evaluated. For the Takei dynamometer, 162 individuals with various Rasopathies and healthy controls were enrolled ([Controls=53, NF1=59, Noonan syndrome=15, Costello syndrome=20, and cardiofaciocutaneous (CFC) syndrome=15]. Maximum kilogram-force (kgf) was assessed using the GRIP-D Takei Hand Grip Dynamometer. The average of 4 measurements (2 from the left and 2 from the right) in each subject was used for comparison. A general linear model was fitted to compare average strength among the five groups controlling for possible confounders such as age, sex, height, and weight. In order to support findings, a second cohort of syndrome participants (n= 29) and normal sibling controls (n=17) were tested using the Martin vigorimeter (kpA), a handgrip instrument less dependent on hand anthropometry.

**Summary of Results:** With the Takei dynamometer, handgrip strength was decreased in individuals with NF1 (p<0.0005), Costello syndrome (p<0.0001), CFC syndrome (p<0.0001) and Noonan syndrome (p<0.005) compared to controls. Other notable group differences included decreased strength in Costello syndrome compared to NF1 (p<0.0002) and Noonan syndrome (p<0.059). Decreased handgrip strength of syndromic groups compared to sibling controls was also seen using the Martin vigorimeter (p<0.0001).

**Conclusions:** Hand and forearm strength, as assessed by a handgrip dynamometer, are decreased in all Rasopathies examined in this study. The
etiology of the decreased muscular forces is not known but likely and combi-
nation of decreased physical activity, mitochondrial dysfunction, myopathy, and/or decreased muscle mass. Physical therapies to increase muscle strength
may help to ameliorate many of the musculoskeletal abnormalities common in
the RASopathies.

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MAPPING GLUCOSE TRANSPORTER-1 POSITIVE NERVE FIBERS IN THE TRANSITIONAL ZONE OF HIRSCHSPRUNG DISEASE
Kennedy A^1, Kapur R^2^1 University of Washington School of Medicine, Seattle, WA and^2 Seattle Children’s Hospital, Seattle, WA.

Purpose of Study: Hirschsprung Disease (HSCR) is a malformation of the
distal intestinal tract that causes functional obstruction due to an absence of
erient ganglion cells. HSCR is treated by resection of the abnormal bowel.
Incomplete resection of the “transitional zone” (TZ) between normal and
ganglionic bowel is a putative cause of post-operative dysmotility. Histop-
athological features of the TZ include the presence of large nerves with
perineural Glucose Transporter 1 (GLUT-1) immunoreactivity. We sought to
map the distribution of GLUT-1-positive nerves through the proximal-distal
extent of the TZ and formulate objective criteria to differentiate the TZ from
normal bowel.

Methods Used: GLUT-1 immunoreactivity was evaluated in sections of
resected colon from 22 HSCR patients [4 long-segment (LS), 18 short-segment
(SS) disease] and 7 controls (rectums from non-HSCR patients). The circum-
ference of each transverse section was divided into 8 sectors and GLUT-1-
positive nerves were counted in the myenteric and submucosal plexuses.

Summary of Results: Transverse sections from non-HSCR controls and
the proximal portions of HSCR resections did not contain more than one
sector with ≥2 GLUT-1-positive nerves in either plexus. In contrast, more
than one sector with ≥2 GLUT-1-positive nerves was observed in one or both
plexuses of sections from a contiguous segment (GLUT-1-positive TZ)
proximal to the aganglionic zone. The GLUT-1-positive TZ was <5cm for
every specimen, except one LS-HSCR case. In 4/22 cases (18%), the
submucosal plexus extended ≥2cm proximal to the myenteric plexus; in 5
cases (23%) the myenteric extended ≥2cm proximal to the submucosal.

Conclusions: Perineurial GLUT-1 immunoreactivity is an objectively
easily quantified finding that serves as a TZ marker in HSCR. In a transverse
section, the presence of more than one GLUT-1-positive nerve in more than
one sector (1/8th circumference segment) is an abnormal finding restricted
to a 5 cm region immediately proximal to the aganglionic bowel in SS-HSCR.
Surgical resection colon at least 5cm above the aganglionic segment may
reduce postoperative complications in SS-HSCR.

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MARSHALL-SMITH SYNDROME PATIENT WITH UNREPORTED FINDINGS AND POSITIVE NFIX MUTATION ANALYSIS
Leon EL^1, Carey JC^1, Longo N^3, Jeffrey S^2, Viskochil D^4 University of Utah, Salt Lake, UT and^2 and^4 ARUP laboratories, Salt Lake, UT.

Case Report: The propositus was born at 35 weeks gestation to healthy
Caucasian parents. Family history is noncontributory. His prenatal
history was remarkable for polyhydramnios, congenital hydrocephalus, and
thrombocytosis expand the understanding of this rare genetic condition.

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NUCLEAR THICKENING AND CYSTIC HYGROMAS: PREDICTING POSTNATAL OUTCOMES FROM PRENATAL ULTRASOUNDS
Longstreet BO^1, Balikrishnan K^1, Perkins J^1, Saltzman B^1, Dighe M^2
^1University of Washington School of Medicine, Seattle, WA and^2 Seattle Children’s Hospital, Seattle, WA.

Purpose of Study: To determine the prevalence and odds ratios of chro-
mosomal anomalies and pregnancy outcomes in babies found to have nuchal
thickening, cystic hygromas or lymphatic malformations during routine pre-
natal ultrasonography.

Methods Used: We queried the UW ultrasound database for abnormal pre-
natal ultrasonograms occurring between 2002 and 2008. We obtained a sample of
326 patients, 76 were excluded because they did not follow up for treatment
at UWMC or demonstrated abnormalities outside the scope of our investiga-
tion, leaving a final study population of 250. We retrospectively charted all fetal
structural abnormalities, chromosomal anomalies and pregnancy outcomes in
this population. Prevalence and odds ratios of various postnatal outcomes were
calculated based upon these prenatal findings.

Summary of Results: A preliminary review of study results suggests that
cyctic hygromas are a statistically more powerful predictor for fetal chro-
mosomal anomalies including trisomy-21, Turner’s and Patau syndrome, as
compared to nuchal thickening alone. Furthermore, babies found to have
cyctic hygromas are much more likely to undergo elective or spontaneous
termination of pregnancy. Lymphatic malformations, on the other hand, are
mixed hearing loss in the left ear. He developed thrombocytosis (1 million)
during the neonatal period which is resolving (600 thousand) without inter-
vention. CMA SNP microarray analysis was negative. NFIX gene sequencing
analysis showed a one-base insertion in exon 6 resulting in frameshift mutation,
c.953dupC. This is the first Marshall-Smith patient with confirmatory NFIX
mutation analysis in the USA. His previously unreported physical findings
including dysplastic tectal plate, hypoplastic pons, inner ear anomalies, and
thrombocytosis expand the understanding of this rare genetic condition.
not related to chromosomal anomalies and have a much higher rate of spontaneous resolution in utero as compared to cystic hygromas.

Conclusions: This ultrasound is standard procedure with numerous diagnostic capabilities yet a great degree of variability exists among physician's opinions regarding the significance of various findings. Confounding terminology and contradictory conclusions among studies has further obscured the physician’s ability to interpret prenatal ultrasounds. We believe that our research provides the clinician with a clearer understanding as to the clinical relevance of nuchal thickening vs. cystic hygromas. This information will ultimately provide for better prenatal counseling to parents and allow the clinician to make more educated decisions about subsequent diagnostic testing and patient management.

271 CONSIDERING A VASCULAR PATHOGENESIS OF SMALL INTESTINAL ATRESIA: RISKS ASSOCIATED WITH 32 SINGLE NUCLEOTIDE POLYMORPHISMS INVOLVED IN HOMOCYSTEINE METABOLISM, COAGULATION, CELL-CELL INTERACTIONS, INFLAMMATORY RESPONSE AND BLOOD PRESSURE REGULATION

Gupta T\(^1\), Yang W\(^2\), Iovannici DM\(^3\), Carmichael SL\(^4\), Stevenson DK\(^5\), Shaw GM\(^6\), Lammer EJ\(^7\) \(^,\) University of California, San Diego, La Jolla, CA; \(^8\) Stanford University, Stanford, CA; \(^9\) Children’s Hospital Oakland Research Institute, Oakland, CA.

Purpose of Study: Small intestinal atresia (SIA) is a rare congenital malformation involving occlusion of the small intestine. The development of SIA, particularly in the jejunum and ileum, has been associated with an increased rate of vascular supply. However, the number of studies of the vascular hypothesis is limited. This study considers the vascular hypothesis by exploring the risks of SIA associated with 32 SNPs of genes involved in the vascular processes of homocysteine metabolism, coagulation, cell-cell interactions, inflammatory response, and blood pressure regulation.

Methods Used: A total of 206 SIA cases were ascertained by the California Birth Defects Monitoring Program, and 573 infants with no major congenital anomalies by their first birthday were selected as controls. Genomic DNA was isolated from newborn bloodspots and genotyped for 32 SNPs involving the following genes: MTHFR, F2, F5, F7, SERPINE1, FGB, ITGA2, ITGB3, SELE, ICAM1, MMP3, TNF, LTA, NOX3, AGTR1, AGT, NPPA, ADD1, SCNN1A, GNB3, and ADRB2. Risks were estimated as odds ratios, adjusted for maternal age and race, with 95% confidence intervals. Cases were considered collectively and by subgroups based on atresia location (duodenal/jejunum/ileum).

Summary of Results: Three SNPs had reduced risks: SERPINE1 11053 T/G, MMP3 (-1717) A6/A5, and ADRB2 gln27glu C/G. Two SNPs had increased risk: ITGA2 873 G/A and NPPA 2238 T/C. No intestinal sub-phenotypes showed a unique pattern of SNP associations.

Conclusions: The association of two SNPs with increased risk lends some support to vascular impairment as a possible mechanism leading to SIA. These results also identify a number of genes that merit further exploration for their association with SIA. Hence, this study makes an important contribution given limited knowledge about SIA pathogenesis and given its exploration of the long-held but not well investigated vascular hypothesis.

273 CHROMOSOMAL MOSAICISM IDENTIFIED BY ACGH: A CASE OF TETRASOMY 12P

Myers A, Bernstein JA, Cherry A, Manning MA Stanford University, Stanford, CA.

Case Report: Genetic mosaicism describes a genetic change present in some but not all cells of the body. The change can appear in a single gene or in the number or structure of chromosomes and generally occurs early in development. Somatic chromosomal mosaicism is well-established cause for birth defects, intellectual disability and certain genetic syndromes. It has been suggested that microarray-based comparative genomic hybridization (aCGH), a powerful tool at detecting DNA copy number changes, may be more sensitive for detecting mosaicism than conventional cytogenetic methodologies. Theories for this include testing of multiple cell lineages (aneuploid cells may be under-represented in the circulation, or may undergo autolysis) and failure of cyogenetically abnormal T lymphocytes to respond to mitogens.

Illustrative of this theory, we report on a male infant with multiple congenital anomalies including diaphragmatic hernia, in whom high resolution chromosomal analysis was normal, but tetrasomy 12p [t(12)(p10)] mosaicism was detected by aCGH and confirmed by fluorescence in situ hybridization (FISH) (57%). aCGH results prompted an additional 100 metaphase cells to be screened and two metaphases (2%) demonstrated the t(12)(p10). Pallister-Killian syndrome (PKS) is a rare genetic disorder usually caused by tissue-limited mosaic partial tetrasomy of 12p, frequently due to an iso- chromosome, formed from duplication of the short arm of chromosome 12 (i(12p)). Prior to aCGH PKS mosaicism was primarily detected in cultured fibroblasts or amniotic fluid cells.

Our results support literature reports documenting usefulness of aCGH in detecting chromosomal mosaicism not identified in stimulated blood cultures and which otherwise require an invasive procedure for identification. However, aCGH using DNA from peripheral blood would not detect tissue-limited mosaicism in which the abnormal cells are present in other tissues but not blood. This case provides an opportunity to test the concept of assaying multi-lineage cells through aCGH, as it does not depend on robust division of aneuploid T-cells or the integrity of DNA in cells in a peripheral blood sample. Studies are planned to determine which cell type in blood contains the i(12p).

274 UP-REGULATION OF TFAP2C BY FGF DURING SHH INDUCTION IN LIMB BUDS

Kim DJ, Pira CU, Oberg KC Loma Linda University School of Medicine, Loma Linda, CA.

Purpose of Study: During development, limb outgrowth has been linked to a reciprocal feedback loop between Fibroblast growth factors (Fgf) and Sonic Hedgehog (Shh). Fgfs emanating from the apical ectodermal ridge (AER) at the distal tip of the limb bud promote secretion of Shh from a cluster of cells in the distal posterior (ulnar) aspect of limb bud mesoderm called the zone of polarizing activity (ZPA). In turn, secreted Shh from the ZPA induces Fgf expression from the posterior AER. This reciprocal loop is also critical to limb regeneration, and previous studies have shown that Shh up-regulation correlates with the capacity of Fgfs to accomplish regenerative limb outgrowth. To determine the mechanism by which Fgfs up-regulate Shh, we performed gene arrays 24 hours after application of exogenous Fgf to the distal limb bud and identified a number of potential downstream targets in the Fgf-Shh pathway. In this report, we examined the expression of Transcription factor AP-2 gamma (Tfap2c), a gene anticipated to either directly or downstream of FGF or upstream of Shh.

Methods Used: To determine the time course of Tfap2c up-regulation in response to Fgf, we implanted Fgf-soaked beads into stage 23 chick wing buds and evaluated Tfap2c expression by in situ hybridization at 3, 6, 12, and 24 hours after Fgf implantation.

Summary of Results: Tfap2c was up-regulated within 3 hours of Fgf exposure; however, treatment with the protein synthesis inhibitor cycloheximide abolished induction.

Conclusions: We conclude that Tfap2c is a close, but indirect, downstream target of Fgf, mediating its function during limb development and regeneration. However, further studies are needed to determine whether Tfap2c participates in the Fgf-to-Shh pathway or plays an alternative role in limb outgrowth.

274 MOLECULAR INTERMEDIATES IN THE INDUCTION OF SHH BY FGF DURING LIMB DEVELOPMENT

Hundley EP, Pira CU, Oberg KC Loma Linda University, Loma Linda, CA.

Purpose of Study: Sonic Hedgehog (SHH) is essential to the patterning of limb outgrowth during development and regeneration. At the tip of the limb bud, the apical ectodermal ridge secretes Fibroblast Growth Factor (FGF) to induce outgrowth and SHH up-regulation. To identify potential intermediates in the FGF-to-SHH pathway, we performed gene arrays 24 hr after FGF2 application to the chick limb bud. MSX1, MSX2, CHD7, WNT6, DCX, and DLX5 were up-regulated, in addition to SHH. We hypothesized that these six gene products would participate in the FGF-induced up-regulation of SHH.

Methods Used: To determine each gene’s temporal position within the FGF-to-SHH pathway, we performed expression time courses on the limb
beads. The embryos were then incubated and harvested at 3, 6, 12, 18, and 24 hours. Gene expression around the beads was demonstrated by whole mount in situ hybridization. These specimens were reexamined in the presence of cyclohexamide, a protein synthesis inhibitor.

**Summary of Results:** CHD7 and MSX2 were the first of the genes to be up-regulated by FG2 within 3 hr, followed by MSX1 at 6 hr, and then WNTs, DCM, and DLX5 at 24 hr. Furthermore, CHD7 up-regulation persisted even in the presence of cyclohexamide, indicating direct FGF induction.

**Conclusions:** Direct induction of CHD7 by FGF promotes chromatin accessibility during the up-regulation of SHH; rapid up-regulation of MSX1 and MSX2 likely maintains the limb bud mesoderm in an undifferentiated state, responsive to SHH induction. Although FGF’s up-regulation of WNT6, DCM, and DLX5 may indicate roles within the FGF-to-SHH pathway, these factors could also be involved in coincident but separate FGF-related pathways. To distinguish between these two possibilities, further studies are needed.

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**IDENTIFICATION OF A REGULATORY REGION WITHIN THE EMX2 LOCUS THAT IS ACTIVE IN THE NEURAL TUBE AND DEVELOPING LIMB**

Schober JP, Pira CU, Oberg KC Loma Linda University, Loma Linda, CA.

**Purpose of Study:** Development requires strict temporal and spatial regulation of essential genes to ensure functional morphology. Conservation of the developmental pathways across species suggests retention of regulatory mechanisms. Thus, conserved non-coding regions (CNCR) may play a role in the genetic regulatory process. EMX2 is a homeodomain transcription factor critical to the development of the central nervous system (CNS) and limb. We have previously identified EMX2 as a target of LMX1B, a transcription factor required for brain development and limb dextralization. We report on a CNR ~ 335 kb downstream of EMX2 we labeled as CNRZ1, that is highly conserved across species and that also contains putative Lmx1b binding sites (FLAT sequences). We hypothesize that CNRZ1 may play a role in regulating EMX2, possibly mediated by LMX1B binding.

**Methods Used:** To test enhancer function, we isolated CNRZ1 by PCR and ligated it into a plasmid containing a thymidine kinase minimal promoter linked to a GFP reporter. The plasmid was introduced into chick embryos by electroporation (EP). Whole embryo EP was performed on Hamburger and Hamilton (HH) stage 4 chick embryos for CNS evaluation and targeted regional EP was done on the presumptive limb mesoderm (somite level 15–20) of HH14 embryos.

**Summary of Results:** Fluorescence was visible by microscopy in the neural tube beginning at 12 hrs post-EP (stage 6), with the strongest signal observed at 48 hrs (stage 10–11). Diffuse fluorescence was also detected in forelimb mesoderm.

**Conclusions:** Co-localization of CNRZ1 enhancer activity with EMX2 and LMX1B expression in the neural tube and developing limb implicates CNRZ1 as an enhancer for EMX2 that is potentially regulated by LMX1B.

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**MATERNAL LOW PROTEIN DIET-MEDIATED CHANGES IN THE LIVER RENIN-ANGIOTENSIN SYSTEM**

Kim T, Goyal R, Longo LD Loma Linda University, Loma Linda, CA.

**Purpose of Study:** Maternal low protein diet (MLPD) during pregnancy can lead to a number of physiological and pathological changes in the fetus. These changes may have immediate effects such as low birth weight, and is also implicated in the developmental programming of hypertension in the offspring. Specifically, we have demonstrated that MLPD is associated with alterations in the systemic renin-angiotensin system (RAS) of the fetus. Of note, the systemic RAS commences in the liver with the synthesis of angiotensinogen, and as the liver is the major metabolic organ that senses nutrition, we investigated the liver local RAS to elucidate the association between MLPD and developmental programming of hypertension. We tested the hypothesis that MLPD during pregnancy leads to alterations in liver RAS expression of the mouse offspring.

**Methods Used:** FVB/NJ mice dams were separated into two groups given control diet (normal protein content) or MLPD (50% normal protein content). We analyzed mRNA and protein expression of various RAS genes in the liver of offspring at ages 3 weeks and 33 weeks for both males and females. (n = 3 to 4, p < 0.05 was considered significant).

**Summary of Results:** MLPD fetal liver showed increased ACE1 (angiotensin converting enzyme) mRNA expression. Although AT2 (angiotensin receptor type 2) mRNA expression was undetectable, MLPD fetal liver showed significant decrease in AT2 protein expression. There was no significant difference in ACE1 protein expression, as compared to control diet.

**Conclusions:** Antenatal MLPD leads to differential regulation of mRNA and protein expression of ACE-1 and AT2 receptors, which may be involved in developmental programming of hypertension in adult life.

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**MATERNAL PROTEIN DEPRIVATION AND LIVER ANGIOTENSIN II RECEPTOR EXPRESSION IN THE DEVELOPMENT OF HYPERTENSION**

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**Purpose of Study:** Hypertension is the most prevalent disease among American adults, and is a major contributing factor to the development of cerebrovascular disease and cardiovascular disease, the two leading causes of death worldwide. Numerous studies have shown that the offspring of mothers suffering from protein deprivation during pregnancy have been associated with an increased risk for the development of hypertension later on in life. It has been widely hypothesized that the systemic Renin-Angiotensin system (RAS) may be involved in the development of hypertension. As the major metabolic organ and the location of angiotensin synthesis, the liver may be a crucial link between gestational nutrition and RAS. Understanding these interactions may yield clues to the prevention or reversal of the MLPD-hypertensive phenotype, and may also lead to improvement of current therapies for hypertension.

**Methods Used:** Here we use immunoblotting and quantitative PCR to investigate the protein and gene expression of the Angiotensin II receptor 1 (AT1), subtypes A and B (AT1a and AT1b) in the liver of maternal low protein diet (MLPD) mouse offspring.

**Summary of Results:** Our results suggest that while there is no significant change in protein expression level in MLPD offspring at 3 or 32 weeks, a significant increase can be appreciated in gene expression, particularly in female MLPD animals at 32 weeks of age.

**Conclusions:** The discrepancy between protein and mRNA expression may suggest the presence of epigenetic regulation mechanisms in the development of hypertension seen in the animal model. We believe these findings may be another step toward understanding the hypertensive phenotype associated with maternal protein deprivation.

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**METHYLATION IN REGIONS OF EXECUTIVE FUNCTION IN THE DEVELOPING HUMAN BRAIN**

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**Purpose of Study:** Despite growing recognition of the importance of DNA methylation for development, the nature and plasticity of DNA methylation remains poorly understood. We performed methylation studies on candidate genes in fetal brain regions responsible for executive function, in order to determine regional methylation status through early brain development, and to determine to what extent a peripheral sample (buccal swab) reflects the central nervous system.

**Methods Used:** Fetal tissue samples were obtained from 4 whole brain specimens 14–22 weeks gestation and the following regions dissected: dorso-lateral prefrontal cortex, orbital frontal cortex, anterior cingulate cortex, and a peripheral (cheek) sample. DNA was isolated using a commercial DNA isolation kit. Methylation profiling was performed using a methylation
BeadChip array (Illumina, USA) on the following genes: dopamine receptor 2 and 4 (DRD2, DRD4), catechol-O-methyltransferase (COMT), and dopamine transporter 1 (DAT1). DNA was converted with sodium bisulfite, amplified, labeled with fluorescent dyes, and hybridized to the BeadChip arrays. DNA methylation values for each CpG site were scored as beta (β) values, calculated as the ratio of the methylated signal over the total fluorescent signal.

Summary of Results: Of the 170 CpG sites in the selected genes, 57 were in COMT, 69 in DAT1, 22 in DRD2, and 22 in DRD4. These CpG sites were distributed across the promoter, 5’UTR, first exon, gene body, and 3’UTR. Preliminary results indicated that it was possible to detect significant variability in methylation at 77 of these CpG sites. There were no detectable differences between methylation at the left and right hemispheres in the brain regions examined, and few significant differences between methylation at CpG sites within brain regions and methylation in cheek samples. Methylation status decreased with increasing gestational age for all 4 genes in all regions.

Conclusions: It is possible to identify regions of epigenetic variation in developmentally important genes in fetal brain samples. Moreover, brain and cheek tissues shared similar DNA methylation patterns within the same individual at the genes of interest. Variably methylated gene regions represent a new target for understanding biological diversity during early development.

279 SR-1 ANTIBODY EXHIBITS DOSE DEPENDENT INHIBITION OF HUMAN UMBILICAL CORD BLOOD CD34+ HEMATOPOIETIC PROGENITOR COLONY FORMATION
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Purpose of Study: SR-1 antibody administration is a potential non-myeloablative conditioning regimen that may improve stem cell engraftment via blockade of stem cell factor (SCF) from binding to the c-kit receptor. These studies focused on determining whether SR-1 antibody could inhibit erythroid, myeloid, and mixed lineage colony formation in human cord blood CD34+ hematopoietic cells in vitro, the SR-1 concentration required for an effect, and whether the effect is dose-dependent.

Methods Used: Flow cytometry was used to characterize the CD34+ umbilical cord blood cells. A subset of cells was grown in conditions with or without SCF and SR-1, and colony counts were compared on day 7 post-culture. A subset of cells was also incubated with an IgG2a isotype control or 1-20 μg/mL SR-1, and colony forming units (CFU-GM, BFU-E, CFU-GEMM) were counted on day 11.

Summary of Results: SR-1 was shown to inhibit the proliferation of human umbilical cord blood CD34+ hematopoietic cells in the presence of SCF and inhibit colony forming units in a dose-dependent manner. The total number of colony forming units was significantly decreased in the presence of 10 μg/mL and 20 μg/mL of SR-1, compared to 1 μg/mL. CFU-GM specific colonies were the most abundant and were significantly decreased in the presence of 5 μg/mL, 10 μg/mL, and 20 μg/mL of SR-1, compared to 1 μg/mL.

Conclusions: Thus, SR-1 antibody may provide a potential method of endogenous hematopoietic stem cell inhibition that could be useful as a non-myeloablative conditioning regimen.

280 A COMPARATIVE STUDY OF PLURIPOTENCY MARKERS IN EMBRYONIC STEM CELLS AND INDUCED PLURIPOTENT STEM CELLS
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Purpose of Study: Embryonic stem cells (ESCs) replicate indefinitely and can differentiate into all three germ layers allowing for their potential utilization in regenerative medicine. However, the use of ESC’s has been limited due to ethical concerns as well as ESC’s not being HLA matched to potential recipients. On the other hand, induced pluripotent stem cells (IPS) are produced from somatic cells that have been “reprogrammed” via integration of pluripotency genes. This method allows for recipient-matched production of tissues. Although IPS exhibit great potential, the quality of IPS derived from different types of somatic cells and their ability to be efficiently reprogrammed into a desired cell type has yet to be thoroughly examined. The aim of this study was to further characterize the expression of pluripotency markers in an ESC cell line (H9), IPS cells derived from cord blood (6.2), and two IPS cell lines derived from fibroblasts (6.1 and 6.6).

Methods Used: Cells were cultured on mouse embryonic fibroblasts with stem cell medium and incubated at 37°C for 3 days. ESC and IPS colonies were examined for spontaneous differentiation using light microscopy. Cells were then washed and placed in tubes. Fluorescently labeled anti-SSEA4, Tra160, and Tra181 antibodies were added and incubated in the dark at 4°C for 30 minutes. Cells were then sorted and counted using a flow cytometer. Results were tabulated using FlowJo software.

Summary of Results: Results showed that 6.1 and 6.6 cells exhibited a greater degree of spontaneous differentiation compared to H9 and 6.2 cells. Flow cytometry revealed that 77.1% of H9 cells expressed both SSEA4 and Tra160, while 87% expressed both SSEA4 and Tra181. On the other hand, 77.4% of 6.2 cells expressed SSEA4 and Tra160, while 81.8% of cells expressed SSEA4 and Tra181. Interestingly, both 6.1 and 6.6 cells had widely different expression: 66.6% and 57.1% for SSEA4 and Tra160, respectively, and 78% and 56.9% for SSEA4 and Tra181, respectively.

Conclusions: Results indicate that cord blood IPS are more similar to fibroblast IPS to ESC in terms of spontaneous differentiation and expression of SSEA4, Tra160 and Tra181 markers. This suggests that the therapeutic potential of cord blood IPS may be greater compared to IPS derived from fibroblasts.

281 INSULIN LIKE GROWTH FACTOR-1 VARIANTS IN THE LIVER ARE ALTERED IN A GENDER SPECIFIC MANNER IN INTRAUTERINE GROWTH RESTRICTED RATS ON A HIGH FAT DIET COMPARED TO CONTROLS
Zalla J, Zinkhan E, Joss-Moore L, Lane RH University of Utah, Salt Lake City, UT.

Purpose of Study: Intrauterine growth restriction (IUGR) negatively impacts the liver of humans and rats. Insulin like growth factor (IGF-1) modulates growth and insulin sensitivity. IGF-1 is made in the liver and has 4 variants, based on promoter usage (P1 and P2), and exon 5 presence (1a and 1b). The determination of which variant is produced appears to be epigenetically modified. IUGR decreases IGF-1 mRNA levels in postnatal humans and rats. A high fat diet (HFD) also decreases hepatic IGF-1 function. What is unknown however is how a HFD will affect hepatic IGF-1 mRNA on IUGR rats. We hypothesize that a HFD in IUGR rats decreases IGF-1 mRNA levels in comparison to controls fed a HFD.

Methods Used: We induced IUGR through bilateral uterine artery ligation of the pregnant rat at E19. At weaning, control and IUGR rats were fed either a regular or HFD giving us 4 groups (HF-IUGR n=13, HF-C n=10, IUGR n=9, C n=11). IGF-1 variant mRNA levels were measured with real time RT-PCR from the liver at day of life 60.

Summary of Results: In male IUGR rats, a HFD decreased mRNA levels of IGF-P1 and IGF-1b (60% +/- 16%, 34%/ +/-9%) compared to IUGR. Conversely in female IUGR rats, a HFD increased IGF-P1 mRNA levels (204% +/- 44%) compared to IUGR, while IGF-1b mRNA levels show a trend (170% +/- 84%) compared to IUGR. Interestingly, IUGR alone in male rats increased levels of IGF-1b (226% +/- 38%, 186% +/-32%) compared to HF-C and C males. IUGR alone in female rats however showed no differences compared to controls. Both variants, IGF-P2 and IGF-1a, showed no significant difference between the 4 groups, nor was there a difference between controls on different diets.

Conclusions: We conclude that a HFD in IUGR rats causes a sex specific response of hepatic mRNA levels of IGF-1. The gender specific response of IGF-1 mRNA is consistent with other organs such as the lung. Sex steroids are key determinants of epigenetic modifications, which is likely the reason behind our novel findings. We speculate that in order to improve outcomes in IUGR rats on a HFD, treatment will need to be sex specific.

282 MATERNAL DHA SUPPLEMENTATION NORMALIZES EFFECTS OF IUGR ON HEPATIC FATTY ACID STABILIZATION AND HEPATIC PPARy2 MRNA IN JUVENILE MALE RATS

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Purpose of Study: In humans, IUGR predisposes to hepatic steatosis (HS), with males often more affected than females. A recent clinical trial suggests that dietary supplementation with docosahexanoic acid (DHA), an omega 3 fatty acid, decreases the severity of HS in children. DHA functions as a ligand for peroxisome proliferator activated receptor gamma 2 (PPARγ2), a transcription factor that promotes lipid storage. In adult mice, increased PPARγ2 expression promotes HS; whereas, decreased PPARγ2 expression protects against HS. We have demonstrated in immature rats that IUGR leads to HS and increases hepatic mRNA levels of PPARγ2. However, whether maternal DHA supplementation prevents the development of HS and decreases hepatic PPARγ2 mRNA levels in IUGR offspring is unknown. We hypothesize that maternal 1% DHA supplementation prevents IUGR induced HS and decreases hepatic PPARγ2 mRNA in IUGR offspring.

Methods Used: To test this hypothesis we used an IUGR rat model. Dams were pair-fed from E13 to term and through lactation (D21) either a regular diet or 1% DHA diet. The model had four groups per gender: control, IUGR, DHA-control, and DHA-IUGR. MRL experiments were performed on juvenile (D21) rats and total intra-hepatic fat quantified. Liver was harvested at D21 and PAPPα mRNA quantified via real time RT-PCR.

Summary of Results: DHA prevented male IUGR increased intra-hepatic lipid levels. D21 male IUGR intra-hepatic lipid levels were significantly increased (150±11%*) compared to male control, DHA-control, and DHA-IUGR. DHA prevented male IUGR increased hepatic PPARγ2 mRNA levels. D21 male IUGR hepatic PPARγ2 mRNA levels were significantly increased (400±100%*) compared to male control, DHA-control, and DHA-IUGR. No impact on PPARγ2 mRNA or intra-hepatic lipid levels were observed in either diet of juvenile females. (*p<0.05).

Conclusions: We conclude that in juvenile male rats, maternal DHA supplementation prevents IUGR induced increased intra-hepatic lipid levels and increased hepatic mRNA PPARγ2 levels. The gender specific impact of DHA upon HS and PPARγ2 is a novel finding. We speculate that DHA activation of PPARγ2 is regulated by a gender specific pathway, and targeting this pathway will have a greater impact on HS in the IUGR animal concurrently treated with DHA.

283 EFFECT OF LEPTIN ON PERTURBED HYPOTHALAMIC NEUROLEPTIC EXPRESSION AND ENERGY BALANCE IN PERINATAL CALORIE RESTRICTION

Gibson L, Shin B, Dai Y, Devaskar S UCLA, Los Angeles, CA

Purpose of Study: Perinatal calorie restriction is associated with neonatal hypoleptinemia that has permanent effects on hypothalamic development and is linked to the obesity phenotype. In animal models, rats subjected to perinatal calorie restriction have increased caloric intake, decreased energy expenditure, and decreased leptin and insulin concentrations. This phenotype is associated with hypothalamic activation of orexigenic Neuropeptide Y (NPY)/Agouti-related peptide (AgRP) and suppression of anorexigenic proopiomelanocortin (POMC)/cocaine-and-amphetamine regulated transcript (CART). In our animal model, we examined the effect of leptin replenishment in the immediate postnatal period. Phenotypic results demonstrated that leptin led to increased energy intake and expenditure. We hypothesize that leptin reverses the energy imbalance caused by perinatal calorie restriction via hypothalamic leptin receptor signaling.

Methods Used: Prenatal-and postnatal calorie-restriction (50%) and control ad lib fed female rat pups (6 pups/litter) were assigned to either daily IP saline injections or leptin (3 μg/g BW/dose) from PN2 to PN8, creating 3 groups: calorie-restricted and control with saline (CR-S;CON-S); CR with leptin (CR-L). Leptin signaling proteins (STAT3 and STAT3) were evaluated by Western blot (PN21). Hypothalamic ObRb, NPY/AgRP, POMC/CART mRNAs (PN21) were profiled by expression arrays and quantified by qPCR. Statistical analysis was performed by ANOVA and Fisher’s PLSD tests.

Summary of Results: Leptin signaling: STAT3 and pSTAT3 decreased in both CR groups vs CON-S (p<0.0001), however pSTAT3/STAT3 ratio only increased in CR-L vs CR-S (p<0.05).

Conclusions: Postnatal leptin intervention normalizes the energy imbalance due to early caloric restriction by stimulating leptin signaling and reversing the anorexogenic/orexigenic neuuropeptide balance.

284 INTRATESTER GROWTH RESTRICTION INCREASES MRNA LEVELS OF CARDIAC GENES IN ADULTHOOD

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Purpose of Study: Intrauterine growth restriction (IUGR) predisposes to adult-onset cardiac hypertrophy in both humans and animal models. Uteroplacental insufficiency-induced IUGR causes right ventricular hypertrophy (RVH) in our rat model at day 120 of age. Genes that encode for ANP, BNP, HCN4, and α-skeletal actin are essential for fetal heart development. These genes are normally repressed in adulthood but abnormally upregulated in RVH. Transcription of these genes is partially regulated by a common master regulatory complex, repressor element-1 silencing transcription factor (REST). We have previously shown that IUGR alters rat heart mRNA levels of these genes at day 21, but it remains unknown whether IUGR changes expression of these genes in the right ventricle of adult rats, when pathologic hypertrophy is seen. We hypothesize that IUGR will increase mRNA levels of the genes that encode for ANP, BNP, HCN4, and α-skeletal actin in the right ventricle at day 120, when RVH is seen.

Methods Used: Bilateral uterine artery ligation surgery was performed on rat dams at E19. Litters were culled to 6 and rats were grown to day 120. Hearts were separated and right (RV) and left ventricle (LV) tissue was obtained. Real-time RT-PCR was performed to assess RV mRNA levels of Nppa (gene that encodes ANP), Nppb (BNP), HCN4, and Acta1 (α-skeletal actin).

Summary of Results: Results are presented as IUGR as % of Control ± SEM. IUGR increased RV mRNA levels of Nppa (258±75%), Nppb (165±8%) and Acta1 (145±10%) in D120 males compared to control. In D120 females, IUGR also increased RV mRNA levels of HCN4 (157±13%) *p<0.05.

Conclusions: We conclude that IUGR increases mRNA levels of genes that code for ANP, BNP and α-skeletal actin in male rats, as well as HCN4 in female rats, in adulthood. The important observation of this study is that IUGR prevents the normal decrease in expression of these genes, which are known to be involved in ventricular hypertrophy. This persists beyond day 21 to day 120. We speculate that IUGR-induced RVH in adult rats results from the prenatal insult of IUGR causing lifelong alterations in the transcription of these genes. We further speculate that IUGR-induced perturbation of REST binding and regulation may account for altered transcription of these genes in adulthood.

285 USING ZEBRAFISH TO MODEL WHITE MATTER DISORDERS: A FOCUS ON OLIGODENDROCYTES

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Purpose of Study: Periventricular Leukomalacia (PVL) is the most common ischemic brain injury to white matter in prematurely born infants. Developmentally, oligodendrocyte precursor cells (OPCs) become the white matter of the brain, wrapping axons as myelin. PVL causes cerebral palsy in 60-100% of infants and the incidence of PVL ranges from 4-26% in neonatal intensive care units. At autopsy, as much as 75% of premature infants show PVL. Cerebral palsy has an array of manifestations including spastic diplegia, quadriplegia, blindness, intellectual and/or developmental impairment. The purpose of this study is to investigate the underlying mechanism of PVL with a focus on OPC survival and how hypoxic conditions, such as those seen in premature birth, may affect this. A hypoxic environment during OPC development uncoouples respiration to ATP production. Furthermore, hypoxic conditions result in higher amounts of naturally occurring reactive oxygen species (ROS). OPCs are particularly vulnerable to ROS because they have a lower level of superoxide dismutase, an enzyme that combats these reactive oxygen derivatives. Similarly, in any stressed environment such as low oxygen one, inflammation can occur leading to collateral damage of surrounding tissue. We hypothesize that a low oxygen environment may interfere
with OPC survival, specifically resulting in either no OPC development, OPC development without specification, or OPC development with subsequent death. Once OPCs are rendered dysfunctional, myelin wrapping of axons is abnormal and PVL will occur.

**Methods Used:** The methods employed in this study are simulating hypoxic conditions in zebrafish embryos (Danio rerio) by applying certain inhibitors to oxidative phosphorylation. The experiment focuses on different inhibitor concentrations at different times in development during a window of vulnerability for OPC specification in the neural tube.

**Summary of Results:** The goal of this study is to gain an insight into the mechanism behind PVL in the context of oxygen deprivation in utero.

**Department:** Pediatric Developmental Biology. Affiliation: University of Colorado.

**School of Medicine. Mentor: Bruce Appel Ph.D. Disclosures: Nothing to disclose. Funded in part by NIH grants (grant # MH080859)**

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**286 CARNOSOL SUPPLEMENTATION DURING CRYOPRESERVATION PREVENTS DNA DAMAGE IN HUMAN SPERMATOZOA**

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**Purpose of Study:** Sperm cryopreservation preserves fertility in men undergoing chemotherapy or vasectomy, but leads to oxidative stress causing DNA damage. Maintaining genetic integrity by preventing DNA damage in banked sperm is important as assisted reproductive technology is increasingly used. Rosemary extract and L-cysteine have been shown to improve post-thaw motility and viability in boar sperm. However it is unknown what component of rosemary has these properties, if there is any effect on DNA stability, or if the effect translates to human sperm. Carnosol, an anti-inflammatory and anti-carcinogenic antioxidant found in rosemary, protects against oxidative stress in HepG2 cells. The purpose of this study is to determine if carnosol is useful for maintaining DNA integrity during cryopreservation of human spermatozoa.

**Methods Used:** Sperm from 4 young healthy men are purified from semen and divided into treatment groups: 1) Control - no additives to the freezing extender, 2) L-cysteine, 3) Carnosol, 4) Snap Freeze (no cryopreservation). Groups 1-3 are cryopreserved for 24 hours before being thawed for 5 minutes at 37°C. Single Cell Gel Electrophoresis Comet Assay is performed to assess for DNA damage and 100 cells per sample are analyzed using visCOMET software. Comet Extent and DNA Break Number (a measure of double stranded DNA breaks) are used as measurement parameters and expressed as a ratio against control values.

**Summary of Results:** Purified spermatozoa treated with 10mM L-cysteine were not significantly different from controls in either comet extent or DNA break number. However, spermatozoa treated with 20μM carnosol had a significant decrease in both parameters, (P<0.05; one way Kruskal-Wallis Test with Dunn’s post hoc test). Furthermore, DNA break number decreased as the concentration of carnosol increased. At 100μM there was no significant difference compared to non-cryopreserved samples.

**Conclusions:** Carnosol significantly decreases the DNA damage that occurs during cryopreservation. Importantly the number of double stranded DNA breaks decreases in a dose dependent manner. These results show for the first time that carnosol can reduce cryoinjury and suggest its potential usefulness in storing samples susceptible to cryopreservation-induced DNA damage.

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**287 FGF-INDUCED ACTIVATION OF THE LIMB SPECIFIC SHH REGULATORY REGION (LSSRR)**

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**Purpose of Study:**: Generation of amputated or denervated chick wings can be induced by Fgf, and upregulation of Shh is an essential step in this process. During development, a 1.8 kb conserved non-coding region up-stream of Shh functions as a limb-specific Shh regulatory region (LSSRR). We wondered whether this same regulatory region was involved in Fgf-induced limb regeneration.

**Methods Used:**: To test our hypothesis, we electroporated (EP) an LSSRR-green fluorescent protein (GFP)-reporter construct into stage 23 chick limb bud mesoderm and then implanted an Fgf-soaked bead to induce Shh expression. Green fluorescence was detected around the Fgf bead 24 hr after implantation, supporting a role for the LSSRR in the up-regulation of Shh by Fgf.

**Summary of Results:**: To determine the sequences within the LSSRR that were required for Shh up-regulation, we isolated 3 separate candidate sequences within the LSSRR that contained Hox binding sites or an RAR/NFkappaB binding site. The candidate sequences (each less than 150 bp) were ligated into a ptk-GFP reporter plasmid and then INP into the presumptive wing mesoderm of stage 14 chick embryos. All 3 candidate sequences showed fluorescence at 48 hr, indicating enhancer activity with these minimal fragments.

**Conclusions:** We conclude that Fgf utilizes the LSSRR during Shh up-regulation and that multiple enhancer elements within the LSSRR may contribute to Shh’s regulation.

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**288 IDENTIFICATION OF A PROTEOGLYCAN-ASSOCIATED REGULATORY REGION ACTING DURING CENTRAL NERVOUS SYSTEM DEVELOPMENT**

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**Purpose of Study:** Lmx1b is a homeodomain transcription factor necessary for limb, kidney, eye and CNS development. In humans, loss of a single Lmx1b allele causes Nail Patella Syndrome characterized by malformed nails and the loss of a patella. In the mouse, total loss of Lmx1b causes hypoplastic calvarial bones, reduction of cerebellum and tectum formation, loss of dopaminergic/serotonergic neurons, ocular malformations, and distal ventral-lateral limb symmetry. No direct downstream target genes of Lmx1b within the brain or limb have been found. Recent microarray studies in the limb have implicated the proteoglycans Keratocan (Kera), Lumican (Lum), and Decorin (Dec) as possible downstream targets of Lmx1b. Interestingly, Kera, Lum, and Dec (KLD) are tightly clustered within the genome. Using in silico analysis, we compared the human KLD locus and surrounding area to five other species. We discovered 11 conserved non-coding regions (CNR), numbering them consecutively. We hypothesize that Lmx1b directly regulates one or more of these proteoglycans via CNRs associated with this locus.

**Methods Used:** When compared across species, Peak 3 CNR demonstrated deep conservation and an overlapping Lmx1b binding site. Peak 3 was isolated with PCR and ligated into a construct containing a thymidine kinase minimal promoter and enhanced green fluorescent protein reporter (pTK-sGFP). This pTK construct was electroporated (EP) into the whole embryo at Hamburger-Hamilton (HH) stage 4 and the brain of HH10 chick embryos. The embryos were viewed under fluorescent microscopy to determine Peak 3 activation.

**Summary of Results:** Peak 3 activation was detected in the neural tube at HH10. At HH19, activation of the Peak 3 enhancer surrounded the developing midbrain and cerebellum. At HH19, Lmx1b, Kera, Lum, and Dec expression overlapped enhancer activity.

**Conclusions:** Together the data suggest Peak 3 CNR plays a role in the regulation of Keratocan, Lumican, and/or Decorin during central nervous system development. Since Peak 3 overlaps Lmx1b expression and contains an Lmx1b binding site, we suspect that its regulation is mediated by Lmx1b. Further studies are underway to evaluate the involvement of Peak 3 CNR in other Lmx1b patterned tissues.

**Neonatology General II**

Concurrent Session

1:00 PM Friday, January 27, 2012
increased amino acid supply on normally growing fetuses. We hypothesize that chronic increased fetal amino acid supply will increase glucose stimulated insulin secretion (GSIS).

**Methods Used:** Singleton ovine fetuses received a direct intravenous infusion of Trophamine (AA, n=8) or saline (CON, n=8) for 10-14 days during late gestation to target a 25-50% increase in fetal branch chain amino acids (BCAAs). BCAAs, glucose, and insulin were measured throughout the infusion. On the final day of infusion, fetal GSIS, arginine stimulated insulin secretion (ASIS), and glucagon secretion were measured using a hyperglycemic clamp and arginine bolus. Pancreatic insulin and glucagon content were measured by ELISA and RIA, respectively. Beta and alpha cell mass were measured by immunofluorescence staining.

**Summary of Results:** Fetal BCAA increased 50% in the AA group compared to CON (p<0.05). Glucose decreased over time in the AA group (22.7±1.5 baseline vs. 17.9±0.4mg/dl final day, p<0.01) but not in CON. Early phase GSIS increased 150% in the AA group (p<0.01) and this difference was sustained (p<0.05). ASIS, pancreatic insulin, and glucagon content were similar between groups. Beta cell mass (0.14±0.02 AA vs. 0.15±0.01g CON) and area (4.49±0.25 AA vs. 4.27±0.3% CON) were unchanged between groups. Baseline glucagon concentrations were increased (117.7±23.2 AA vs. 57.4±8.12pg/ml CON, p<0.05) and arginine stimulated glucagon concentrations were increased (5 min after arginine 279.2±45.5 AA vs. 135.4±16.8pg/ml CON, p<0.01). Alpha cell mass (0.08±0.02 AA vs. 0.08±0.01g CON) and area (2.58±0.26 AA vs. 2.24±0.39% CON) were unchanged between groups. Fetal and pancreatic weights were similar.

**Conclusions:** Chronic increased amino acid supply to the normally growing ovine fetus in late gestation potentiated GSIS. GSIS was potentiated by ASIS, was not, and pancreatic insulin content and beta cell mass were unchanged. Therefore, we speculate that amino acids upregulate glucose metabolism and generation of secondary messengers in the beta-cell, and that this is enhanced by increased paracrine action of glucagon on the beta cell.

### 290 PROLONGED INFUSION OF AMINO ACIDS INCREASES LEUCINE OXIDATION IN THE OVINE FETUS


**Purpose of Study:** Human maternal high protein supplementation during pregnancy appears to increase the risk for IUGR and small for gestational age birth. In pregnant sheep, increased amino acid supply to the fetus decreases fetal glucose uptake, perhaps substituting amino acid carbons for oxidative metabolism. Thus, fetal amino acid supplementation may change substrate utilization balance in a way that adversely affects fetal growth. We hypothesize that a direct fetal amino acid infusion promotes a shift in fetal utilization of substrates by increasing leucine oxidation.

**Methods Used:** Singleton fetal sheep were intravenously infused with a complete amino acid mixture (AA, n=8) or saline (C, n=10) for an average of 12 days during late gestation. On the final day of infusion a metabolic study was performed using [1-13C]leucine to measure protein metabolic rates. Fetal arterial plasma was sampled for insulin, IGF-1, glucagon, cortisol, and norepinephrine (NE) concentrations. Protein from fetal skeletal muscle was used to quantify mTOR signaling.

**Summary of Results:** There was a significant increase in fetal leucine oxidation in the AA group (AA 3.12±0.45 vs. C 1.35±0.55 μmol/min/kg, P<0.05). There was no difference between AA and C with respect to protein accretion (AA 2.61±0.45 vs. C 2.22±0.55 μmol/min/kg), protein synthesis (AA 6.17±0.83 vs. C 6.98±0.91 μmol/min/kg), or protein degradation (AA 3.55±0.59 vs. C 4.47±1.02 μmol/min/kg). Insulin and IGF-1 did not change. There were no differences between groups for Akt, mTOR, p70S6K, rpS6, 4E-BP1, eEF2, and eIF2α in fetal skeletal muscle. Glucagon was increased in AA (AA 118.9±23.5 vs. C 59.4±9.1 pg/ml, P<0.05), and cortisol and NE tended to be higher in the AA group (AA 16.5±6.0 vs. C 7.8±2.7 ng/ml, P=0.17 for cortisol and 149.0±15.6 vs. C 419.0±75.5 pg/ml, P=0.06 for NE). Un平衡ed glucagon uptake was inversely proportional to fetal glucagon (r=0.38, P<0.05), cortisol (r=-0.31, P<0.05), and NE (r=2.05, P<0.05).

**Conclusions:** Prolonged infusion of amino acids directly into normally growing fetal sheep increased leucine oxidation but had no effect on protein accretion, synthesis, or regulation through mTOR. Amino acid stimulated increases in fetal glucagon, cortisol, and NE may contribute to a shift in substrate oxidation by the fetus from glucose to amino acids.

### 291 THE EFFECTS OF ACIDIFICATION ON HUMAN MILK’S CELLULAR AND NUTRITIONAL PROPERTIES

Erickson TA, Gill G, Chun GM University of Utah, Salt Lake City, UT.

**Purpose of Study:** Human milk is the feeding of choice for infants because of the milk’s cellular and nutritional properties. However, human milk cannot meet the nutritional needs for the preterm infant. Fortification of human milk is necessary and common newborn intensive care unit (NICU) practice. Currently, human milk is being acidified from a fortifier for preterm infants. However, there are little data on the acidification effects on mother’s milk. The aim of this study is to evaluate the effects of acidification on human milk’s cellular and nutritional composition.

**Methods Used:** 65 milk samples were collected from 8 mothers who had infants in the NICU. All milk samples were frozen at 4°C. The frozen samples were thawed and divided into two equal aliquots, control and acidified. The control milk sample had its pH determined while the other sample was acidified to pH 4.5 using citric acid. Each milk sample was examined for pH, white cells, total protein, creatamorotic, lipase activity, and free fatty acids. Results of the acidification were expressed as a percent of the controls.

**Summary of Results:** Milk was collected from day 5 to day 32 of lactation. Mean pH of the human milk samples was 6.8 ± 0.1 (ME: SD) with a range of 7.2 to 6.4. The control milk had 8 × 10^{-3} to 2 × 10^{-3} white cells/ml, 1.5 ± 0.1 g/dl total protein, 259 ± 162 U/L lipase, 6083 ± 2103 μM free fatty acids, and 5.5 ± 1 % creatamorotic. Acidification of human milk decreased white cells to 20 ± 9% controls (P<0.01), 88 ± 5% controls in total protein (P<0.001), and 52 ± 17% controls in lipase (P<0.01). However, the creatamorotic of the acidified milk was 135 ± 18% controls (P<0.002). There were no differences between the two groups in free fatty acids (104 ± 40% controls).

**Conclusions:** Acidification of human milk causes a significant change of the milk’s cellular and nutritional components that may not be beneficial to infants.
accumulation but decreased SREBP2 and HMGCoAR mRNA levels in fe-
male rats fed CD. Therefore we speculate that IUGR bypasses normal tran-
scriptional regulatory mechanisms in the setting of HCD.

293
AN INTERVENTION TO INCREASE BREASTMILK USAGE IN
VERY LOW BIRTH WEIGHT INFANTS ACROSS
CALIFORNIA NICUS

Lee HC1, Kurtin P1, Danielsen B4, Sharek P2, UCSEF Pleasanton, CA; 2Stanford, Stanford, CA; 3Rady Children’s Hospital, San Diego, CA and 4Health Information Solutions, CA.

Purpose of Study: To evaluate the effect of a bundle of potentially better practices to promote breastmilk feeding in very low birth weight (VLBW) infants during a 12-month 11-site quality improvement project.

Methods Used: Eleven neonatal intensive care units (NICUs) participated in the California Perinatal Quality Care Collaborative (CPQCC) / California Children’s Services Breastmilk Nutrition Quality Improvement Collaborative, a comprehensive “change package” of evidence-based and other best practices to promote breastmilk in VLBW infants. The primary outcome of interest was breastmilk feeding at discharge home. Secondary outcomes / balancing measures were incidence of necrotizing enterocolitis and length of stay. The 11 CPQCC hospitals that did not participate in the project served as a comparison group. Data were analyzed during a baseline phase one year prior, during, and 6 months after completion of the project (sustainability phase).

Summary of Results: Rates of breastmilk feeding at discharge to home significantly increased in quality improvement participants but not in the non-participants for the intervention and sustainability phases (Table). The incidence of necrotizing enterocolitis decreased for both groups during the study period. Length of stay was longer in the intervention period but decreased in the sustainability period.

Conclusions: The CPQCC quality improvement project to improve breastmilk and nutrition practices resulted in an increase in breast milk provision and sustainability phase after the project had ceased. This is the first report of a successful collaborative project to improve breast milk feeding in VLBW infants.

<table>
<thead>
<tr>
<th></th>
<th>Baseline period (10/1/11-6/30/11)</th>
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<th>Sustainability period (1/1/12-6/30/11)</th>
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<td>697</td>
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<tr>
<td>N - Non-participants</td>
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<td>3184</td>
<td>5414</td>
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<td>34.6%</td>
<td>61.7% ★</td>
<td>64.9% ★</td>
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<tr>
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<td>67.8%</td>
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<td>2.5% ★</td>
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<tr>
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<tr>
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<td>60.2</td>
<td>61.1</td>
<td>59.6 ★</td>
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</tbody>
</table>

★ p < 0.05 from baseline period

294
LIMITING FEEDING CHANGES APOPTOSIS AND
PROLIFERATION IN THE LIVER OF PRETERM LAMBS
SUPPORTED BY NASAL HIGH-FREQUENCY VENTILATION


Purpose of Study: Feeding intolerance is a frequent problem with preterm neonates who develop neonatal chronic lung disease (CLD). The consequence of inadequate feeding on molecular participants in organ injury is unknown. Our preterm lamb model of neonatal CLD provides opportunity to test the role of inadequate feeding because preterm lambs supported by mechanical ventilation (MV) for 21d repeatedly have residual milk in their stomach. In contrast, preterm lambs supported by nasal high-frequency ventilation (HFV) for 21d rarely have residual milk in their stomach. Associated with prolonged MV is poor somatic growth and decreased hepatocyte proliferation. Whether decreased hepatocyte proliferation, as an index of liver injury, is related to inadequate feeding is not known. We hypothesized that limiting feeding of preterm lambs supported by nasal HFV for 21d will change injury indicators in the liver.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV for 21d or nasal HFV for 21d (n=4/group). A third group of PT lambs (paired-feeding 2nd) was supported by nasal HFV and limited to the same amount of ewe’s milk that is tolerated by PT lambs supported by MV. Apoptosis (cleaved caspase 3) and proliferation (proliferating cell nuclear antigen, PCNA) were assessed by immunoblot.

Summary of Results: The paired-feeding group tolerated less milk daily (mL/Kg/d; p=0.05) than the nasal HFV group, and the same amount as the MV group. At 21d, body weight of the groups was not different. In the liver, cleaved caspase 3 protein abundance was the same among the groups. On the other hand, PCNA protein was less (p=0.05) in the paired-feeding group than the nasal HFV group (p=0.05), and the same as the MV group.

Conclusions: Limiting nutrition to chronically ventilated preterm lambs may contribute to poor liver outcome by reducing hepatocyte proliferation. IGF-1 may be a relevant growth factor because it is subject to epigenetic changes that may be determined by nutrition. (HL110002, HL062875, HL056401, HD41075)

295
ENDOTHELIAL PR REGULATES UTERINE NEUTROPHIL
TRAFFICKING

Enciso JM1, Goddard L2, Izraela-Arispe M2, 1David Geffen School of Medicine at UCLA, Los Angeles, CA and 2UCLA, Los Angeles, CA.

Purpose of Study: Progesterone receptor (PR) is a member of a large family of ligand-activated nuclear transcription regulators, which includes receptors for steroids, retinoids, thyroid hormones, and vitamin D. PR is the primary mediator of the actions of the hormone progesterone on multiple cell types in the uterus. High expression of PR in uterine vascular, stromal, and epithelial cells highlights the importance of progesterone and its receptor in this organ. Progesterone interaction with its receptor has been shown to antagonize pro-inflammatory pathways by reducing the influx of innate cells into the uterus. The specific PR-expressing cell that mediates progesterone’s anti-inflammatory effects is not known. We hypothesize that PR expressed on vascular endothelial cells (EC) mediates the trafficking of inflammatory innate cells to the uterus.

Methods Used: Using Cre-loxP site recombination, uterine inflammation was evaluated in vivo in mice that conditionally lack EC PR expression. To achieve EC-specific inactivation of PR, mice homozygous for the floxed PR locus containing exon 1 (Hashimoto-Partyka et al. 2006) were crossed to VE-Cadherin Cre mice wherein Cre expression is driven specifically in EC (Alva et al. 2006). Uterine leukocytes were isolated from both wild-type (WT) mice and mice with EC-specific deletion of PR. Immune cell populations were identified by Gr1 and Mac1 staining and quantified by flow cytometry.

Summary of Results: Compared to WT mice, mice with conditional PR deletion in the vascular endothelium had increased uterine recruitment of Gr1+Mac1+ cells (PMNs). This finding was unique to the uterus and was not observed in other organs such as the lung or liver which lack PR expression. Furthermore, an increase in Gr1+Mac1+ cells was not observed within the hematopoietic compartment (spleen, bone marrow, and blood) of mice with EC-specific deletion of PR.

Conclusions: In all, our data lend support to a cell-specific role for endothelial PR as the central regulator of uterine neutrophil trafficking. Further understanding of molecular pathways mediated by PR on the vascular en-
dothelium may provide new targets for modulating uterine inflammation associated with pathological processes such as preterm labor, endometriosis, and implantation failure.

296
MATERNAL AND INFANT CAROTENOID STATUS: BIRTH TO
4 MONTHS OF AGE

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Purpose of Study: Carotenoids are important nutrients for newborn infants. They have anti-oxidant properties and are important for eye development. Before the introduction of fruits and vegetables, infants receive their carotenoids mainly from mother's milk and from some infant formulas. The purpose of this study was to evaluate the mother and infant carotenoid status during first 4 months of life.

Methods Used: This was a prospective study of healthy mothers who delivered term infants. After informed consent, feeding type and infant's weight, length, and head circumference were measured and recorded at birth, 4, 8, and 16 weeks of age. Mother's and infant's carotenoid skin status was measured by Raman spectroscopy. Correlation with infant skin Raman counts and total serum carotenoid by high pressure liquid chromatography is good with $R=0.44$, $P=0.01$. Since fruits and vegetables are high in carotenoids, 48-48 hr recall of the maternal daily intake of fruits and vegetables were also recorded.

Summary of Results: Ten mothers and infants participated in this study. Mean birth weight for term infants was 3127 g. Mother's carotenoids averaged 37,142 $\pm$ 15,059 $(\pm SD)$ Raman units (RU) while infant's carotenoids averaged 12,137 $\pm$ 10,966 RU over the 16 weeks. Mother's carotenoid status was correlated with her daily fruits and vegetable intake ($R=0.53$, $P=0.05$). At birth, infant's carotenoids were highly correlated with maternal carotenoid status ($R=0.90$, $P<0.01$). Infant's carotenoids increased during the study from birth (5159 $\pm$ 4360 RU) to 16 weeks of age (19,608 $\pm$ 8,836 RU). Breast fed infants tend to have higher carotenoid levels compared to formula fed infants.

Conclusions: Newborn term infant's carotenoid status is dependent on mother's status. Mother's carotenoid status correlates with her intake of carotenoid enriched fruits and vegetables. By 4 months of age, infant's carotenoid levels are approaching adult's levels.

297 RATES OF VITAMIN D AND IRON SUPPLEMENTATION AMONG FORMER VERY PRETERM ($<=$32 WEEKS) INFANTS AFTER DISCHARGE FROM THE NEONATAL INTENSIVE CARE UNIT


Purpose of Study: The American Academy of Pediatrics (AAP) recommends that infants receive 400 IU/day of vitamin D from the first few days of life through 12 months of age. The recommendation for iron supplementation is 2mg/kg/day from the first month through 12 months of age. Very preterm infants ($<$32 weeks gestation) have higher rates of vitamin D and iron deficiencies compared to those of term infants. This study looks at rates of vitamin D and iron supplementation in very preterm infants who received follow-up care at the Loma Linda University (LLU) High Risk Infant Follow-up Clinic (HRIF) over a six-year period.

Methods Used: The LLU HRIF database consists of 670 high-risk infants who were seen between 2005 and 2011. From this database, 253 very preterm infants with complete birth, discharge and follow-up information were included in this study. Patients not only came from the LLU Medical Center but also from a large number of community neonatal intensive care units (NICUs). Vitamin D and iron supplementation data was obtained from the patient medication section.

Summary of Results: Upon discharge from the NICU, 34% and 42% of the very preterm infants did not receive vitamin D and iron supplementation, respectively. Among those infants who received vitamin D at the time of discharge, only 44% and 30% remained on supplementation at their four-month and eight-month (corrected age) visits, respectively. Among those who received vitamin D at the time of discharge, only 24% and 16% remained on supplementation at their four-month and eight-month visits.

Conclusions: Most infants will require some form of vitamin D supplementation to achieve the AAP recommendations. Furthermore, very preterm infants are at greatest risk for vitamin D deficiency. They are also at increased risk for iron deficiency. Our data suggests that a large number of very preterm infants are not receiving vitamin D or iron supplementation in their first year of life. Education of health care professionals is vital to increasing adherence to current AAP recommendations.

298 RATES OF BREAST FEEDING IN HIGH RISK INFANTS


Purpose of Study: The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for the first six months of life, and for a minimum of fruits and vegetables along with solids. The benefits of breastfeeding at feeding are well established and are even more significant for preterm infants. Unfortunately infants requiring hospitalization in the neonatal intensive care unit (NICU) are less likely to be exclusively or partially breastfed due to delays in feeding and interruption of maternal-infant bonding. We evaluated the rates of breastfeeding in infants hospitalized in a NICU and followed in a high-risk infant follow-up (HRIF) clinic over 6 years in order to assess the rates of breast feeding in preterm infants.

Methods Used: A retrospective study was done on 670 infants who received care in the HRIF Clinic at Loma Linda University (LLU) between 2005-2011. Infants were from either the LLU NICU or referred from community NICUs. High-risk criteria are determined by California Children’s Services. Only infants for whom information on breast milk use at NICU discharge, 4 months corrected age and 8 months corrected age were included.

Summary of Results: Out of 670 infants, 31% had information on feeding for discharge and at four and eight months corrected age. Among infants 23-29 weeks gestation, 49% were discharged on some form of breast milk. By 4 months corrected age only 18% were receiving any breast milk and at eight months corrected age 11% were receiving breast milk. Among infants 30-36 weeks gestation, 69% were discharged on some form of breast milk. By four months corrected age only 16% were receiving breast milk and by eight months corrected age only 14% were getting breast milk. In the term group (37-41 weeks gestation) 85% were discharged on breast milk and 23% remained on some breast milk by four months corrected age. At eight months corrected age, the number receiving breast milk remained at 23%.

Conclusions: Rates of breastfeeding decreased with decreasing gestational age. However by four months corrected age, all three groups had dropped off substantially in the use of breast milk. Considering the substantial benefits of breast milk, especially in the preterm population, mechanisms to increase the use of breast milk in the NICU and even more during the first year of life are crucial to improving outcomes.

299 RATES OF TRANSITIONAL FORMULA USE IN PRETERM NEONATAL INTENSIVE CARE GRADUATES


Purpose of Study: While standard infant formulas have traditionally been used for preterm infants, there are now transitional formulas with higher energy and nutrient value. Some studies have shown improved growth and/or developmental outcomes in preterm infants receiving these formulas. Effects seem to be greatest if infant remains on transitional formula until at least 9 months corrected age. There are currently no American Academy of Pediatrics (AAP) recommendations for the use of transitional formulas. If these formulas do provide benefit to the preterm infant, it is important to know the rates of use at discharge and beyond. This study seeks to describe the rate of usage of transitional formulas in preterm infants at NICU discharge and at 4 and 8 months corrected age.

Methods Used: 670 infants followed by the Loma Linda University (LLU) high-risk infant follow-up clinic (HRIF) were available in the database covering 2005-2011. Of these, 559 were preterm ($<=$37 weeks). Of these preterm infants, 376 were discharged on either transitional formula (TF) or preterm formula (PTF) and returned for follow up at 4 and 8 months corrected age. These infants were divided by gestational age into three groups: 34-37 weeks, 30-34 weeks and <30 weeks.

Summary of Results: Of the 235 preterm infants < 30 weeks, 61% were still on TF at 4 months corrected age and 28% by 8 months corrected age. Of the 126 infants 30-34 weeks who were on TF at discharge, 37% were on TF at 4 months corrected age and 17% at 8 months corrected age. Of the preterm infants who were 34-37 weeks and on TF at discharge, 20% remained on TF at 4 months corrected age and 0% by 8 months corrected age.

Conclusions: A significant number of preterm infants (61%) were discharged from the NICU on transitional formula. Because these formulas are more costly than standard formula, it is crucial that benefits be established in larger trials. If transitional formulas are indeed beneficial for preterm infants, there will need to be significant education of primary healthcare providers and parents in order to keep infants on these formulas for longer periods of time.
300 ANTENATAL METYRAPONE NORMALIZES MATERNAL FOOD-RESTRICTION-INDUCED MYOGENIC LUNG PHENOTYPE

Paek D, Li Y, Sakurai R, Torday J, Rehan VK. Harbor UCLA Medical Center, Torrance, CA.

Purpose of Study: Maternal food restriction (MFR) causes in utero growth restriction (IUGR), a known risk factor for developing chronic lung disease (CLD) through a stress-mediated response, evidenced by elevated fetal glucocorticoid levels. Metyrapone (MTP), an inhibitor of corticosteroid synthesis, may reverse the detrimental effects of IUGR-induced MFR on the lung, which hypothetically differ between genders.

Methods Used: Rat dams were fed an ad libitum diet or a 50% caloric restriction diet. Maternal liver heme oxygenase (HO) activity was measured by gas chromatography. ZnBG towards inhibiting liver HO activity at 3 and 6h post-administration only. No inhibition was seen 12 and 24h post-ZnBG. Spleen HO activity showed parallel results.

Conclusions: The administration of 0.325-μmol ZnBG/kg BW has a very rapid and short duration of action in inhibiting liver and spleen HO activity in the context of a heme load. Thus, we conclude that ZnBG has potential for use in the treatment of neonatal hyperbilirubinemia due to hemolytic diseases. Further study is required to determine the efficacy of repeat or higher doses of ZnBG towards inhibiting HO activity in this setting.

% Control (VV) of Liver HO Activity (mean±SD, n=5)

<table>
<thead>
<tr>
<th>Time Post-ZnBG (h)</th>
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<th>12</th>
<th>24</th>
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</tr>
<tr>
<td>ZnBG</td>
<td>84±18*</td>
<td>111±14*</td>
<td>145±19</td>
<td>91±17</td>
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</table>

*p<0.01 vs HV

301 EFFECT OF A LOW DOSE OF ZINC DEUEROPOPHYRIN BIS GLYCOL IN INHIBITING HEME OXYGENASE ACTIVITY AFTER HEME-LOADING

Katayama Y, Kalish FS, Zhao H, Wong RJ, Stevenson DK. Stanford University School of Medicine, Stanford, CA.

Purpose of Study: Heme oxygenase (HO) is the rate-limiting enzyme in the degradation of heme to produce bilirubin. Because excess bilirubin production due to hemolysis can lead to neonatal hyperbilirubinemia, the use of HO-inhibiting drugs, such as metalloporphyrins (Mps), may be an ideal preventative strategy. Although tin mesoporphyrin (SnMP) has been studied in human neonates, its property as a photosensitizer and ability to induce HO-1 prevents its use in the treatment of neonatal hyperbilirubinemia. We have reported an in vitro method for evaluating efficacy of PT devices through determination of t50%, the time to photodegrade 50% BR for BR destruction in human serum albumin. This method was adapted for the present study. Our objective was to determine the AS for BR photodegradation to diazo-negative products, using light emitting diodes (LEDs) and band pass filters.

Methods Used: Sets of (n=9) LEDs, with peak emissions in ~10nm increments from 390 (blue)-530nm (green), were mounted on heat sinks. The LED assemblies were successively mounted on a specially-constructed device that contained the appropriate 10nm band pass filter, a reflecting barrel and a sample exposure platform. Hematocrit tubes with 25μL buffer with 25% BR/BL 4% human serum albumin (HSA), pH 7.4, at 37±1°C, were exposed to each 10-nm wavelength range portion at a normalized photon level (4.10e-12 moles) as measured with an Ocean Optics Spectrometer. After 0-60min, solutions in the tubes were reacted with diazo reagent and the concentrations of BR remaining, were graphed and t50%'s were interpolated.

Summary of Results: Irradiance mapping of the sample exposure footprint demonstrated that the samples were exposed to light of uniform intensity. The t50%'s, determinations yielded a U-shaped AS profile with the nadir at 500nm (18min) and maxima at 390±65min and 530nm (46min), respectively. The t50% at 460nm was 32min. With increasing temperature from 0-60°C, BR degradation at 500nm increased exponentially. BR photodestruction was negatively correlated to rising HSA concentration.

Conclusions: The data show that BR photodestruction in vitro is greatest at wavelengths 500-10nm (turquoise), a wavelength longer than that most commonly used currently for PT (460±10nm). Further studies are needed to confirm these results in vivo.

302 IN VITRO BILIRUBIN PHOTODESTRUCTION ACTION SPECTRUM REVISITED

Schulz S, Veerman HJ, Wong RJ, Cline B, Stevenson DK. Stanford University School of Medicine, Stanford, CA.

Purpose of Study: In 1958, Cremer et al. determined the action spectrum (AS) for bilirubin (BR) photodestruction in human serum in vitro through direct spectrophotometric BR measurements. Others have also addressed this issue; however, questions remain about the most effective wavelength range for BR photodestruction as this relates to the efficacy of phototherapy (PT) for management of neonatal hyperbilirubinemia. We have reported an in vitro method for evaluating efficacy of PT devices through determination of t50%, (time to photodegrade 50% BR) for BR destruction in human serum albumin. This method was adapted for the present study. Our objective was to determine the AS for BR photodegradation to diazo-negative products, using light emitting diodes (LEDs) and band pass filters.

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Conclusions: The data show that BR photodestruction in vitro is greatest at wavelengths 500-10nm (turquoise), a wavelength longer than that most commonly used currently for PT (460±10nm). Further studies are needed to confirm these results in vivo.
continuous administration of anesthetic to avoid pain and discomfort. The contribution of anesthetics to molecular participants in organ injury in such preterm neonates is not known. Our preterm lamb model of neonatal CLD provides an opportunity to test the role of anesthetics on outcomes. Preterm lambs supported by MV develop lung and brain injury. These lambs require continuous administration of increasing dosage of anesthetic. On the other hand, preterm lambs that are not intubated but instead are supported by nasal HFV for 21d. This group was given the same amount of pentobarbital that is necessary for PT lambs supported by MV. Apoptosis (cleaved caspase 3) and proliferation (proliferating cell nuclear antigen, PCNA) were assessed by immunohistochemistry.

Summary of Results: The paired pentobarbital group received more pentobarbital daily (mg/Kg/d; p<0.05) than the nasal HFV group, and the same amount as the MV group. In the lung, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group. In the brain, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group.

Conclusions: Pentobarbital dosage did not change the parameters of lung and brain injury that we assessed. We speculate that other mechanisms associated with MV, such as acute lung injury, inflammation, oxygen toxicity, and/or lipid peroxidation, may contribute to poor outcomes in the lung and brain of preterm neonates who require prolonged MV.

304 A CASE OF ARTERIAL THROMBOEMBOLISM-CAused BY DISSEMINATED INTRAVASCULAR COAGULATION IN A NEONATE
Kim S, Oh S, Park S Soonchunhyang University, Bucheon, Republic of Korea.
Case Report: Newborn infants who are seriously ill are susceptible to case report: Soonchunhyang University, Bucheon, Republic of Korea. BY DISSEMINATED INTRA VASCULAR COAGULATION IN A CASE OF ARTERIAL THROMBOEMBOLISM-CAused BY DISSEMINATED INTRA VASCULAR COAGULATION IN A CASE OF ARTERIAL THROMBOEMBOLISM. Summary of Results: The paired pentobarbital group received more pentobarbital daily (mg/Kg/d; p<0.05) than the nasal HFV group, and the same amount as the MV group. In the lung, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group. In the brain, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group.

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Preterm (PT) lambs, treated with antenatal steroids and parameters of lung and brain injury. These lambs require less frequent and smaller dosing of anesthetic. We hypothesized that giving more anesthetic to preterm lambs supported nasal HFV will change parameters of lung and brain injury.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV or nasal HFV (n=4 each) for 21d. A third group of PT lambs (paired pentobarbital group) was supported by nasal HFV for 21d. This group was given the same amount of pentobarbital that is necessary for PT lambs supported by MV. Apoptosis (cleaved caspase 3) and proliferation (proliferating cell nuclear antigen, PCNA) were assessed by immunohistochemistry.

Summary of Results: The paired pentobarbital group received more pentobarbital daily (mg/Kg/d; p<0.05) than the nasal HFV group, and the same amount as the MV group. In the lung, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group. In the brain, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group.

Conclusions: Pentobarbital dosage did not change the parameters of lung and brain injury that we assessed. We speculate that other mechanisms associated with MV, such as acute lung injury, inflammation, oxygen toxicity, and/or lipid peroxidation, may contribute to poor outcomes in the lung and brain of preterm neonates who require prolonged MV.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and parameters of lung and brain injury. These lambs require less frequent and smaller dosing of anesthetic. We hypothesized that giving more anesthetic to preterm lambs supported nasal HFV will change parameters of lung and brain injury.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV or nasal HFV (n=4 each) for 21d. A third group of PT lambs (paired pentobarbital group) was supported by nasal HFV for 21d. This group was given the same amount of pentobarbital that is necessary for PT lambs supported by MV. Apoptosis (cleaved caspase 3) and proliferation (proliferating cell nuclear antigen, PCNA) were assessed by immunohistochemistry.

Summary of Results: The paired pentobarbital group received more pentobarbital daily (mg/Kg/d; p<0.05) than the nasal HFV group, and the same amount as the MV group. In the lung, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group. In the brain, neither cleaved caspase 3 nor PCNA protein abundance was affected compared to the nasal HFV group.

Conclusions: Pentobarbital dosage did not change the parameters of lung and brain injury that we assessed. We speculate that other mechanisms associated with MV, such as acute lung injury, inflammation, oxygen toxicity, and/or lipid peroxidation, may contribute to poor outcomes in the lung and brain of preterm neonates who require prolonged MV.

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Conclusions: Pentobarbital dosage did not change the parameters of lung and brain injury that we assessed. We speculate that other mechanisms associated with MV, such as acute lung injury, inflammation, oxygen toxicity, and/or lipid peroxidation, may contribute to poor outcomes in the lung and brain of preterm neonates who require prolonged MV.
[Table]. By immunoblot, active caspase-3 protein was not detected in squirrel kidneys but was increased in CI mouse kidneys. Apoptotic RTC did not increase after 48 hours of CI in squirrels vs. a significant increase in mice. To investigate the mechanism of this protection, we immunoblotted for X-linked inhibitor of apoptosis (XIAP). XIAP protein was found in squirrel kidneys exposed to CI, but was markedly reduced in mouse kidneys. To confirm the in vivo resistance to apoptosis, we treated squirrel and mouse RTC in culture with cisplatin, an agent known to cause apoptosis. In squirrel RTC exposed to 50 μmol cisplatin, there was: (a) < 1% TUNEL positive (apoptotic) RTCs (b) constitutively present XIAP protein (c) absent caspase-3 protein. In cisplatin-treated mouse RTC, there was: (a) > 50% TUNEL positive cells (b) reduced XIAP protein (c) increased caspase-3 protein.

**Conclusions:** 13-lined ground squirrel RTC are protected against apoptotic cell death induced by CI and also cisplatin. Future studies examining inhibition or over-expression of XIAP protein may provide insight into the intriguing protection of organs during hibernation.

# 307 IMPROVING DECEASED DONOR TRANSPLANTATION FOR HIGHLY-HLA SENSITIZED PATIENTS

**Jordan SC**, **Reinsmoen N**2,1, **Lai C**2,1, **Kahwaji JA**1, **Peng AA**1, **Villicana R**1, **Vo AA**1, **Cedars-Sinai Medical Center, Los Angeles, CA and 2 Cedars-Sinai Medical Center, Los Angeles, CA.

**Purpose of Study:** For broadly-HLA sensitized patients (HS), options for deceased donor (DD) transplantation are extremely limited. Data from UNOS transplantation on the UNOS waitlist who has a panel reactive antibody (PRA) > 50% T cells (or 30% B cells) and a positive donor specific T and/or B cell FCMX. In (80/108) HS DD recipients after desensitization. Forty two of 80 patients (80%) transplanted had a positive donor specific T and/or B cell FCMX. A total of 80 patients transplant recipients after desensitization. Forty two of 80 patients transplanted had a positive donor specific T and/or B cell FCMX. In this data set of 80 patients transplanted, we saw an AMR rate of 24%. Patient & graft survival were 90%/97% at 3 years. The 3 year patient survival of 97% compares to 78% for a large group of age and sex matched ESRD patients who remained on dialysis for 3 years. Thus, there is a life-extending benefit of transplanting HH patients. Analysis of infectious complications associated with desensitization in 171 HS patients was compared to 190 non-sensitized patients. Briefly, there were no significant differences noted in the rates of any infection or serious infections at 4 years.

**Conclusions:** Desensitization of HS patients awaiting deceased donor transplantation is effective in reducing DSAs to levels permissive for successful transplantation. The safety of this approach was also demonstrated.

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**308 THE EFFECTS OF ETHNICITY ON ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND KIDNEY FUNCTION IN PATIENTS WITH DIABETES:**

**Sinha SK**, **Nicholas SB**1,2, **Shaheen M**1, **Pan D**1 **Charles R. Drew University of Medicine and Science, Los Angeles, CA and 2 UCLA, Los Angeles, CA.

**Purpose of Study:** Studies show that ethnic differences alter the rate of progression of diabetes and diabetic nephropathy (DN) and that African Americans (AA) have a more rapid course than Whites. We postulated that elevated indicators of inflammation in AA may potentially explain this disparity possibly reflected by levels of the inflammatory marker C-reactive protein (CRP). We examined CRP and chronic kidney disease in different ethnic groups (AA, Hispanics and Whites) in data from the National Health and Nutrition Examination Surveys (NHANES) 1999-2008.

**Methods Used:** We analyzed data from 3203 adults aged ≥20 years who were told had type 2 diabetes or had fasting blood sugar ≥125 mg/dl. Descriptive statistics characterized the subjects. We use stratified analysis by race and ethnicity. C-reactive protein, eGFR and microalbuminuria were categorized using cut-points 0.5 mg/dl, 60 ml/min/1.73 m2 and 30 μg/mg, respectively. We performed logistic regression to test the relationship between CRP and renal function in AA, Whites and Hispanic adjusting for age, sex, body mass index (BMI), hypertension, hypercholesterolemia, hyperglycemia, cardiovascular disease. We present the data as adjusted odds ratio and 95% confidence interval (CI).

**Summary of Results:** The data (mean ± SD) indicate that CRP and urinary albumin were significantly higher in AA compared to Whites (0.81 ± 1.33 mg/dl, 335 ± 1388 μg/mL and 0.61 ± 1.20 mg/dl, 106 ± 546 μg/mL, respectively, p < 0.01). Estimated GFR was significantly higher in AA and Hispanic (81.18 ± 27.42 and 84.99 ± 25.15 ml/min/1.73 m2) compared to Whites (70.64 ± 20.76 ml/min/1.73 m2, p < 0.01). Multivariate logistic regression showed marginally significant association between CRP and urinary albumin (p = 0.06) in AA only. However, there was no association between CRP and eGFR in any ethnic group.

**Conclusions:** Concentration of CRP and urinary microalbumin is higher in AA compared to Whites and there is a marginally significant association between CRP and urinary albumin in AA. The results suggest that more complex inflammatory processes might explain the more rapid progression of type 2 DN in AA patients and should be further examined. Funded by: NIH/NCCR Accelerating Excellence in Translational Science grant #U54RR026138.

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**309 GLOMERULOSCLEROSIS PREDICTS RENAL FUNCTION FOLLOWING LIVER TRANSPLANTATION**

**Huskey J**, **Pichler R**, **Davis C** University of Washington, Seattle, WA.

**Purpose of Study:** To determine if certain histologic features of renal biopsies can provide guidance in determining whether simultaneous liver-kidney transplantation (SLK) versus liver transplant alone (LTA). We performed histologic review of 59 patients with ESLD and chronic kidney disease (CKD) defined as an eGFR < 50 ml/min/1.73m2 and/or proteinuria > 500 mg/24 hours. One pathologist reviewed each biopsy and classified each as having mild, moderate, or severe interstitial fibrosis. The degree of glomerulosclerosis was expressed as percentage of globally sclerosed glomeruli. Lupus for SLK was approved with > 40% global glomerulosclerosis, > 30% interstitial fibrosis, or dialysis dependence for > 2 months prior to liver transplantation.

**Summary of Results:** Membranoproliferative glomerulonephritis (23%) was the most common finding on renal biopsy, followed by IgA nephropathy (19%), and acute tubular injury (19%). The best histological predictor for post-transplant eGFR in the LTA group was the extent of glomerulosclerosis (p = 0.001). Based on biopsy criteria, kidney allocation was avoided in 70% of patients. Estimated GFR was similar between patients with SLK vs. LTA up to 1 year post-transplant (Figure 1).

**Conclusions:** Renal biopsy can be performed safely in these high risk patients and can elucidate the etiology of CKD in patients with ESLD. Findings on renal biopsy can help determine the likelihood of reversibility of...

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renal insufficiency after liver transplantation which has important implica-
tions in kidney allograft allocation.

Average Pre- and Post Liver Transplant eGFRs in patients who underwent
SLK versus LAT. Values are expressed as average +/- standard deviation.

310 SODIUM THIOSULFATE
Patel D, Burns E, Hall J University of Missouri-Kansas City, Kansas
City, MO.
Case Report: Case: A 28-year-old female with end-stage renal disease was
referred to dermatology for painful, violaceous plaques over the pre-tribia.
Clinical findings were consistent with calciphylaxis without necrosis. The
patient was started on sodium thiosulfate 25 g infusion three times weekly
post-dialysis, and she noted dramatic pain relief within days of initiating
treatment. Nearly 60% of plaques resolved after one month of therapy. After
shortly stopping treatment, the patient developed new plaques without ne-
crosis on her arm. She was restarted on sodium thiosulfate. After completing
5 months of continuous therapy, nearly all plaques had regressed.
Discussion: Calciphylaxis is a rare vasculopathy classically found in
end-stage renal disease patients. In 98% of all reported cases [1], calciphy-
laxis manifests as painful, subcutaneous nodules of infarction that progress to
non- or poorly healing ulcers. Sodium thiosulfate has been identified as an
effective treatment for necrotizing ulcers of calciphylaxis. To our knowledge,
sodium thiosulfate has never been reportedly experimented in non-ulcerating
calciphylaxis. In our experience, its use in plaque-only calciphylaxis has
proved highly effective for treating ulcer formation. Physicians should be
vigilant in identifying the plaque-only presentation of calciphylaxis and of-
fering intravenous sodium thiosulfate as treatment to avoid ulcer formation,
infections, sepsis, multi-organ failure, and mortality.

311 CASE REPORT: BILATERAL OBSTRUCTIVE URIC ACID
CALCULI IN A 7 YEAR OLD BOY ON THE COG 9952 REG B
PROTOCOL FOR TREATMENT OF LOW GRAD
ASTROCYTOMA
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Vancouver, BC, Canada and 2BC Childrens Hospital, Vancouver, BC,
Canada.
Purpose of Study: This is a case of a 7 year old boy diagnosed with right
thalamic pilocytic astrocytoma treated with the COG 9952 reg B protocol,
and who subsequently developed bilateral calculi resulting in acute kidney
failure. It is intended to highlight the need for investigation of the relation-
ship between chemotherapeutic agents and development of renal calculi. Low
grade astrocytomas (LGA) comprise the majority of brain cancers in children.
Treatment of LGAs in the pediatric population has advanced in recent years.
At present, surgery is the primary treatment of resectable LGA, with adjuvant
chemotherapy as indicated. There have been no reported cases of renal calculi
associated with treatment of astrocytoma.
Methods Used: A retrospective chart review was conducted.
Summary of Results: A 7 year old boy who presented with a six month
history of progressing focal neurological symptoms. Investigations included
neuroimaging, biopsy, and partial excision of a right thalamic pilocytic as-
trocytoma, WHO grade 1. Due to the rapidly progressing presentation and
residual tumor, chemotherapy was indicated and the COG 9952 reg B pro-
tocol was initiated. Specifically, the combination of chemotherapeutic agents
used for this boy included procarbazine, thioguanin, CCNU, and vincristine.
Approximately a week after initiating chemotherapy, he presented with anuria
secondary to bilateral obstructive calculi resulting in acute renal injury. Urine
analysis found increased amino acid levels suggestive of tubular dysfunction
due to chemotherapy. He was treated with the placement of bilateral ureteral
stents and allopurinol with the resolution of the obstructing calculi.
Conclusions: This patient had an isolated diagnosis of LGA. He had no
relevant past medical history, family history, or risk factors that would make
him vulnerable to the development of renal calculi. Although rare, bilaterally
obstructing calculi can cause anuria in both children and adults. This case
highlights the importance of urinary tract imaging to rule out obstruction as a
cause for anuria and renal failure in patients undergoing chemotherapy.

312 MATERNAL PROTEIN DEPRIVATION MEDIATED CHANGES
IN THE LIVER RENIN- ANGIOTENSIN SYSTEM
Wirawan S, Goyal R, Longo LD Loma Linda University School of Medicine,
Loma Linda, CA.
Purpose of Study: Maternal malnutrition during pregnancy is known to
cause diseases in the offspring. Importantly, antenatal maternal low protein
diet has been implicated in the genesis of hypertension in the offspring.
Moreover, the renin-angiotensin system is important in the regulation of long-
term blood pressure. Thus, we tested the hypothesis that maternal protein
derivation during pregnancy is associated with a change in liver renin
mRNA and protein expression.
Methods Used: We conducted studies on FVB/NJ mice and administered
control and 50% protein deprived diet during gestation. Tissues were col-
lected from the offspring at 3 and 32 weeks of age. We analyzed renin
promoter, mRNA, and protein levels by real-time PCR and western immu-
noblot analysis.
Summary of Results: In the liver, we observed a decrease in renin protein
expression in 3-week-old females from maternal protein deprived mice. We
also observed a significant increase in the renin protein expression in the liver
of 32-week-old females. No renin mRNA was detected in the liver. We also
were not able to amplify the renin promoter. However, we were able to

REFERENCES:
Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors,

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amplify the renin DNA after degrading the histones holding the DNA with a Proteinase K treatment.

Conclusions: We conclude that a maternal diet low in protein has the ability to affect Renin and the Renin-Angiotensin System. This consequently affects the development of hypertension in later life.

Pulmonary and Critical Care Concurrent Session
1:30 PM
Friday, January 27, 2012

313 COMPARISON OF TWO-RESCUER BAG-VALVE-MASK VENTILATION TECHNIQUES ON AN AIRWAY MANIKIN
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1University of New Mexico, Albuquerque, NM; 2University of New Mexico, Albuquerque, NM

Purpose of Study: Bag-valve-mask ventilation (BVMV) is used by medical practitioners of all levels in both hospital and pre-hospital settings. Two-person BVMV is the preferred approach to ventilating a patient when feasible. This study compared air leak equivalency, measured by differences in expiratory tidal volumes and peak airway pressures, between a standard "E-C" (EC) technique and an alternative "thener emanence" (TE) technique.

Methods Used: 65 EMT Basic students performed each technique on a manikin model while a ventilator delivered breaths and measured volumes and pressures in the circuit. After performing the two techniques providers were asked to score their preference for each technique on a brief 100 mm visual analog scale score sheet. Repeated measures and multivariate analysis of variance analysis were used to compare the two techniques over a 5 minute time period.

Summary of Results: Returned tidal volume measurements ranged from 0.441 L to 0.450 L for EC and from 0.439 L to 0.455 L for TE. Similarly peak airway pressure measurements ranged from 25.36 cmH2O to 25.47 cmH2O for EC and from 25.40 cmH2O to 25.51 cmH2O for TE. There was not a significant difference in returned tidal volume or peak airway pressure between the two groups. Additionally the difference in preference scores was 26 mm (95% CI 16 to 36, p < 0.001) in favor of the EC technique.

Conclusions: There was no significant difference in returned tidal volume or peak airway pressure between the two groups. In two-person BVMV the EC technique is preferred to the TE technique while sharing equivalent air in expiratory tidal volumes and peak airway pressures, between a standard "E-C" (EC) technique and an alternative "thener emanence" (TE) technique.

314 EFFECT OF ENDOTOXIC SHOCK AND ECMO ON REGIONAL BLOOD FLOW
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Purpose of Study: Endotoxin (ETX)-induced shock results in endogenous cardiovascular hormone compensatory systemic vasoconstriction. Recent studies have indicated that differential constriction of vascular beds may result in shifts in regional blood flow (RBF) to preserve perfusion of vital organs. Improving microcirculation to all organs is a therapeutic goal to improve survival outcomes. Venous-arterial ECMO is being explored as a treatment strategy for endotoxic shock; however, the effect of ECMO on RBF distribution is unknown.

Objective: To characterize RBF shifts with ETX-induced shock, and to determine whether ECMO can be effective in normalizing RBF distribution.

Methods Used: In anesthetized 8 kg piglets, shock was induced using E. coli ETX to achieve a 30 percent decrease in mean arterial pressure (MAP). Hemodynamic parameters were measured, and RBF was determined via the injection of colored microspheres at baseline and after established hypotension. Results of untreated endotoxic shock piglets (n = 10) were compared with that of controls (n = 7) and endotoxic shock piglets treated with ECMO for 2 hours (n = 6).

Summary of Results: ETX caused a dramatic decrease in MAP (84 ± 2 to 57 ± 2 mm Hg, p < 0.05) and cardiac output (CO, 174 ± 13 to 100 ± 8 ml/kg/min, p < 0.05). CO was unchanged from ETX levels when piglets were put on ECMO; however, ECMO improved stroke volume (SV) towards baseline (1.1 ± 0.1, 0.5 ± 0.1, 0.8 ± 0.2 ml/kg/beat, at baseline, ETX shock, and ECMO, respectively, p < 0.05). ECMO thus allowed heart rate to decrease from shock levels back to baseline levels (208 ± 18 to 142 ± 20 bpm, p < 0.05). RBF was not different across the three groups at baseline. In the ETX groups, blood flow was notably decreased to the pancreas, kidneys, liver, and spleen, but was maintained in the heart and brain. Changes to RBF distribution during endotoxic shock was not altered by ECMO.

Conclusions: ECMO was able to support CO by improving SV during endotoxic shock. ECMO was not able to restore RBF in piglets with endotoxic shock in areas with decreased perfusion. These findings suggest that ECMO has a role in decreasing cardiac work load in endotoxic shock, but does not alter RBF distribution. Additional therapies are needed to improve microcirculation in septic shock.

315 THE IMPACT OF RESPIRATORY VIRUSES ON ACUTE REJECTION AND ALLOGRAFT DYSFUNCTION IN LUNG TRANSPLANT RECIPIENTS
UCSF, San Francisco, CA

Purpose of Study: To assess the short-term effects of community acquired respiratory virus infection (CARV-I) on lung allograft function and acute rejection in lung transplant recipients (LTR).

Methods Used: We identified all LTR at our center diagnosed with CARV-I between June 2009 and May 2011 by either direct fluorescence antigen (DFA) testing of a respiratory specimen, or polymerase chain reaction testing of the same specimen if the DFA was negative. Results of routine spirometry and transbronchial biopsies performed before and approximately 1 month after CARV-I were extracted from a clinical database. Outcomes were: (1) change in allograft function defined by the change in FEV1 from the pre-CARV-I baseline value to the first measure 30 days or more after CARV-I, and (2) the incidence of biopsy-proven acute rejection (AR) (grade >A0) between 1-2 months after CARV-I. The incidence of AR in all other LTR (n = 526) without CARV-I over the same study period served as the referent. Further, outcomes were analyzed in 2 a priori subgroups: cases of rhinovirus (RV) infection, and cases of infection with any CARV other than rhinovirus. Change in FEV1 was analyzed with the paired t-test; proportions were compared with Fisher's exact test.

Summary of Results: 87 cases of CARV-I were identified. CARV-I was associated with a non-significant decline in allograft function (FEV1: 2.18 ± 0.82 L post-CARV-I vs 2.32 ± 0.71 L pre-CARV-I, p = 0.08). This decline was significant in the non-RV subgroup (2.06 ± 0.74 L vs 2.25 ± 0.74 L, p = 0.048), but not in the RV subgroup (2.27 ± 0.88 L vs 2.36 ± 0.69 L, p = 0.39). The incidence of AR following CARV-I was similar to the incidence of AR in the referent LTR cohort without CARV-I (8.9% vs 13.1%, p = 0.69). Within the CARV-I cohort, there was no difference in the incidence of post-viral AR between the RV and non-RV subgroups (7.1% versus 11.8%, p = 0.62).

Conclusions: Among LTR, infections with CARVs other than rhinovirus appear associated with a non-significant decline in allograft function that does not seem to be mediated through acute cellular rejection. Indeed, CARV-I does not appear to be associated with an increased incidence of acute rejection in the 1-2 month post-infection period.

316 EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON THE HYPOXIC VENTILATORY RESPONSE AND ACCLIMATIZATION TO CHRONIC HYPOXIA IN HUMANS
Ho B1, Ellis E1, Zarrndt R1, Hopkins S2, Powell F1,2 UCSD School of Medicine, San Diego, CA and 2UCSD School of Medicine, San Diego, CA.

Purpose of Study: Recent animal studies show that inflammatory processes contribute to respiratory chemoreflex plasticity during chronic hypoxia. Ibuprofen (a non-steroidal anti-inflammatory drug, NSAID) blocks the

Methods Used: To test this, we measured the isocapnic hypoxic ventilatory response (HVR) in 5 subjects at sea level and during two days at high altitude (3,800 m above sea level) using a randomized, double-blinded repeated measures protocol. Ibufrofen (400mg x 3 times/day) or placebo was administered over 48 hours at sea level and over 48 hours at 3,800 m. The HVR was measured after 24 and 48 hours of treatment (e.g. Ibufrofen) at sea level and 3,800 m. Subjects returned to sea level for at least one month before repeating the protocol with the other treatment (e.g. placebo).

Summary of Results: Results showed no significant difference in the HVR between placebo and ibuprofen treatments at sea level. With placebo, there was a significant increase in the HVR at altitude indicating normal ventilatory acclimatization. However, ibuprofen blocked the increase in HVR at altitude. Repeated measures ANOVA showed significant effects of drug and location on the HVR and a significant interaction between treatment and altitude.

Conclusions: The precise role of inflammatory signals in acclimatization to chronic hypoxia remains to be determined and the results may have implications for the treatment of acute mountain sickness at high altitude with NSAIDs.

317 INTRONIC CYTOCHROME P450 POLYMORPHISM AND PEDIATRIC ASTHMA CONTROL WITH INHALED FLUTICASONE PROPIONATE

Stockmann C 1, Ward R 1, Nkoy F 1, Moore C 1, Roberts J 1, Uchida D 1, Gariglio R 2, Leeder S 2, Yost G 1, Fassl B 1

1University of Utah, Salt Lake, UT and 2University of Utah, Salt Lake, UT

Purpose of Study: Inhaled glucocorticoids are the preferred preventative therapy for persistent asthma in children. Despite their widespread use, up to 40% of asthmatics fail to respond to therapy. Fluticasone propionate (FP) is a commonly used inhaled glucocorticoid which is metabolized by CYP3A4. A single nucleotide polymorphism (SNP) in intron 6, designated CYP3A4*22, is associated with decreased CYP3A4 activity. We hypothesize that the presence of this SNP is associated with improved asthma control in children treated with inhaled FP. Our objectives were to 1) determine the frequency of CYP3A4*22 (rs35599367, C>T), in children treated with FP for persistent asthma and 2) assess the relationship between CYP3A4 intron 6 genotype and asthma severity.

Methods Used: We enrolled asthmatic children 2-17 years of age. Saliva samples were collected and CYP3A4 genotyping was performed. A questionnaire based upon modified National Heart Lung and Blood Institute expert panel guidelines was used to assess the effectiveness of daily FP treatment to control persistent asthma. Composite asthma control scores were analyzed as a numeric variable ranging from 0 (well-controlled) to 15 (poorly-controlled). Multiple regression models were constructed to assess the association between CYP3A4*22 and composite asthma control scores.

Summary of Results: Among 324 children enrolled, 133 were treated with FP. Genotyping was performed upon 131 (98%). Of these, 12 (9%) children featured a CYP3A4*22 allele. Composite asthma control scores were analyzed as a numeric variable ranging from 0 (well-controlled) to 15 (poorly-controlled). Multiple regression models were constructed to assess the association between CYP3A4*22 and composite asthma control scores.

Conclusions: This study correlates pediatric asthma control by inhaled FP with the CYP3A4*22 allele. The presence of this SNP was significantly associated with improved asthma control in our study population. We speculate that decreased CYP3A4 activity may improve asthma control with inhaled FP by prolonging its anti-inflammatory effects.

318 RELATIONSHIP BETWEEN PULMONARY VASCULAR VOLUME AND LUNG STRUCTURE AND FUNCTION IN HUMANS

Levy SB 1, Wong EC 2, Wheatley CM 2, Cassuto NA 1, Daines CL 1, Gilbertson D 1, Snyder EM 2, Martinez FD 1, Morgan WP 1, University of Arizona, Tucson, AZ and University of Arizona, Tucson, AZ

Purpose of Study: The growth and morphogenesis of the airways is dependent on vascular growth and development. Vascular endothelial growth factor (VEGF), a protein stimulating the growth of new vessels, has been determined to play a critical role in both early lung morphogenesis and the emergence of the pulmonary vascular networks in utero. Inhibition of VEGF has been shown to attenuate airway morphogenesis. We sought to determine if lung blood volume (determined through CT-imaging of the pulmonary vessels) was related to airway structure and function in 40 healthy humans.

Methods Used: For this study, we recruited 40 subjects who were previously enrolled in the Tucson Children's Respiratory Study. Each subject underwent pulmonary function testing (forced vital capacity, fVC, forced expiratory volume at 1-second, FEF1, total lung capacity, TLC, vital capacity, VC, inspiratory capacity, IC, and residual volume, RV) before and 15 minutes after receiving a β-agonist (albuterol sulfate, 60 mcg per dose, administered via metered-dose inhaler) to ensure maximal bronchodilation. We determined the subjects’ lung volumes using a nitrogen washout. CT-imaging of the lungs was performed at TLC and end-expiratory lung volume (EELV). Volumes during scanning were ensured using a Jaeger Viasys system.

Summary of Results: Lung vessel volume (LVV) was higher at TLC when compared to EELV (158 ± 7 vs. 83 ± 3 ml, for TLC and EELV, respectively, p < 0.05). Lung vessel volume (LVV) was related to height (r = 0.62, p < 0.001) and height2 (r = 0.64, p < 0.001). As such, we corrected pulmonary vascular volume for H2 for all analyses. At TLC, LVV/H2 was related to percent predicted values for FVC, FEF1, TLC, VC, IC, and RV (r = 0.42, 0.37, 0.46, 0.45, 0.44, 0.33, p < 0.05 for each). There was no significant relationship between LVV/H2 and pulmonary function at EELV. There was a significant relationship between tracheal lumen diameter corrected for H2 and LVV/H2 at EELV, but not at TLC (r = 0.35, p < 0.05).

Conclusions: These results demonstrate that pulmonary vascular volume is important for lung structure and function, even in healthy adults.
there was no difference in colocalization among the treatments (p = 0.75). While there was no difference in overall colocalization, the subcellular location of these colocalized proteins within individual cells did change indicating CSC caused redistribution of Rho and GEF-H1. The colocalization of phosphorylated GEF-H1 and Rho was not anticipated and requires further investigation to determine the nature of this observed colocalization.

320 POOR SOCIAL SUPPORT PREDICTS BASELINE AND INCIDENT DEPRESSION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE
Zutler M1,2, Cisternas M3, Singer J1,2, Katz P5, Blanc P1,2,4 1University of California, San Francisco, San Francisco, CA; 2University of California, San Francisco, San Francisco, CA; 3MGC Data Services, Carlsbad, CA; 4University of California, San Francisco, San Francisco, CA and 4University of California, San Francisco, San Francisco, CA.

Purpose of Study: We sought to determine whether poorer social support is either associated with baseline depression or can predict the development of incident depression in a cohort of subjects with chronic obstructive pulmonary disease (COPD).

Methods Used: We analyzed data from a cohort study of adults with COPD (aged 40-65) followed longitudinally with telephone-administered structured interviews and physical assessment, including spirometry. At baseline, social support was measured using the Duke-UNC Functional Social Support Questionnaire (FSSQ), an eight-item, six-point Likert-scale instrument (range 8-48; higher scores reflect poorer perceived social support). We measured depressive symptoms at baseline and follow-up using the 15-item Geriatric Depression Scale (GDS) [range 0-15; depression defined by score >5]. Using baseline FSSQ data, we assessed the FSSQ based on internal consistency (Cronbach’s α). We tested the correlation between the FSSQ and baseline depression, and used logistic regression to test the FSSQ as a predictor of incident depression at follow-up, controlling for change in forced expiratory volume in one second percent predicted (FEV1%) pred.

Summary of Results: Among 594 subjects, the FSSQ (mean 13.5 ± 7.6) demonstrated high internal consistency (Cronbach’s α = 0.89) and was positively correlated with GDS (r = 0.43, p = 0.001). There were 156 subjects (26%) with depressive symptoms at baseline (GDS≥5). Excluding those with baseline depression, 35 of 438 (8%) developed incident depression by follow-up. Adjusting for the change in FEV1% pred, poorer FSSQ social support predicted incident depression (OR 1.11 per one point change; 95% CI 1.06-1.17; p < 0.0001).

Conclusions: In this cohort, the FSSQ by telephone administration demonstrates good internal consistency, correlates with baseline depression, and predicts incident depression. The FSSQ may be a tool for identifying persons with COPD at risk for depression.

321 ATTENUATED BETA ADRENERGIC RECEPTOR MEDIATED PULMONARY VASODILATION IN HIGH ALTITUDE TERM-FETAL SHEEP
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Purpose of Study: Beta adrenergic receptors (beta-AR) are important for pulmonary artery vasodilation. An increase in circulating catecholamines and increase in beta-AR density associated with birth is thought to contribute to the vasodilatory responses and the increase in lung blood flow in the newborn. Lambs born at high altitude have pulmonary hypertension and chronic hypoxia in newborn piglets attenuates the increase in beta-AR density and may contribute to pulmonary hypertension in newborns. Yet, in adult mice beta-AR pulmonary vasorelaxation is preserved following chronic hypoxia induced pulmonary hypertension. What is more, calcium and voltage activated K channels (KCa) are important to beta-AR mediated pulmonary vasorelaxation, suggesting KCa channel dysfunction may contribute to chronic hypoxia induced pulmonary hypertension in the newborn.

Methods Used: In this series of studies, we tested the hypothesis that beta-AR dependent pulmonary arterial vasorelaxation is dependent on KCa channels and that vasodilatory responses increase following birth in sheep that live at high altitude, a naturally occurring chronic hypoxic environment. The vasorelaxant ability of the selective beta-AR agonist isoproterenol (ISO; 1 micromolar) were examined in serotonin (1 - 5 micromolar) pre-constricted endothelium intact pulmonary arterial rings from term-fetal sheep, ~10 days old newborns, and in adult ewes that lived at 3,200 meters for <100 days.

Summary of Results: Serotonin-induced tension was reduced substantially by ISO (~ 35%) in pulmonary arteries from 3 newborn and 6 adult sheep, but the reduction was smaller (~15%) in arteries from 7 fetal sheep. Tetraethylammonium (1 mM), a KCa channel inhibitor attenuated the vasodilatory response by roughly one-half in newborns and adults, but did not affect vasodilation in fetuses.

Conclusions: Results suggest beta-adrenergic agonists may provide therapeutic benefit in newborn infants with pulmonary hypertension.

322 INTER- AND INTRA-OBSERVER VARIATION IN MEASURING PART-SOLID LUNG NODULES USING CONVENTIONAL AND SEMI-AUTOMATED METHODS
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Purpose of Study: Lung cancer remains the leading cause of cancer death for both women and men in the US. Majority of lung cancers are diagnosed at an advanced stage, with a dismal prognosis. Survival rates in lung cancer vary significantly by stage; with early diagnosis at stage IIA, the survival approach 70%, but with later diagnosis at stages IIA and IIIA, the survival rates fall dramatically to 34% and 13% respectively. These statistics underscore the importance of early detection of lung cancer. Low-dose CT scans is sensitive to detect lung nodules - potentially early stage cancer. However majority of these small nodules are benign. Growth of these small nodules is considered as surrogate biomarker for malignancy. But there are limitations in accurate measurement of small nodules. Our study involves part-solid nodules as the rate of malignancy for part-solid nodules is higher than for pure ground glass and solid nodules (62.5 %, 19% and 7% respectively). Recent studies have shown that the solid component of part-solid nodules represent the invasive part of adenoacarcinoma. It is believed that volumetric measurements of nodules are more accurate compared to longest diameter, which were supported by few small cases for solid-nodules. However there is no previous study evaluating the part-solid nodules. We believe there will be greater variability in the measurement of part-solid nodules. We will assess the inter- and intra-reader variability in measurement of part-solid nodules using manual measurement on PACS and a semi-automated volumetric method.

Methods Used: This retrospective study used low dose chest CT scans performed with similar technique from a lung cancer screening study. Five solid nodules and 5 part-solid nodule cases (one nodule/case) were chosen for this study. Three trained readers measured the nodules in a random fashion independently using two methods twice on the same day with preset breaks in the reading sessions. There were a total of 60 measurements per reader and 180 for the study. McKesson PACS system was used to manually measure the longest diameter (RECIST). Siemens Oncology Workstation was used for semi-automated measurements of volume and longest diameter using a single seed-based algorithm/threshold for the entire part-solid nodule and for the solid portion.

Summary of Results: -

Conclusions: -

323 PLACEMENT OF A FULLY COVERED, SELF-EXPANDING NITINOL AIRWAY STENT UNDER DIRECT FLEXIBLE BRONCHOSCOPIC VISUALIZATION
Poon C, Ismail H, Y oneda K UC Davis, Sacramento, CA.

Purpose of Study: Expandable airway stents are used to manage malignant and non-malignant airway obstruction. Traditional silicon stents do not allow ingrowth of tumor, airway epithelium or granulation tissue, are removable
and have a long track record of use. However, their use is limited by the requirement for placement with a rigid bronchoscope under general anesthesia. Expandable stents may be placed with a flexible bronchoscope under moderate sedation, potentially expanding the pool of physicians capable of performing airway stent placement, improving patient’s access to this procedure and reducing costs. The purpose of this study was to evaluate the safety and efficacy of placement of the AERO DV® airway stent using a German intubating airway, direct flexible bronchoscope visualization and moderate sedation, a technique that has not been previously described.

Methods Used: This is a single center, retrospective case series evaluating the efficacy of the placement of a unique self-expanding, fully covered, nitinol airway stent (MeritMedical Endotek AERO DV®). All cases using this stent placed using direct flexible bronchoscopic visualization were reviewed. Data points including patients’ age, sex, chest imaging reports, surgical pathology, complications, and operative bronchoscopy reports were compiled. An analysis of the advantages and disadvantages of this technique were then reviewed.

Summary of Results: Expandable stents can be placed effectively with a flexible bronchoscope under moderate sedation with minimal risks and reduced costs. Typically, precise placement of airway stents may be difficult and require flexible bronchoscopy airway measurements. Education and guidance for the use of fluoroscopy. A new design of the AERO was to allow placement under direct, flexible bronchoscopic visualization, potentially eliminating the need for fluoroscopy, rigid bronchoscopy and general anesthesia.

Conclusions: Use of the AERO DV® airway stent using a German intubating airway, direct flexible bronchoscope visualization and moderate sedation is an efficient means of managing both malignant and non-malignant airway obstruction.

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INTER-ALPHA INHIBITORY PROTEIN IN PEDIATRIC SEPSIS - ANALYSIS OF A CONTROL POPULATION
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Purpose of Study: This paper presents the results of statistical tests run against the control group of 60 patients recruited at the University of New Mexico Pediatric Emergency Department in an effort to characterize the population and uncover confounders or biases within the control data.

Methods Used: The power for this study was calculated using the two sample student t-test to be 42 patients in the control group. The levels of IαIP were compared with other clinical data collected from study participants and analyzed using Statgraphics Centurion XV version 15.2.06 (StatPoint, Inc., Herndon, VA). Tests were run to find significant associations or possible confounders within the dataset. A total of 70 statistical tests were run. Due to the large number of statistical tests run against the control data, the Bonferroni multicomparison correction was used to minimize the chance of a test having a false significant result (p = 7.14 x 10^-4).

Summary of Results: There were no significant associations found in the control data after p-value correction using the Bonferroni multicomparison correction. However, the Percent Variant Lymphocytes would have had a significant p-value (0.0025) when compared with the IαIP level if left uncorrected.

Conclusions: These data supports the idea that IαIP is an independent marker for pediatric sepsis. However, the mean level of IαIP in this population (270.5 mg/L) was lower than previous studies in neonates and adults (608 mg/L and 613 mg/L respectively), perhaps due to the use of a different assay. The uncorrected Percent Variant Lymphocytes p-value (0.0025) may be worth pursuing for future research. Now that the control population is characterized and no significant associations have been found, the next phase involves recruitment of septic pediatric patients and comparison of their levels of IαIP with the control population.

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CONTINUOUS INFUSION OF CROTALINE FAB ANTIVENOM FOR MANAGEMENT OF SEVERE MULTI-SYSTEM ENVENOMATION
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Case Report: 61 year old previously healthy female presents after a rattlesnake envenoming and multi-organ failure. She immediately developed acute encephalopathy and angioedema, and trachea was intubated. She also had diffuse fasciculation and rhabdomyolysis requiring neuromuscular blocking agents in conjunction with fentanyl and versed. Additionally she developed consumptive coagulopathy within hours of envenomation. Her fibrinogen was unmeasurable, platelet count was 39K, and partial thromboplastin and prothrombin time were elevated at 92 and 43 respectively. During the course of 7 days in the intensive care unit, she was given total of 37 vials of crotaline Fab antivenin. Majority of antivenin was administered in continuous infusion, 3-4vials/500ccNS/24hrs. Vecuronium was stopped on the 4th day of intensive care unit, and she was successfully liberated from mechanical ventilation on 5th day. In patients with severe coagulopathy, recurrence of coagulopathy after envenomation has been described; however the mechanism of recurrent coagulopathy is poorly understood. Furthermore optimal dosing to prevent recurrent coagulopathy has not been studied. We started a continuous crotaline fab antivenin infusion in an effort to prevent recrudescence of life threatening coagulopathy from venom effects. There are challenges to a continuous infusion of crotaline fab antivenin. The manufacturer package insert and prescribing information recommend to using within 4 hours. This is presumably due to labile nature of purified Fab binding fragments (Fab) derived from antibodies. Moreover, stability of crotaline Fab antivenin over 24 hours in room temperature is not known. Based on the manufacturer package insert, continuous infusion of crotaline Fab antivenin does not comply with the prescribing recommendation. Continuous infusion of 3-4 vials/24 hour crotaline Fab antivenins in a patient with severe rattlesnake envenoming may be appropriate to prevent recurrence of life threatening coagulopathy.
Adolescent Medicine and General Pediatrics
Concurrent Session
1:00 PM
Saturday, January 28, 2012

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ADVOCACY AT A NATIONAL LEVEL DURING RESIDENCY: A RESIDENT’S REFLECTIONS ON LESSONS LEARNED
Kar R¹, Weiss M², Yang S¹ ¹UCSF Fresno, Fresno, CA and ²Western University, Pomona, CA.
Purpose of Study: Advocacy projects during residency take time and effort. Few residents have the opportunity to work on projects that advocate on a national level. The purpose of this study is to describe a pediatric resident’s reflections on the challenges, successes, and lessons learned from her advocacy work at a national level that was completed during residency.
Methods Used: The American Academy of Pediatrics (AAP) supports a national annual collaborative forum at the conference where medical students, residents, and fellows in training (SOMSRT) can become involved with developing nationally supported resolutions. In 2011, AAP SOMSRT District IX proposed an idea to fund physical education by implementing a “junk food tax”, using tobacco tax laws as a model. The resolution went through many revisions, both locally and regionally. The final form: “sugar sweetened beverage tax to fund obesity prevention programs,” was presented at the AAP Annual Leadership Forum (ALF) in Chicago.
Summary of Results: The idea was voted as one of the top ten resolutions of SOMSRT 2011. It passed as a nationally supported resolution and is currently in the appropriations committee. One of the most important experiences for the pediatric resident was interfacing with her colleagues and mentors, and strengthening her own pedagogical skills via engagement in different forums. This resulted in a reification of her commitment to her field, and new forms of productivity, which will be reflected in her future practice. As the primary author, it is imperative to consistently be involved in this project, as it has the potential to take on a life of its own. The background writing and amendments occurred over months, with many un-credited co-authors. One lesson learned, is that it would be conducive to have a heightened level of scheduling transparency between project coordinators.
Conclusions: Advocacy is a worthwhile, educationally rich venture. Through this project, the resident developed invaluable networking and communication skills. Future directions include an examination of the scope of advocacy experiences in residency training programs and the impact of this type of experience on residents’ careers and practice of pediatrics.

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ATTITUDES OF PARENTS TOWARD CHILDHOOD VACCINATION IN THE UNDERSERVED POPULATION
Dinh U², Cho AK¹ ¹David Geffen School of Medicine at UCLA, Los Angeles, CA and ²Cedars Sinai Medical Center, Los Angeles, CA.
Purpose of Study: Amidst the growing anti-vaccination campaigns, this qualitative study aims to assess the attitudes of a unique population of parents toward childhood vaccination as well as their risk perception of disease and vaccination.
Methods Used: The accessibility of the Cedars-Sinai Medical Center’s Community Outreach Assistance for Children’s Health (C.O.A.C.H. for Kids and their families) mobile clinics in the greater Los Angeles area allows us to openly interview 50 parents from different underserved ethnic groups as they seek free comprehensive care for their uninsured and underinsured children.
Summary of Results: We hypothesize that the parents that selectively seek free preventive care for their children generally have positive attitudes toward childhood vaccination. Results show parents are largely accepting to childhood immunizations that are required for school entry; however, they are wary of recommended vaccines such as influenza. As opposed to American born parents, immigrant parents from Latin countries were least informed and least skeptical toward the vaccines that their children were getting.
Conclusions: The differences in knowledge about vaccination and the more critical attitudes of certain parents toward elective vaccines can emphasize the importance of parents’ perspectives when designing strategies to increase childhood vaccination among the underserved population. From a public health point of view, expanding awareness and coverage of under-immunized children can lead to prevention of potential outbreaks of diseases and improve overall health for society.

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PREDICTABILITY OF ABNORMAL ECGS IN THE PEDIATRIC POPULATION
Sandoval M¹, Whitefield J², Tennison M², Green A³ ¹Univ. School of Medicine, Albuquerque, NM, ²University of New Mexico, Albuquerque, NM and ³Children’s National Medical Center, Washington, DC.
Purpose of Study: ECGs in the pediatric population are obtained for many reasons. Amongst them are: syncope with palpitations, congenital heart disease, cyanosis, chest pain with any of the above, family history of sudden death, ALTE (acute life threatening event), thoracic trauma, Kawasaki disease, electrolyte abnormalities and toxic ingestions. While much has been written about the diagnostic approach to these, including ECGs as part of the workup, no published data are available regarding algorithms with indications for ECGs in the pediatric population. Data regarding the same for ECGs in the adult population are very inclusive, as abnormal ECGs are very common. This is not the case in pediatrics, as most ECGs obtained in pediatric emergency departments are normal. This is not the case in pediatrics, as most ECGs obtained in pediatric emergency departments are normal. We need to re-define our indications for obtaining ECGs through more specific algorithms.

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SWIMMERS MAY NOT FOCUS ON THEIR MOST INJURED BODY REGION DURING DRYLAND TRAINING
Hancock KJ¹, Brabek BJ¹, Drake S² ¹University of Washington, Seattle, WA and ²University of Arkansas State University, Jonesboro, AR.
Purpose of Study: The literature suggests that the majority of swimming injuries occur during practice sessions, with up to half occurring during dryland (out-of-pool) training. Most studies investigating the relation of swimming injuries to practice have focused on in-pool training and neglect dryland training. The present study aims to describe the current use of dryland training in swim programs and how dryland varies by the age of the swimmers.
Methods Used: This study was a cross-sectional online survey of randomly selected swim clubs throughout the United States. The survey focused on dryland training use, frequency, mode of exercise and exercise by body region in specific groups. Clubs were divided into the following age categories: 10 years and younger, 11-14 years, 15-18 years, collegiate athletes, and non-collegiate adults.
Summary of Results: The percentage of teams using any form of dryland training was 56% for ages 10 and under, 83% for 11-14-year-olds, 93% for 15-18-year-olds, 79% for collegiate, and 24% for non-collegiate adults. The most common training modality for all age categories except non-collegiate adults was body weight resistance exercises. Stretching was the second most common training modality for 10 years and younger, 11-14 year and, 15-18 years, and weight training was the second most common for collegiate swimmers. Non-college adult swimmers utilized weights followed by cardio training. The most common body region exercised during dryland training for all categories except non-collegiate adults was the spine/core followed by the back.
proximal legs. Non-college adult swimmers focused on the shoulder region followed by the spine.

**Conclusions:** Dryland training is being utilized in the majority of programs for all age categories except non-collegiate adults. Most age group swimmer programs utilized body weight and stretching exercises, while college and non-college adults utilized body weight and weight exercises. Although the shoulder is the most common injury site in swimming, it is only the third most emphasized region in dryland training. This finding warrants further investigation and may represent an opportunity to decrease shoulder injury rates through increased emphasis on the shoulder during dryland training.

**331** **SPORTS CONCUSSION EVALUATION AND MANAGEMENT IN WASHINGTON STATE HIGH SCHOOLS**

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**Purpose of Study:** Concussions are estimated to account for 8.9% of all high school sports injuries, with nearly 4 million sports and recreational concussions reported each year. Female and girls’ soccer players have the highest rates of concussions in high school athletics. Youth athletes are at great risk for serious health complications if they are not properly evaluated following a suspected concussion. This exploratory study attempts to gain a better understanding of concussion evaluation and management in Washington State high schools.

**Methods Used:** High school athletic directors were contacted and school district websites searched to obtain emails of varsity head football coaches, head soccer coaches and certified athletic trainers (ATCs). The final number of participants recruited for the study was: 161 football coaches, 125 girls’ soccer coaches and 170 ATCs. An anonymous online survey was sent to study participants. Survey questions were framed to explore concussion evaluation and management. Data analyses were conducted with SPSS software (version 19.0), using the Pearson Chi-Square statistic.

**Summary of Results:** In response to being asked who evaluates youth athletes for potential concussions in their school, 75 coaches (83.3%) indicated that coach(es) perform this role; in contrast, only 7% of ATC’s specified coaches as being responsible for evaluating potential concussions. ATCs used more tools than coaches to make return-to-play decisions, with 32.8% using the Sideline Concussion Evaluation Tool 2 (SCAT2). Chi-square analysis demonstrated a statistically significant relationship between school designation (urban vs. rural) and SCAT2 use. (χ² = 5.39; p = 0.02).

**Conclusions:** There is still much ambiguity around who evaluates suspected concussions in high school athletics. Youth athletes are at great risk for serious health complications if they are not properly evaluated following a suspected concussion. This exploratory study attempts to gain a better understanding of concussion evaluation and management in Washington State high schools.

**333** **WHITE MATTER INTEGRITY IN INSULA AND FORNIX IMPLICATED IN BULIMIA NERVOSA NERVOSA**

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**Purpose of Study:** This study investigated brain white matter (WM) functionality in bulimia nervosa (BN) in order to better characterize brain function in this disorder.

**Methods Used:** Twenty-one control women (CW, mean age 27 ± 7 years) and 19 women with BN (mean age 25 ± 5 years) underwent diffusion tensor imaging (DTI) of the brain to calculate fractional anisotropy (FA) and the apparent diffusion coefficient (ADC; reflecting WM cell damage). Additionally, these measures were correlated with behavioral data collected.

**Summary of Results:** Insula and fornix FA were significantly reduced in BN and FA values in those regions were negatively correlated with state and trait anxiety in CW but not BN. ADC values were increased in BN in the fornix, frontal WM regions, and the superior longitudinal fasciculus. BN ADC values were positively related to bulimia symptoms and adverse childhood events.

**Conclusions:** WM integrity is disturbed in BN, and fornix and insula WM axon abnormalities are particularly implicated in BN, as previously reported in anorexia nervosa. Bulimic behavior and adverse childhood life events seem to be directly related to WM cell break down in BN.

**334** **EXPLORING RISK FACTORS FOR STONE FORMATION AMONG RURAL UGANDAN CHILDREN**


**Purpose of Study:** Death from renal disease is common in young Ugandans and clean water is a rarity. During earlier work we identified urinary tract (UT) symptoms as common amongst a group of Ugandan children and observed poor oral intake of water. We hypothesised that poor oral intake would contribute to renal pathology (stones), and that providing access to clean water would increase voluntary fluid intake thus promoting better hydration and minimizing risks of stone formation.

**Methods Used:** Residents at a school/orphanage in Uganda were approached and following informed consent a history and physical exam were performed with special reference to UT signs & symptoms. On study Days 1 & 2 we obtained 1) baseline 1st AM urinalysis (Siemens Multistix 10SGC) and 2) the prior day’s dietary and fluid intake using a validated dietary report form modified to reflect local foods. This data was recollected on Days 3 & 4 following our intervention. The intervention consisted of offering one or more 500 cc bottles of water on Days 2 & 3 and offering encouragement “try to drink 2 bottles”.

**Summary of Results:** 36 males were enrolled (3 excluded). The mean age of the 33 subjects was 17.4 ± 4.0 (range 11-25) years. All drank at least 1 additional bottle/day, and daily fluid intake increased from a mean
of 931 ± 385 ml to 1551 ± 561 ml (p < 0.0001). Mean urine SG decreased from 1.026 ± 0.05 to 1.017 ± 0.06 (p < 0.0001) and mean pH increased from 5.8 ± 0.5 to 6.4 ± 0.4 (p < 0.0001). The incidence of urine pH<5 decreased from 23/70 to 1/70 from Days 1 & 2 to 3 & 4. Ancillary findings of hypertension (2/33) and ketonuria on days 1 & 2 (3/33) were also present. All cases of ketonuria resolved by Day 3 & 4.

Conclusions: In our small small interventional trial, provision of clean water appears to have produced a voluntary and marked increase in oral fluid intake with statistically significant reduction in urine SG and increase in urine pH; both known risk factors for urinary stone formation1. While we are unable to confidently state that this intervention has or would lead to improved long term health outcomes, provision of clean water is an established global health goal and would seem to be a simple way to reduce the risk of certain UT pathologies such as stones; hence warranting further study.

335 CASE REPORT: BILATERAL OBSTRICTIVE URIC ACID CALCULI IN A 7 YEAR OLD BOY ON THE COG 9952 REG B PROTOCOL FOR TREATMENT OF LOW GRADE ASTROCYTOMA
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Case Report: Purpose of Study: This is a case of a 7 year old boy diagnosed with right thalamic pilocytic astrocytoma treated with the COG 9952 reg B protocol, and who subsequently developed bilateral calculi resulting in acute kidney failure. It is intended to highlight the need for investigation of the relationship between chemotherapeutic agents and development of renal calculi. Low grade astrocytomas (LGA) comprise the majority of brain cancers in children. Treatment of LGAs in the pediatric population has advanced in recent years. At present, surgery is the primary treatment of resectable LGA, with adjuvant chemotherapy as indicated. There have been no reported cases of renal calculi associated with treatment of astrocytoma. Methods Used: A retrospective chart review was conducted. Summary of Results: A 7 year old boy who presented with a six month history of progressing focal neurological symptoms. Investigations included neuroimaging, biopsy, and partial excision of a right thalamic pilocytic astrocytoma, WHO grade 1. Due to the rapidly progressing presentation and residual tumor, chemotherapy was indicated and the COG 9952 reg B protocol was initiated. Specifically, the combination of chemotherapeutic agents used for this boy included procarbazine, thiouquin, CCNU, and vincristine. Approximately a week after initiating chemotherapy, he presented with anuria secondary to bilateral obstructive calculi resulting in acute renal injury. Urine analysis found increased amino acid levels suggestive of tubular dysfunction due to chemotherapy. He was treated with the placement of bilateral ureteral stents and allopurinol with the resolution of the obstructing calculi. Conclusions: This patient had an isolated diagnosis of LGA. He had no relevant past medical history, family history, or risk factors that would make him vulnerable to the development of renal calculi. Although rare, bilaterally obstructing calculi can cause anuria in both children and adults. This case highlights the importance of urinary tract imaging to rule out obstruction as a cause for anuria and renal failure in patients undergoing chemotherapy.

336 LEARN PEDIATRICS: EVALUATION OF A WEB-BASED RESOURCE FOR MEDICAL STUDENTS LEARNING PEDIATRIC CLINICAL SKILLS

Purpose of Study: Learn Pediatrics is a web-based resource created for medical students learning pediatric clinical skills. Evaluation may identify areas for improvement and guide future directions.

Methods Used: Evaluation of Learn Pediatrics utilizes website traffic statistics from Google Analytics. Data includes demographics of visitors, source of internet traffic, time spent on website, bounce rate, and number of pages visited over an 8 month period. Surveys for pre and post use of website were collected from medical students at our university prior to clerkship to measure students’ comfort levels of performing various pediatric physical exams. Medical students ranked preferred learning methods: small group teaching, didactic or lecture based, textbook descriptions, videos accessible via web-sites, and videos provided on CD ROMs. A numeric rating scale was used for evaluation.

Summary of Results: Over 8 months Learn Pediatrics reached a large audience spanning many countries since easily accessible via various search engines such as Google. Usage of the resource peaked during typical exam period of schools, suggesting students are utilizing it. Average visit time on website was 2 minutes, perhaps artificially low due to 70% bounce rate. Survey responses however, were positive. Students ranked small group teaching as the most preferred learning method, closely followed by videos accessible via online resource. Students were more comfortable at performing pediatric physical exams after visiting the website. Students reported layout of website as effective, information presented in the modules useful and easy to find. Respondents requested promotion of the resource earlier in medical studies. Visitors gave an average rating of 4.3/5 on a total of 27 rated content pages. 122 students completed the pre-user survey in class (80-90% of attendees); 11 students the post-user survey. Respondent discrepancy is largely due to the method of survey distribution. Pre-user survey was collected in class; post-user survey was done online. Timing of survey distribution was another factor: pre-user survey was released prior to the final exam; post-user survey after the exam.

Conclusions: Learn Pediatrics has been shown to be an effective multimedia resource for medical students learning pediatric clinical skills.

337 MEDICAL STUDENT INVOLVEMENT WITH LEARNPEDIATRICS.COM: AN EDUCATIONAL WEB-BASED RESOURCE

Purpose of Study: LearnPediatrics.com is an online resource dedicated to educating medical students about pediatric clinical skills. It relies on medical students for content and input. The motto of the website is By students for students. Medical students are responsible for creating written content, and encouraged to provide feedback. Students are also employed in coordinating and content-editing. The website is under the supervision of pediatric residents who ensure the validity and accuracy of the resource.

Methods Used: Opportunities exist for medical students to become involved with learnpediatrics.com: writing articles, providing feedback, as video production editor, and as a coordinator. Articles on the website are written by medical students-interested students may volunteer to write on a particular topic. Instructions and guidelines are provided for reference. The article is reviewed by a pediatric resident; the student makes needed changes and the article is published on the website. Online users of the website are encouraged to evaluate the effectiveness of the resource by leaving comments or completing a post-user survey. Medical students assist in video production and project coordination and editing raw footage for a clinical skills exam. Videos are then reviewed and approved by the pediatric resident and then posted to the website by media services. The project student coordinator was responsible for recruiting medical students to write articles, to raise awareness about the website and be part of the planning committee on how to evaluate and promote the resource.

Summary of Results: Online users of the website evaluated the effectiveness of the resource by leaving comments and/or by completing a post-user survey.

Conclusions: LearnPediatrics.com promotes a novel approach in medical education while providing medical students with an opportunity to create content and provide input for their learning resource. By writing articles, students are encouraged to explore important medical topics in greater detail with an opportunity for publication. Future directions include raising greater awareness among medical students in our university to increase student involvement and use of the website.

338 PATTERNS AND PREDICTORS OF MEDICATION USE IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER
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Purpose of Study: The aim of this study was to examine patterns of psychotropic medication use in children with autism spectrum disorder (ASD; n = 75) in a longitudinal study conducted from age 3-4 years to age 15 years. We additionally examined how family characteristics (parenting stress and socioeconomic status) at age 3-4 years, and child characteristics (cognitive functioning and severity of behavioral symptoms) at age 3-4 years were related to medication use in children and adolescents with ASD from age 3 to 15.

Methods Used: Children met diagnostic criteria for ASD and were enrolled in the longitudinal study at age 3-4. Family and child characteristics were collected through clinician assessment and parent questionnaire packets at ages 3-4, 6, 9, and 15 using Holroyd’s Questionnaire on Resources and Stress, Hollingshead Four Factor Index of Social Status, Mullen Scales of Early Learning and the Aberrant Behavior Checklist. Telephone interviews were conducted every 6 months to collect monthly medication history from age 3 to 15.

Summary of Results: A total of 57% of the sample used at least one medication between ages 3 and 15. The proportion of individuals taking multiple medications simultaneously (polypharmacy) increased as children began grade school from 1.4% at age 3 to 20% at age 7. Stimulants (41.3%) were the most commonly used class of medication, followed by anti-depressants (34.7%) and antipsychotics (28.0%). In a hierarchical linear model, family characteristics at age 3-4 years did not predict the number of medications used over time. Similarly, child characteristics at age 3-4 years did not predict medication use over time.

Conclusions: These findings suggest that children and adolescents with ASD are frequently treated with psychotropic medications, and polypharmacy is common. However, family and child characteristics in the preschool years did not predict future medication use. Thus, further investigation of factors predicting medication use is needed.

339 PARENTAL ATTITUDES TOWARDS CIRCUMCISION
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Purpose of Study: The American Academy of Pediatrics states that potential medical benefits of male circumcision exist, however, there is not sufficient data to recommend routine neonatal circumcision. Despite current recommendations, parents have continued to make the decision to circumcise their sons. The purpose of this study is to explore parental reasoning for circumcising or not circumcising their sons by surveying parents in the UNM newborn nursery immediately after they have made the decision. The survey options include health reasons, religious practice, so child looks like father, so child looks like peers, and so child looks like brothers among other options. The study will also explore cultural and socioeconomic factors that may contribute to the parents’ decision. Lastly, the study will explore where the families at the UNM Newborn Nursery have a diverse cultural and socioeconomic background and will be a great place to explore parental attitudes towards circumcision.

Methods Used: Parents will be consented to participate in this study after they inform hospital staff of their decision to circumcise or not circumcise their son. A survey created by Robert Adler et al will be given to parents who inform hospital staff of their decision to circumcise or not circumcise their son. The families at the UNM Newborn Nursery have a diverse cultural and socioeconomic background and will be a great place to explore parental attitudes towards circumcision.

Results will be analyzed mainly using descriptive statistics. For forced choice items, a 2-way contingency table analysis using cross-tabs will be used. Results pending data collection, which will begin October 2011.

Conclusions: Conclusions pending results, which will be available by January 2012.

340 MATERNAL CHILD HEALTH NEEDS ASSESSMENT IN DOLPA DISTRICT, WESTERN NEPAL
Westmoreland K, Dickerson T, Nkoy F, Fassl B University of Utah, Salt Lake City, UT.

Purpose of Study: Dolpa is one of the most remote and least developed districts of Nepal. No public health data regarding maternal and infant mortality, health infrastructure, maternal-child health (MCH) practices exists. Prior to implementing a MCH program, more information is needed. Objectives are to 1. Estimate maternal and neonatal mortality in recently delivered women (RDW), 2. Describe existing health infrastructure and gaps in MCH care delivery and 3. Describe community and health provider attitudes and perceptions of MCH.

Methods Used: We conducted a MCH rapid assessment survey following standard procedures. Using a standardized health facility evaluation instrument, we surveyed 1 district hospital (DH), 5 health posts (HP), and 3 birthing centers (BC). We conducted a knowledge attitude practice survey of local government leaders (n=5), health workers (n=15) and traditional healers (n=2). A focus group survey of 23 community members was used to assess perceptions and attitudes towards MCH. Interviews of 87 RDW were completed to determine birth outcomes.

Summary of Results: The survey of 87 births in RDW revealed 7 maternal (8%), 16 neonatal (18%) and 29 infant (33%) deaths. All deaths occurred at home without a skilled birth attendant (SBA). Health infrastructure in Dolpa includes: 1 DH, 23 HP, 3 BC, 2 Tibetan hospitals, and community based lay providers (CBLP) in every village. The DH has 1 physician who has no obstetric or pediatric training, 1 nurse, and 2 SBA. The DH lacks equipment and trained personnel to provide basic emergency obstetric care or newborn resuscitation. 9/23 HP are not operational; 1/23 are often closed and have no SBA. Only 1 of 3 BC is operational and has 2 SBA. Referral to the DH is complicated by late recognition of need, rugged terrain, and lack of roads. Tibetan hospitals do not provide MCH care and CBLP have not been trained to assist in deliveries or neonatal care. Community members, health professionals, political and religious stakeholders are aware of high morbidity and mortality of women and infants and strongly support implementation of a MCH program.

Conclusions: Dolpa lacks basic health infrastructure, trained personnel, equipment and a functional referral system to provide adequate MCH care. Implementation of a comprehensive program to improve infant and maternal health is highly needed.

Endocrinology and Metabolism III Concurrent Session
1:15 PM
Saturday, January 28, 2012

341 REGULATION OF MYOGENIC DIFFERENTIATION AND CELL PROLIFERATION IN MUSCLE SATELLITE CELLS BY FOLLISTATIN
Braga M1, Bhasin S2, Jasuja R2, Pervin S1,3, Singh R1,3 1Charles Drew University, Los Angeles, CA; 2Boston Medical Center, Boston, MA and 3David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Testosterone (T) administration is associated with increased satellite cell number and muscle hypertrophy. We have previously identified follistatin (Fst) as a novel T-induced protein that mediates the pro-myogenic effects of T in multipotent mesenchymal stem cells. The goal of this study is to investigate the role of Fst during myogenic and proliferative action of T, and identify key molecular targets involved during the process.

Methods Used: Primary cultures of satellite cells were isolated from levator ani (LA) and gastrocnemius (gastroc) muscles from C57BL6j and Fst-over expressing F66 male mice. Cells were allowed to differentiate under myogenic conditions or under growth conditions for proliferation assay after various treatments. Protein expression was analyzed by quantitative IHC, and western blot. QIG-PCR and PCR Array analysis was used to analyze gene expression levels. Small inhibitory RNA (siRNA) was used to down-regulate Fst expression in LA satellite cells.

Summary of Results: Basal levels of androgen receptor (AR), Fst and Pax7 were significantly higher in LA compared to the gastroc cells. T treatment up regulated Fst gene and protein expression; and induced myogenic differentiation in both cell types, which was blunted in presence anti-Fst antibody. Fst siRNA significantly inhibited myogenic differentiation and blocked T-induced myogenesis. TGF-β-induced inhibition of myogenic differentiation and proliferation in both LA and gastroc satellite cells was antagonized by T or Fst treatment. Several genes involved in TGF-β pathway were significantly inhibited in Fst over expressing F66 LA or T-treated LA
satellite cells. T-induced inhibition of these genes in TGF-β pathway was significantly abrogated in LA satellite cells treated with Fst siRNA.

Conclusions: In satellite cells of different muscles, is a critical mediator of T-induced myogenic differentiation and proliferation. The pro-myogenic and proliferative effects of T and Fst in satellite cells are mediated by inhibition of TGF-β signaling in both muscle types. However, a clear mechanistic difference based on the abundance of AR levels was not identified between LA and gastroc cells after T or Fst treatment.

**342 ACCURATE MEASUREMENT OF THYROGLOBULIN IN SERUM IN PRESENCE OF ANTI-THYROGLOBULIN AUTOANTIBODIES**

Kushnir MM1,2, Rockwood AL1,2, Roberts WL1,2, Hoofnagle AN3, Meikle A1,2,1ABUP Laboratories, Salt Lake City, UT; 2University of Utah, Salt Lake City, UT; and 3University of Washington, Seattle, WA.

**Purpose of Study:** Quantitative measurement of thyroglobulin (Tg) plays an important role in the follow-up of patients treated for thyroid cancer. Circulating Tg autoantibodies (Tg-AAB) can mask epitopes and cause false negative immunoassay (IA) results. The prevalence of Tg-AAB in healthy individuals is approximately 10%, and up to 40% in patients with differentiated thyroid carcinoma. As a result, commercially available Tg IAs are unreliable for accurately measuring Tg in many patients. In addition, there is poor agreement among Tg IAs. We developed a LC-MS/MS method that overcomes the drawbacks of commercial IAs and allows accurate measurement of Tg in the presence of Tg-AAB.

**Methods Used:** Limit of quantitation of Tg in serum was 1 ng/mL (1.5 fmol/mL of the Tg dimer). The mean value of imprecision of triplicate measurements of Tg in serum samples (n=7, concentrations range 4 to 100 ng/mL) was 5.2%. Comparison with Beckman Coulter Dxl 800 IA using serum samples free of Tg-AAB showed good agreement between the methods. LC-MS/MS = 0.89*IA + 2.9, r=0.992, Sy/x = 5.1. In an experiment with Tg spiked into a set of patient samples positive for Tg-AAB, Tg recovery was 94% of the expected values. In a set of Tg-AAB positive samples tested negative for Tg using IA, concentrations determined using LC-MS/MS method were at or above 1 ng/mL in 29% of samples.

**Conclusions:** This method allows quantification of femtomolar quantities of Tg in the presence of Tg-AAB. Proteolytic digestion of serum samples releases Tg peptide targeted in the method and removes (by digestion) endogenous Tg-AAB that can interfere with traditional IA.

**343 CONGENITAL HYPOTHYROIDISM CAUSED BY EXCESS MATERNAL IODINE INGESTION: A CASE SERIES**

Connelly K1, Boston B1, Pearce E2, Sesser D3, Lafranchi S1,2 OHSU, Portland, OR; 2Boston University School of Medicine, Boston, MA and 3State of Oregon Public Health Laboratory, Portland, OR.

**Case Report:** Congenital hypothyroidism (CH), detected by newborn screening programs, is most commonly caused by thyroid dysgenesis or dysmorphogenesis. The recently reported increase in incidence suggests that other etiologies may be emerging, including milder and transient causes. This is a report of 3 newborns detected with CH, with evidence supporting excess maternal iodine ingestion as the etiology (see table, below). Novel testing included measurement of serum iodine extracted from newborn screening (NBS) filter paper specimens. Case 1 is a term infant whose mother took iodoral tablets containing 12.5 mg of iodine daily throughout pregnancy. Cases 2 and 3 are twins whose mother took iodoral 12.5 mg daily throughout pregnancy and had elevated serum and urine iodine levels. These infants also had elevated urinary iodine. Case 1 had a normal urinary iodine level after mother discontinued supplemental iodine, but previously breast milk iodine was elevated at 3,228 μg/L. Neonatal iodine exposure was confirmed in all three cases by measuring iodine in serum isolated from newborn screen filter paper samples. Serum iodine levels of our cases were 10 times above the mean level of 10 control samples. In cases 2 and 3, levothyroxine was discontinued after excess maternal iodine ingestion was discovered. Thyroid function tests two weeks later were normal; the hypothyroidism appears to have been transient in these two cases. The infant of case 1 remains on levothyroxine at 27 months of age. These case reports serve to call attention to a potential increase in the use of nutritional supplements containing iodine in amounts 50 fold higher than RDA during pregnancy. This etiology of CH may be missed if not investigated by history and confirmed by laboratory testing. Excess maternal iodine may be part of the explanation for the reported increasing incidence of CH.

**344 USE OF LOW-DOSE ACTH STIMULATION TO DETECT ACTH INSUFFICIENCY IN A PEDIATRIC POPULATION: IDENTIFYING IDEAL CORTISOL COLLECTION TIMES**

Ramirez VA1,2, Kinman R1,2 1UCSF Fresno, Fresno, CA and 2Children’s Hospital Central California, Madera, CA.

**Purpose of Study:** ACTH insufficiency is a life-threatening condition; however, testing for this diagnosis remains problematic. Although the insulin tolerance test is the gold standard to assess the hypothalamic-pituitary-adrenal (HPA) axis, risks include hypoglycemia and death, and it is thus contraindicated in infants and not recommended as a routine diagnostic test in children. Alternative methods to test the HPA axis include low-dose (LDT, 1 mcg) and standard-dose (SDT, 250 mcg) ACTH stimulation tests. Although LDT is more sensitive than SDT in detecting subtle states of adrenal insufficiency, LDT can yield false positive results leading to life-changing implications for the patient. Problems inherent with LDT include the very low dose used and individual variations in timing of the cortisol peak after stimulation. This study was thus performed to determine if addition of 2 extra sampling times would help eliminate false positive results and thus unnecessary treatment.

**Methods Used:** All patients undergoing low-dose ACTH stimulation testing in the Children’s Hospital Central California Endocrine Clinic were included. 102 subjects (0.5 to 20 years old) underwent 114 tests over 20 months. 1 mcg Cortrosyn (ACTH) was diluted by the pharmacy and given intravenously followed by 5-10 ml of saline. Cortisol levels were collected at baseline, and 20, 30, 40, and 60 minutes following Cortrosyn administration.

**Summary of Results:** 26 patients (23%) were diagnosed with ACTH insufficiency as a result of the test. Although 50% of females and 35% of males obtained peak cortisol levels 40 min after ACTH administration, only 3 patients (2.6%) would have had a false positive test without the addition of 20 and 40 min sampling times.

**Conclusions:** Adding 20 and 40 min sampling times to a low-dose ACTH stimulation test identified a 2.6% false positive rate. Although this rate is small, these additional time points should be considered to avoid unnecessary treatment. However, attention also needs to be paid to other factors that can result in a false positive diagnosis, including ensuring a fasting study, early morning testing, and pharmacist-assisted dilution of the ACTH dose with a normal saline bolus immediately following ACTH injection to ensure complete administration of dose.

**345 THE USE OF 17-α-HYDROXYPROGESTERONE TO 11-DEOXYCORTISOL RATIO IN NEWBORN SCREENING OF CONGENITAL ADRENAL HYPERPLASIA**

Hicks RA, Ferreira BF, Mao CS, Vee JK, Lee W Harbor-UCLA Medical Center, Torrance CA.

**Purpose of Study:** In newborn screening, an elevated 17-α-hydroxyprogesterone (17-α-OHP) level is used for the identification of neonates at risk for the diagnosis of congenital adrenal hyperplasia (CAH). In order to reduce the number of false positive tests, in California a second tier test is performed using the ratio of 17-α-OHP plus androstenedione divided by cortisol (ratio > 1 is a positive result). The purpose of this retrospective review of a group of infants with positive screening for CAH is to evaluate

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**Table:**

<table>
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<tr>
<th>Case</th>
<th>Age (NBS)</th>
<th>T4 (μg/dL)</th>
<th>TSII (ml/L)</th>
<th>Age (serum)</th>
<th>Free T4 (μg/dL)</th>
<th>TSII (ml/L)</th>
<th>Age (urine)</th>
<th>Urinary iodine (μg/L)</th>
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<tbody>
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<td>1</td>
<td>24</td>
<td>4.24</td>
<td>10.28</td>
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<td>FkA</td>
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<td>5.11</td>
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<td>8</td>
<td>0.5</td>
<td>419.51</td>
<td>FkA</td>
<td>10.474</td>
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<td>QNS</td>
<td>217.122</td>
<td>FkA</td>
<td>695</td>
</tr>
</tbody>
</table>

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whether the ratio of 17α-OHP to 11-deoxycorticosterone, a direct precursor-to-product ratio, can distinguish neonates with 21-hydroxylase deficiency from those without CAH as well as the current 2nd tier test.

Methods Used: Laboratory results were reviewed on all neonates referred to Harbor-UCLA Pediatric Endocrine Center for elevated 17α-OHP levels on the California Newborn Screening Program between April 2006 and August 2011. The ratio of 17α-OHP to 11-deoxycorticosterone was calculated for all neonates with both results available. A one-tailed t-test with unequal variances was performed, comparing the mean ratios for neonates identified as having CAH (N = 5). A subgroup analysis was also performed comparing the mean ratios for neonates testing positive on the 2nd-tier test and identified as having no disorder (N = 7), to the mean ratios for neonates identified as having CAH (N = 31). A summary analysis was performed comparing the mean ratios for neonates identified as having CAH, no disorder (N = 7), to the mean ratios for neonates identified as having CAH.

Summary of Results: The mean ratio for neonates with CAH was significantly increased when compared to neonates with no disorder (35.8 ± 12.44 versus 1.52 ± 0.18, p < 0.05), and when compared to neonates with 2nd tier positive testing, but no disorder (1.26 ± 0.31, p < 0.05).

Conclusions: These results suggest that the ratio of 17α-OHP to 11-deoxycorticosterone may reliably separate neonates with CAH due to 21-hydroxylase deficiency from those without CAH than the currently used 2nd tier test. Whether the ratio of 17α-OHP to 11-deoxycorticosterone would be as sensitive and specific as the current 2nd tier test remains to be evaluated across a larger sample population.

### 346

**ROLE OF GLYCEMIA IN INSULIN SENSITIVITY IN ADOLESCENTS WITH TYPE 1 AND TYPE 2 DIABETES**

Alam S1, West A1, Downey M1, Forster-Harwood J1, Reusch JE1, Nadeau KJ1, University of Colorado Denver, Aurora, CO and 1Eastern Virginia Medical School, Norfolk, VA.

**Purpose of Study:** Interest in the role of insulin resistance (IR) in type 1 diabetes (T1D) and its potential mechanisms is increasing, due to its correlation with cardiovascular disease in type 2 diabetes (T2D). Using a hyperinsulinemic euglycemic clamp, we found significant IR in T1D youth relative to BMI-matched, nondiabetic controls. The IR was unrelated to acute fasting glucose or Hba1c, suggesting IR in T1D youth was unrelated to glycemia. We then assessed more detailed measures of glycemia in relation to IR in adolescents with T1D and T2D using continuous glucose monitoring (CGMS).

**Methods Used:** 15 T2D (BMI 33 kg/m2; duration 32 mos) and 23 T1D (BMI 22 kg/m2; duration 66 mos) sedentary 12–19 year olds had 72 hours of CGMS while on a weight maintenance diet (7 kcal/kg; 55% CHO, 30% fat, 15% protein). Subjects then underwent a fasting 80mU/m2/min hyperinsulinemic euglycemic clamp to assess IR as determined by the glucose disposal rate, normalized to fat free mass from DEXA scan. Using linear regression analysis, potential confounders (duration, pubertal stage, BMI, % of CGMS in daytime) remained in the final model if they significantly impacted IR.

**Summary of Results:** IR correlated significantly with fasting glucose and Hba1c in T2D youth, while IR was significantly negatively associated with % CGMS time over 250 mg/dL in T1D youth. While hyperglycemia predicted IR in the T2D cohort, T1D youth with CGM values in the highest range were the least IR, implying a unique mechanism of IR in T1D. Potential explanations include: peripheral insulin delivery of T1D may worsen IR, thus under-insulization may improve IR; hyperglycemic T1D subjects may have been acutely in negative energy balance, decreasing IR; or hypoglycemia, seen more in T1D, may worsen IR. Further research is required to determine methods to improve IR in T1D.

**Workplace**

<table>
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<tr>
<th>Workplace</th>
<th>Number of Participants</th>
<th>Hba1c</th>
<th>% with Current DM</th>
<th>% with 5.5–6.0% Hba1c</th>
<th>% with 5.5–6.0% Hba1c</th>
<th>Age &amp; Correlation with Hba1c %</th>
<th>% with Current DM</th>
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</thead>
<tbody>
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<td>5.7±0.1</td>
<td>9.8</td>
<td>39±5.6±1.0</td>
<td>52±5.6±1.0</td>
<td>42±10±1.0</td>
<td>42±10±1.0</td>
</tr>
<tr>
<td>Motor Sports</td>
<td>181</td>
<td>5.7±0.9</td>
<td>5.0</td>
<td>36±5.6±1.0</td>
<td>36±11±1.0</td>
<td>46±5.6±1.0</td>
<td>46±5.6±1.0</td>
</tr>
<tr>
<td>Solvent Package</td>
<td>128</td>
<td>5.8±0.1</td>
<td>10.9</td>
<td>35±5.7±1.0</td>
<td>50±5.7±1.0</td>
<td>50±5.7±1.0</td>
<td>50±5.7±1.0</td>
</tr>
</tbody>
</table>

### 347

**HOW SWEET IT IS: GLYCATED HEMOGLOBIN IN THREE GROUPS OF WORKERS**

Raymond LW1, Pankowski J2, Sensenbrenner K2, Shillitoe H1, Univ of North Carolina, Chapel Hill, Chapel Hill, NC and 2Carolinas HealthCare System, Charlotte, NC.

**Purpose of Study:** Glycated hemoglobin (Hba1c) is a standard of care to assess glycemic control, but its use as a prospective marker for the development of diabetes (DM) is controversial. Zhang et al. (Diabetes Care, 2010) reviewed 16 studies on the use of Hba1c to estimate the likelihood of future diabetes (DM), reporting that values of 5.5 to 6.0% were associated with a 5-year likelihood of DM from 9 to 25%. The likelihood increased to 50% as Hba1c approached 6.5%. It is not known if these estimates apply to working populations, nor if counseling in the workplace can reduce the chance of developing DM. We therefore measured Hba1c in healthy workers in 3 industries. We also wished to establish baselines for future comparisons.

**Methods Used:** Hba1c was determined in venous blood of non-fasting workers by ion-exchange high-performance liquid chromatography as part of employer-provided wellness programs. Descriptive statistics were calculated using commercial software (Microsoft Excel).

**Summary of Results:** Workers in a municipality (N = 291), a motor sports firm (N = 181) and a solvent package (N = 128) had similar demographics and mean values of Hba1c (Table). Overall, the 5-year likelihood of DM was in the range of 25 to 50%. Current DM was suspected in 7% of workers. Linear correlation coefficients of Hba1c with age and girth were modest but significant (p < 0.01), being higher for girth than age.

**Conclusions:** Hba1c levels suggest a 5-year likelihood of DM in a substantial fraction of current workers. It remains to be seen whether counseling can favorably affect this likelihood.

### 348

**GESTATIONAL DIABETES AWARENESS IN A HIGH-RISK GROUP: REACHING HISPANIC WOMEN IN BELLINGHAM, WA**

Piazza A1, University of Washington School of Medicine, Seattle, WA.

**Purpose of Study:** Gestational diabetes mellitus (GDM) affects Hispanic women at a rate nearly twice higher than non-Hispanic white women. Sea Mar Community Health Center in Bellingham, WA is an underserved primary care clinic with a patient panel that is 40% Latino. The health consequences of GDM can be managed with early diagnosis and proper control; both of which are accessible at Sea Mar, but these services are underutilized by high-risk Hispanic women in the community. The purpose of this project was to decrease the morbidity and mortality of GDM by creating culturally appropriate GDM awareness materials specifically targeted to Hispanic women.

**Methods Used:** Discussions with Sea Mar medical providers, diabetes education specialists, and a nutritionist were used to identify a specific health need in the community. A literature review was performed to examine the correlation between GDM and Hispanic women. Currently available GDM resources, educational materials, and major contributors to underutilization were identified. A Spanish-language pamphlet was designed based on evidence-based approaches to cross-cultural health education and distributed to clinical providers, community leaders, and local hubs where Hispanic women might come across it, and the information presented at a local health fair.

**Summary of Results:** The material was presented at a Sea Mar health fair at a farm labor camp. 109 residents of a farm labor camp attended and had

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their blood glucose measured. The pamphlet was distributed to women and all the pregnant women (3) were given individual consultations and referred to the diabetes self-management specialist. Healthcare providers and health education specialists were both receptive and supportive of this project.

**Conclusions:** Preventing the morbidity and mortality associated with GDM requires early diagnosis and disease management education, both of which are available at Sea Mar, but underutilized. Major contributors to its underutilization include lack of knowledge, fear of diagnosis, and lack of resources. Increasing utilization of established resources can be accomplished by educating this high-risk group through culturally appropriate educational materials in Spanish and community outreach. Continued support of such an educational program could result in an improvement in maternal and child health in the community.

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**349 PROMOTING DIABETES SELF-MANAGEMENT IN INDIAN AND EAST AFRICAN PATIENTS**

McGuflin S University of Washington, Seattle, WA.

**Purpose of Study:** Type 2 diabetes is a growing health problem in King County that disproportionately affects individuals in lower socioeconomic positions and certain ethnic groups. Self-management is a critical component to diabetes health maintenance. Unfortunately, many diabetes educational resources are not designed to meet the needs of underserved patients like those at King Country Public Health Centers where low literacy, poverty, and cultural differences present additional challenges. A low-literacy educational pamphlet was designed to foster healthy eating and diabetes self-management behaviors among Indian and East African patients. The pamphlet also serves as an interactive tool to help guide conversation and learning between patients and providers.

**Methods Used:** Interviews with patients and providers elucidated specific health needs and concerns of Indian and East African patients. A literature review was conducted to examine approaches to providing culturally competent care in underserved populations. The literature review also validated the need for diabetes educational materials appropriate for the target populations.

**Summary of Results:** Interactive and low-literacy educational pamphlets were designed to provide culturally competent information about healthy eating and diabetes self-management to Indian and East African patients. Visual representations of proper portion sizes and food groups were shown. Traditional foods and eating habits unique to each population were included. Space was provided to prompt discussion between patients and providers, as well as allow for the incorporation of foods important to the patient. Simple nutritional tips were presented at a 4th grade reading level. A chart for personal goal identification promotes patient-provider collaboration and encourages patients to take an active part in their health management.

**Conclusions:** Diabetes is a growing epidemic that disproportionately affects certain populations. Culturally and linguistically appropriate resources for many at-risk subgroups are limited and exacerbate disparities in health outcomes. The pamphlets presented here promote healthy eating, self-management behaviors, and patient-provider collaboration among underserved Indian and East African patients with diabetes. The pamphlets are designed for two specific populations but can be easily adapted for other ethnic groups.

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**350 EVALUATION OF COMPREHENSIVE DIABETIC EDUCATION PROGRAM IN TAOS COUNTY**

Seiler M1,2, Ismaiel G1, Eldredge J2, Tandberg D2 (Holy Cross Hospital, Taos, NM) and 3University of New Mexico School of Medicine, Albuquerque, NM.

**Purpose of Study:** To evaluate the effectiveness of comprehensive diabetic education on patient compliance.

**Methods Used:** Collaborative Action for Taos County Health is a not for profit organization that provides Comprehensive Diabetic Education, among other services, to the population of Taos County. A retrospective cohort study was performed using chart review to collect HgA1c, LDL and blood pressure on 95 randomly selected patients. Measurements prior to the start of diabetic education and for a minimum of two years following were collected in order to evaluate the effect of education on clinical measures of disease severity and assess possible dose response with the number of educational visits attended. Standard summary statistics (means, proportions, confidence intervals) were used to calculate all numeric variables. Analysis of the effect of education over time on HgA1c, LDL and BP is being carried out using linear regression with repeated measures.

**Summary of Results:** Statistical analysis is in progress but initial results suggest that even initiation of diabetic education results in statistically significant improvements in HgA1c. However, the same trends have yet to be seen with LDL and the program failed to record an adequate number of blood pressures to for meaningful analysis.

**Conclusions:** Comprehensive diabetic education appears to be effective in improving HgA1c, however, other important preventative measures such as LDL and blood pressure have not been adequately addressed in the curriculum.

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**351 DIABETES CONNECTED HEALTH EVALUATION**

Ling E1, Mohammed M2, Kvedar J2, Jethwani K2 1UC Davis School of Medicine, Sacramento, CA and 2Partners HealthCare, Boston, MA.

**Purpose of Study:** To determine patient and provider engagement on a web-based diabetes self-management portal and its association with clinical outcomes.

**Methods Used:** Patient engagement was determined by number of blood glucose readings and uploads, and provider engagement was determined by number of logins to the web portal. Clinical outcomes were determined by change in HbA1c over one year in the program.

**Summary of Results:** 166 patients were enrolled in Diabetes Connect (DC). Of these, 98 (~62%) engaged (at least 1 upload/month) within 2 months; 43% were never active. Engaged patients consistently uploaded 10-20 blood glucose readings/upload, 2-3 times/month. Less than half remained active after 7 months. The 67 patients with available clinical outcomes were on average 60 years old (SD: 13.9), 64% male and had started insulin within the past 3 years. Patients engaged in DC had average HbA1c change of 1.5 g/m%, while inactive patients had a HbA1c change of 0.4 g/m%, (p<0.03). Patients with better outcomes (HbA1c change of greater than 0.8 g/m%) typically took less than 10 days to engage, while patients with worse outcomes (increase in HbA1c) took an average of 65 days to upload. Patients with more engaged providers had a better HbA1c change (1.39 v. 0.87 for practices with average provider logins of 74 v. 30).

**Conclusions:** Outcomes in a collaborative web-based diabetes self-management tool are impacted positively by their consistent engagement in the program. Patients who engage early and remain active for longer have better clinical outcomes than unengaged patients. Patients who had positive outcomes uploaded consistently over time. Also, patients with engaged providers are more engaged in the program, leading to better clinical outcomes.

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**352 PREDICTORS OF WITHDRAWAL IN A TRIAL OF SAW PALMETTO FOR TYPE-2 DIABETES**

Buerger AE, Martin JT College of Osteopathic Medicine Western University of Health Sciences, Pomona, CA.

**Purpose of Study:** Adherence to medication regimen among type-2 diabetes (DM2) patients is important for controlling disease progression. Predicting patient withdrawal and non-compliance long-term is important in designing an efficient research study of any condition but particularly for DM2. Compliance during recurring monthly visits for herbal therapy has not been well studied. This study evaluates the influence of unpleasant side effects, gender, and initial H1A1c (hemoglobin a1c) levels on subject withdrawal during a clinical trial of Saw Palmetto (SP), which was added to their regular DM2 medication regimen.

**Methods Used:** Of 118 DM2 subjects enrolled in a 6 month, double-blind, placebo controlled trial, 22 were medically released, 55 participated until the final visit (V6), and 40 dropped out before V6. Subjects took a placebo or SP extract daily, completed a monthly survey reporting unpleasant side effects, and submitted blood samples for measuring H1A1c levels. Medically released subjects had a change in regular medications or H1A1c levels that were outside the inclusion criteria. Ratios were calculated for subjects based on the number of times they reported unpleasant side effects. Medically released subjects were excluded from the statistical analysis.

**Summary of Results:** There was no significant difference between unpleasant side effects reported by the placebo versus SP groups. The number of unpleasant side effects reported by subjects who withdrew before V6 and
silkure remaining to V6 did not differ significantly. Females reported significantly more unpleasant side effects than males (Fisher's exact test, p = 0.001). A greater proportion of females and males who withdrew did not differ significantly. Subjects who withdrew before V6 had significantly lower HA1c levels at V0 (t=2.20, df=91, p=0.0304).

Conclusions: Lack of compliance does not appear to be due to unpleasant side effects from SP or be related to the subject's gender. Withdrawal prior to V6 among subjects with low initial HA1c levels could be due to subject's stage of DM2 progression or satisfaction with medication regimen in controlling DM2 symptoms. Subjects entering study with higher HA1c may place more importance on the trial as an opportunity to control DM2 progression and symptoms with additional treatment options.

353 Silymarin, a Drug that Lowers Glycemia in Type 2 Diabetes, Augments Glucose-Stimulated Insulin Secretion Via its Effects to Increase CAMP Levels and Close KATP Channels in HIT-T15 Cells

Vallerie SN1, Meng R2, Parazzoli S1, Mahadevan J1, Robertson R1,2. Pacific Northwest Diabetes Research Institute, Seattle, WA and University of Washington, Seattle, WA.

Purpose of Study: Silymarin (SIL), a collection of flavonoids extracted from milk thistle, has been demonstrated to have antioxidant, anti-inflammatory, and cytoprotective effects. Two randomized double-blind, placebo-controlled clinical trials reported SIL improved fasting blood glucose and HbA1c levels in type 2 diabetic (G2D) patients. However, no mechanistic studies of SIL effects on insulin secretion have been reported. Therefore, we examined the effects of SIL on intracellular peroxides, glucose-stimulated insulin secretion (GSIS), and cyclic AMP (CAMP) levels in the beta cell line HIT-T15.

Methods Used: HIT-T15 cells were cultured in RPMI with 10% FBS for 2 hours before all assays. Intracellular peroxides were measured by a ferric ion complex orange method. GSIS assays and insulin content was measured by RIA. CAMP was measured by ELISA.

Summary of Results: The maximal stimulatory effect on GSIS was seen at 100 μM SIL, a concentration that lowered endogenous peroxide levels by >84.6 % of 8.4%. However, this augmentation occurred in the absence of endogenously added oxidants. Consequently, we next examined whether SIL also had independent effects on exocytosis by treating the cells with epinephrine (EPI, an inhibitor of G-proteins), nifedipine (NIF, which closes KATP channels), and diazoxide (DIAZ, which keeps KATP channels open). Augmentation of GSIS (11.1 mM glucose) by 100 μM SIL was 209%; addition of inhibitors reduced secretion (1 μM EPI = 69.6%, 20-50 μM NIF = 65.8%, and 50 μM DIAZ = 84.9%; all p <0.05). This suggests SIL acts upstream of exocytosis. Since KATP channels are regulated by cAMP, we measured CAMP levels in SIL treated cells and found them to be elevated compared to control (100 μM SIL = 11.1 ± 0.326 pmol/ml vs. 4.81 ± 0.83 pmol/ml, p <0.05). No effects of SIL on basal insulin secretion or insulin content were observed.

Conclusions: We conclude that the beneficial effects of SIL on beta cell function are likely to be 2-fold, i.e. via its protective antioxidant effects and by its stimulatory effects on GSIS via KATP channel closure.

354 Rates of Weight Loss in Diabetic Versus Non-Diabetic Subjects in an Outpatient Very Low Calorie Diet Program

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Purpose of Study: To evaluate differences in the efficacy of a very low calorie diet (VLCD) in promoting weight loss in diabetic and non-diabetic patients.

Methods Used: Patients enrolled in a self-paid, university-based, outpatient weight loss program and prescribed VLCD (500-800 Cal/day), an exercise regimen, and group behavioral counseling were studied retrospectively. Patients entering the program for the first time and attending all weekly clinic visits for >8 weeks were included in the analysis. Repeated measurement analysis was used to determine whether weight loss was different in DM (Diabetes Mellitus) subjects compared to those subjects without DM.

Summary of Results: A total of 326 patients with Type 2 DM and 3209 without DM entering the program from 1991 to 2010 met all the inclusion criteria and were included in the analysis. In the linear mixed effects model, DM subjects had a slower rate of weight loss by 0.01632 lb/day compared to non-DM subjects (p=0.0006). Initial body weight upon entering the program was negatively associated with weight loss rate (p<0.001). Age was positively associated with weight loss rate (p<0.001) and gender had no effect on the difference in weight loss rate observed (p=0.258). When subjects were compared according to BMI groups, there was no statistical difference in the rate of weight loss observed between patients with DM and without DM in the BMI ranges of 30-35 or >45.

Conclusions: Patients with Type 2 DM may lose weight at a slightly slower rate than non-DM patients, regardless of gender, when enrolled in a structured outpatient program. Further analysis will be carried out to better understand the reasons for the observed difference, including factors which could affect compliance among the DM subjects.

355 Evaluation of Insulin Resistance in Young Adults with Acute Coronary Syndrome (EIRYS) - A 10 Year Retrospective Study

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Purpose of Study: Age is a well-established prognostic factor for acute coronary syndromes (ACS). 10% of ACS occurs in young adults. We investigated insulin resistance (IR) along with other risk factors for ACS in young adults compared to age matched controls and older ACS patients.

Methods Used: Using ICD 9 codes for ACS (NSTEMI/STEMI) we identified young adults age <50 years (n=761) and older adults age >50 (n=4959) discharged from an academic, acute care hospital between Jan 2000 and Dec 2009. To obtain age matched controls for each group of ACS patients, non-ACS patients were selected by the ICD codes for pneumonia and obesity for ages <50 and >50 years. A randomized sample of 100 patients was selected for collection of demographic and clinical data on cardiac risk factors from each of the four patient groups (i.e. ACS <50, non ACS <50, ACS >50, non ACS >50). Angiographic features were also gathered for the ACS groups.

Summary of Results: ACS young adults were more likely to be males (p<0.001) and smokers compared to older counterparts (p<0.005) and young non-ACS patients were not associated with ACS in young ACS adults. Drug abuse was not more common in young or old ACS patients compared to controls. IR defined as TG/HDL ratio > 3.5 was significantly higher in young ACS compared to older ACS (p=0.006) and controls (p>0.001). ACS young had significantly higher mean TG 201.8±211.1 mg/dl (p=0.021), and LDL 99.5±43.1 mg/dl (p=0.012) in contrast to young controls and older non ACS controls. The lower mean HDL 37.9±9.7 mg/dl in young ACS was not significantly different (p=0.415). BMI, race and diabetes did not differ between all groups. ACS young adults had a one vessel disease more commonly than older ACS (p=0.014) and were less likely to have LCX disease.

Conclusions: Young ACS patients are more likely to be male & smokers. Increase prevalence of IR was seen in young ACS compared all other groups. In young ACS the mean LDL was higher; however the absolute mean LDL was still not high enough to trigger clinical suspicion of high-risk for CAD (i.e. the mean LDL remained below levels for which NCEP III recommends initiating treatment beyond diet/exercise). This suggests IR may be able to identify these young adults at risk for ACS.
Purpose of Study: Although poisonings occur frequently in the California Poison Control System (CPCS), they are poorly described in the medical literature; hence this study was done in an attempt to characterize them.  
Methods Used: A computerized search of free-text entries in CPCS Dotlab was performed. Search terms included jail, prison, detention, correctional, institution, inmate and prisoner. The computer-selected records were then manually reviewed to include only inmate poisoning exposures occurring while incarcerated in California's penal institutions, including jails, prisons and juvenile halls.  
Summary of Results: 627 inmates with 807 poison exposures in 2009 and 2010 were identified. Average inmate age was 49 years, with 85% male and 15% female. Identified exposures included drugs (666 incidents, or 75% of exposures) and non-drugs (141 incidents, or 16% of exposures). Reasons for exposure were: intentional self-harm (540), unintentional (106), abuse (75), misuse (67), therapeutic error (37), adverse reaction (13), drug withdrawal (3) and unknown (20). Outcomes were death in 3 cases, major effect in 14 and moderate effect in 114 (as defined by the Society of Toxicology). 51 patients were admitted to hospital critical care units and another 49 to non-critical care units. 263 other inmates were seen in emergency departments.  
Conclusions: Our study provides a significant epidemiological glimpse into inmate poisonings occurring in penal institutions in California. Most of the exposures were to over the counter analgesics (OTC), psychotropic medications, anticonvulsants, cleaning agents and street drugs. In-custody methamphetamine and heroin use was surprisingly high. These cases had an unusually high rate of hospital utilization (58%) and a mortality rate of 0.48%. Overall, the annual mortality rate for poisonings reported to the United States poison control centers averaged about 0.05% as reported to the National Poison Data System. These numbers suggest that persons in need of substance abuse treatment in California may instead receive jail confinement with or without treatment of their substance abuse problem.

357 DEVELOPING EVIDENCE-BASED SENTINEL SURVEILLANCE IN THE GLOBAL SOUTH: EVALUATION OF A PILOT PROJECT UTILIZING TIME SPACE SAMPLING TO DETERMINE HIV PREVALENCE AMONG MSM IN URBAN PERU  
Blair C, Clark J, David Geffen School of Medicine at UCLA, Los Angeles, CA; 1David Geffen School of Medicine at UCLA, Los Angeles, CA.  
Purpose of Study: Utilizing accurate and effective methods to determine HIV prevalence and sociobehavioral risk factors associated with HIV and STI transmission is imperative for the development of evidence-based intervention strategies. Despite targeted outreach efforts, a disproportionately high HIV seroprevalence (18-22%) has consistently been reported among men who have sex with men (MSM) in urban Peru. As this high risk sub-population is a significant barrier to effective sentinel surveillance and outreach efforts, the development and utilization of evidence-based sampling strategies is imperative in determining accurate HIV prevalence and socio-behavioral risk factors among MSM in urban Peru. Consequently, this study serves to contribute to the formative evaluation of Time Space Sampling (TSS) as a sentinel surveillance method for HIV and syphilis among MSM in Lima, Peru.  
Methods Used: A formative evaluation of TSS recruitment outings was conducted through participant observations and in-depth interviews. Respondent questionnaires were evaluated based upon the following: content, consistency, flow, potential for accurate respondent recall, cultural suitability, and bias.  
Summary of Results: TSS teams were consistent in achieving participant recruitment goals for on-site syphilis and HIV testing. Lengthy testing time (1-1.5 hours) combined with an on-site testing capacity of two concurrent participants introduces the potential for loss to follow-up among prospective recruits. Despite successfully addressing numerous sociobehavioral and sociocultural risk factors associated with HIV transmission, minor inconsistencies in portions of the participant questionnaire have the potential for introducing bias and creating barriers for effective implementation in the field.  
Conclusions: TSS has the potential to be an extremely powerful tool in accurately capturing HIV prevalence and risk behaviors among MSM in Peru. Findings from this study indicate that further evaluation of TSS as a sampling methodology for HIV prevalence among MSM is an important step towards the development of evidence-based sentinel surveillance strategies for high risk sub-populations in urban Peru.
cost-effective way to reduce the risk and rate of falling in seniors. Seniors residing in Hamilton were educated about this association and connected with the resources available in the community. Those who participate as instructed will hopefully improve their balance, strength, and experience less social isolation.

360 FALL PREVENTION IN COMMUNITY DWELLING ADULTS OVER 65

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Purpose of Study: This intervention provides tools for preventing falls to community dwelling adults 65 years and older.

Methods Used: More than one third of people 65 and older fall each year. Of these falls, 30% require medical attention. Approximately one half of hospitalizations in older people result from falls. In 2007 there were 18,000 deaths related to falls, averaging one every 35 minutes. Fear of falling is prevalent. In one study, 78% of the elderly population reported a fear of falling, and 82% of these avoided leaving home because of it. In Anaconda, a town of 9,000 in southwestern Montana, those 65 years and older comprise 18.9% of the population, compared to the national average of 12.6%, lending extra significance to an intervention aimed at preventing falls.

Exercise-based interventions with balance and strength are effective in reducing risk of falling, by an average of 17% according to one study. Best outcomes are observed with a 15 minute program performed three or more times weekly. In addition to reducing risk of falls, this reduces fear of falling. This project provided a simple exercise program designed by physical therapists to challenge strength and balance. A checklist of simple home improvements from the CDC was given, as well as a recommendation for participants to seek assistance from primary care providers for further fall prevention.

Summary of Results: The fall prevention program took place at the Metcalf Senior Center in Anacconda. Twenty seniors 65 and older participated. They interacted with fall prevention items such as sturdy shoes, mountable hand rails, and sticky-mats for rugs. Facts and information were visually presented on a poster. Twelve of the audience participated in the exercise program, and many expressed interest in following up with local health care providers on fall prevention. Copies of the CDC Check for Safety home-improvement checklist were distributed to more than 70 seniors receiving meals at home from the center.

Conclusions: This program was a good initial step. To progress, a continuity of care relationship with the participants will need to be established to encourage adherence. As a result of information learned in this project, the senior center is planning to provide their facility for exercise during inclement weather. Further evaluation will be necessary to measure long term results.

361 FOOT-SPECIFIC EDUCATION AND EXERCISE FOR OLDER ADULTS IN SITKA, ALASKA

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Purpose of Study: People are more likely to experience foot problems as they age. In Sitka, a town located on Baranof Island in Southeast Alaska, approximately 17% of the population is aged 55 and older. It is not uncommon for older adults to come into clinic with hammertoes, bunions, and plantar fasciitis. Literature suggests that foot care is crucial to preventing pain, mobility issues, and falls in older adults, but few programs focus specifically on the foot. The goal of this project is to implement a group foot exercise program to educate older adults about proper foot hygiene, common foot problems, and foot-specific exercises.

Methods Used: Clinic visits and conversations with older adult patients revealed the need to relieve foot discomfort and prevent associated problems. A literature review was performed to confirm the prevalence of foot concerns and how it can negatively affect the quality of life of adults in this age group. Information and exercises obtained from the review were compiled into handouts for participants. A foot exercise class was organized at a local senior center in collaboration with community agencies.

Summary of Results: 5 older adults attended the exercise class. At the end of the session, they each took home a set of sandals, a golf ball, and handouts to continue exercises at home. 2 additional adults took handouts, but did not attend the session. Participants were engaged and enthusiastic about the program and wanted additional classes to help share the experience with others.

Conclusions: Literature and clinical observations agree that foot problems are associated with increased falls and decreased mobility in older adults. Foot problems are difficult to treat so prevention is critical. In this project, a foot-specific exercise class equipped older adults with the knowledge to take self-care measures at home. Participants recognized the importance of maintaining strength and flexibility in their feet. In the future, additional group classes and the incorporation of foot-specific exercises to existing older adult focused programs are recommended.

362 YOGA FOR ANXIETY REDUCTION IN WOMEN RECOVERING FROM ADDICTION

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Purpose of Study: In recent years, methamphetamine has emerged as the illicit drug of choice in Wyoming and represents a significant threat due to its correlation with violent crime, domestic violence and child abuse. The purpose of this project was to reduce stress and anxiety among adult women who are in treatment for drug and alcohol addiction through the practice of yoga.

Methods Used: Four yoga classes were provided within a two week period for several women living in a Residential Treatment Center in Pine Bluffs, Wyoming. Classes consisted of 26 postures and 2 breathing exercises, including deep breathing and rapid breathing, for a 60 minute series. As students advanced in their practice, they deepened into their postures rather than altering the postures as they progressed. Instruction manuals were provided to these women for their subsequent practice of meditation, breathing exercises and physical postures.

Summary of Results: Breathing exercises, cardiovascular poses, stretch- ing, meditation, and positive interactions with a class and an instructor were beneficial to the participants. In an anonymous post-interventional survey, they reported feeling calmer, less tense, more self-aware and more energized after each yoga class. At least one student reported that she slept better after yoga class, and a few others had decreased emotional reactivity reporting that they felt “clear-minded,” “happier,” and “no longer in a bad mood” after practicing yoga. The students all felt that after four yoga classes they had increased strength, flexibility, and balance. All participants expressed a desire to continue to practice yoga in the future and found the yoga instruction manuals to be useful.

Conclusions: Literature supports that yoga has the potential to reduce stress, depression, and anxiety. Since stress levels have a positive correlation with future pathologies, yoga practice may be beneficial to populations experiencing significant stress. Yoga may be a valuable tool by reducing stress and anxiety when incorporated into a multicomponent treatment plan for women recovering from addiction to drugs and alcohol.

363 PROMOTING PHYSICAL ACTIVITY WITH FRISBEE GOLF IN DELTA JUNCTION, ALASKA

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Purpose of Study: National studies estimate that over 60 percent of Americans are overweight. The CDC reports that obesity rates in adolescents aged 12-19 and children aged 6-11 are 18% and 20% respectively. In 2008, the medical care costs related to obesity were $147 billion. Many rural Alaskan communities endure 9-month winters that feature limited daylight and temperatures of sixty below zero, making it difficult to maintain an active lifestyle. 67% of rural Alaskans are overweight, which is significantly higher than the national average as well as urban areas of the state. The purpose of the project was to promote physical activity in the rural community of Delta Junction, Alaska by increasing public interest in the town’s new Frisbee Golf course.

Methods Used: In order to increase community interest in Frisbee Golf, an event was held at the town’s new Frisbee Golf course. The event was free and featured an overview of the game rules, a tour of the course, and group lessons from members of the Professional Disc Golf Association. People who attended also received a free Frisbee Golf disc and a brief lecture on the health benefits of physical activity. Promotion for the event was accomplished with the use of flyers and the recruited help of city hall and the course creator. The local outdoor survival store was also convinced to begin selling Frisbee Golf discs to the community.
Summary of Results: People of all ages spend the afternoon in the park learning about Frisbee golf. Over 25 Frisbees were given away. Many members of the community who had never heard of Frisbee Golf learned the rules as well as valuable health information. The local outdoor store sold-out of Frisbee Golf discs within the week and the traffic on the local course increased.

Conclusions: Obesity has become one of the most significant health concerns for Americans, especially those living in rural Alaska. Studies have indicated the importance of regular physical activity in preventing the multitude of health issues associated with obesity. Promoting an interest in Frisbee Golf, a sport that is affordable, easy to participate in, and accessible to all ages, will hopefully encourage people in Delta Junction to engage in a more active lifestyle, thus improving the health of the community.

Methods Used:

Purpose of Study: The primary objective of this study was to evaluate vitamin D treatment regimens and their dose response relationship in repleting vitamin D serum levels. Secondary outcomes included evaluation of the frequency of monitoring vitamin D serum levels and prescription adherence.

Methods Used: This was a multicenter, retrospective electronic data extraction and analysis in patients who initiated monotherapy with cholecalciferol or ergocalciferol between 1/1/2005 to 12/31/2010. Patients were excluded if they did not have baseline or follow-up labs within 1 year of treatment initiation. Serum 25(OH)D was used as a marker for vitamin D. Ergocalciferol and cholecalciferol groups were separately analyzed using quartiles by dosing ranges to evaluate the impact on 25(OH)D.

Summary of Results: A total of 6,412 patients met inclusion criteria for monotherapy treatment with cholecalciferol (n=4,140) and ergocalciferol (n=2,272). Cholecalciferol quartiles I, II, and III had mean daily doses between 600 IU, 900 IU, and 1,100 IU that were associated with an 8, 8.5, and 9.1 ng/mL 25(OH)D increase from baseline, respectively (p<0.05 between groups). Cholecalciferol quartile IV had a mean daily dose of 2,700 IU, which was associated with a significantly greater increase from baseline of 12.7 ng/mL 25(OH)D when compared to quartiles I, II, and III (p<0.005). Ergocalciferol doses of 6,000 IU, 7,150 IU, and 7,150 IU, representing quartiles I, II, and III were associated with a 16.5, 14.1, and 17 ng/mL 25(OH)D increase from baseline, respectively (p<0.05 between groups). Quartile IV of ergocalciferol had a mean daily dose of 11,000 IU, which was associated with a significantly greater increase from baseline of 19.9 ng/mL 25(OH)D when compared to quartiles I, II, and III (p<0.05).

Conclusions: Lower cholecalciferol and ergocalciferol maintenance doses had similar modest affects on serum vitamin D levels when compared to the highest mean dose used. The dose-response relationship results of the study reinforce current guidelines and literature. Cholecalciferol and ergocalciferol dose-response relationships found in this study may indicate dosing thresholds exist, and with future analysis, may help narrow and optimize vitamin D repletion regimens.

Methods Used: Adult male smokers were recruited to attempt smoking cessation during the 5-day study period. The evolution of subjective symptoms was assessed by the Patient Health Questionnaire-9 (PHQ-9) and visual analog scales. Success or failure in abstaining from smoking and/or nicotine ingestion was determined by assay of blood samples on Days 1, 3 and 5 for cotinine, a nicotine metabolite.

Summary of Results: Of the 22 participants, 12 succeeded in smoking cessation and did not ingest nicotine as determined by negligible cotinine levels on days 3 and 5. Seven subjects failed to abstain from ingesting nicotine during the study but continued to completion, while three subjects withdrew. Over the course of the study, visual analog scores for desire to smoke, withdrawal symptoms, anxiety, irritability, and stress all decreased significantly in the group that succeeded at smoking cessation (p<0.05). The mean PHQ-9 total severity score at baseline for study completers (n=19) was 6.8±5.2, which was within the range of “minimal symptoms of depression.” The subgroup that succeeded at smoking cessation reported a mean baseline PHQ-9 score of 8.2±5.2 (n=12) which improved to a score of 5.3±5.5 on day 5, not quite reaching statistical significance (p=0.135). Mean PHQ-9 scores for the group who failed to abstain did not change (4.3±4.4 vs. 4.7±5.3; n=7; p=0.298).

Conclusions: Men who successfully quit smoking in this study reported reduced mood- and anxiety-related symptoms. In addition, smokers as a group reported minor depressive symptoms at baseline. The demonstrated improvement in subjective measures for smokers who quit may alleviate fear of experiencing these negative states upon cessation of smoking. Further study is warranted to determine if smoking cessation can augment antidepressant and psychotherapy efforts to treat mood and anxiety disorders in tobacco smokers.

General Internal Medicine and Aging
Concurrent Session
1:30 PM
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EVALUATING VITAMIN D REPLETION REGIMENS AND THEIR RELATIONSHIP TO CHANGES IN VITAMIN D SERUM LEVELS IN VETERAN PATIENTS

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Purpose of Study: The primary objective of this study was to assess changes in serum vitamin D levels, using cholecalciferol or ergocalciferol, to determine how best to treat patients with vitamin D levels below 10 ng/mL serum 25(OH)D levels.

Methods Used: This was a multicenter, retrospective electronic data extraction and analysis in patients who initiated monotherapy with cholecalciferol or ergocalciferol between 1/1/2005 to 12/31/2010. Patients were excluded if they did not have baseline or follow-up labs within 1 year of treatment initiation. Serum 25(OH)D was used as a marker for vitamin D. Ergocalciferol and cholecalciferol groups were separately analyzed to determine the optimal cut-off point for vitamin D serum levels. Secondary outcomes included evaluation of the frequency of monitoring vitamin D serum levels and prescription adherence.

Methods Used: This was a retrospective study conducted over a 2-year period. ROC curve was used to determine the optimal cut-off point for DBP as a continuous scale against death. Multivariate logistic regression (LR) assessed for independence of low DBP as a risk for all-cause mortality.

Conclusions: Blood pressure (BP) management can be challenging in outpatient setting. The old doctrine of “lower is better” has been disputed since 1979. The current JNC guidelines recommend therapeutic BP target <130/80 for hypertension associated with CAD, CKD, and DM. However, studies have noted increased cardiovascular events, including death, when diastolic BP (DBP) is above as well as below certain threshold, described as the J curve phenomenon. We sought to determine the association between all-cause death and DBP and optimal BP treatment goal in a VA population with complex co-morbidities.

Methods Used: A retrospective cohort study of 14,270 outpatients aged 45 to 85 years was conducted over a 2-year period. ROC curve was used to determine the optimal cut-off point for DBP as a continuous scale against death. Multivariate logistic regression (LR) assessed for independence of low DBP as a risk for all-cause mortality.

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paradigm with the guidelines including a minimum as well as a maximum BP target.

367 THE IMPACT OF INCARCERATION ON LINKAGE TO, RETENTION IN, AND OUTCOMES OF CARE AMONG LOW-INCOME, HIV-POSITIVE PERSONS

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Purpose of Study: BACKGROUND: Incarceration is common for HIV+ persons and is thought to be a barrier to HIV prevention and treatment. However, little is known about whether previous incarceration is associated with delays in linkage to and retention in HIV care, antiretroviral therapy (ART), or health outcomes. GOALS: We evaluated the cross-sectional and prospective associations of previous incarceration with measures of linkage to and retention in care, ART, and health outcomes for multi-ethnic, low income, HIV+ persons in Los Angeles.

Methods Used: We examined a prospective cohort of 223 HIV+ persons self-identified as lacking medical care, having missed 2+ visits in the past 6 months, or as wanting more services to address their needs. From 2004-2006, interviews were conducted at baseline and 6 months; record reviews were conducted to collect clinical data. The retention rate was 78% at 6-month follow-up. ANALYSES: We used bivariate and multivariate logistic and linear regression analyses to examine associations between incarceration history and main outcomes of linkage to care, retention, ART, and change in viral load, controlling for socio-demographic and clinical variables.

Summary of Results: Previous incarceration was significantly associated with longer times before seeing a provider after testing HIV+ at baseline (beta=31.00, p=0.02) but not at follow-up (beta=11.33, p=0.3). The mean time for previously incarcerated persons to see a doctor after testing HIV+ was 27.93 days; the never incarcerated sample had a mean of 11.41 days. There were trends in association of incarceration with more missed appointments (OR=1.64, CI=0.82,3.28), fewer doctor’s visits in the prior 6 months (OR=0.64, CI=0.21,1.95), less ART (OR=0.68, 95% CI =0.32,1.41), and a lower likelihood of suppressing viral load (OR=0.40, 95% CI=0.10,1.53).

Conclusions: Previously incarcerated individuals had significant delays in linkage to care after testing HIV+ at baseline, and upon linkage, they tended to have worse retention in care, less ART, and worse health outcomes at follow-up. After release, incarcerated individuals face many challenges to successful HIV care. Interventions need to be developed that improve linkage to and retention in HIV care among persons released from jail and prison.

368 USE OF PSYCHOTROPIC MEDICATIONS AMONG UNDERSERVED AFRICAN AMERICAN SENIORS

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Purpose of Study: To identify prescribing trends of psychotropic medications in African American seniors. This study aims to determine if the most current classes of medications, with the most favorable adverse effect profiles, are being used in this population.

Methods Used: Participants were recruited from 16 African American churches and community centers located in South Los Angeles. This study included an intervention to notify participants and their primary care providers when the team pharmacist identified instances of poor adherence, medication duplication, use of expired medication, misuse of any prescription or over-the-counter medication, or any instances which were of concern. A comprehensive collection of participants’ medication use and self-reported knowledge and adherence to prescribed regimens was obtained through the use of a survey instrument.

Summary of Results: Two-hundred sixteen (216) African Americans age 65 or older were included. The age range is 65-95, mean age 74 years. More than 17% of participants take at least one psychotropic medication. The most common class of psychotropic medication was benzodiazepines (11). Antidepressant agents used included selective serotonin reuptake inhibitors (SSRIs) (8), tricyclic antidepressants (7), and other antidepressants (4). Typical antipsychotics (5) and atypical antipsychotics (6) were prescribed. Other medications prescribed were for insomnia (4) and non-benzodiazepine anxiolytics (1).

Conclusions: Several classes of medications with worse side effect profiles were used at greater or similar frequencies as medications with fewer side effects. Most concerning was the use of benzodiazepines, specifically diazepam and flurazepam, which can have serious adverse effects in the elderly. Other medications for insomnia and anxiety were used less frequently. Tricyclic antidepressants were taken almost as frequently as SSRIs, although SSRIs typically have fewer side effects. Similarly, typical antipsychotics were prescribed almost as frequently as atypical antipsychotics, despite the fact that typical antipsychotics can have more adverse effects. These results raise concerns that participants are not being prescribed the most effective psychotropic medications with the most favorable side effect profiles.

369 DEPRESSION AMONG THE ELDERLY: AWARENESS EDUCATION IN BUTTE, MONTANA

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Purpose of Study: Butte, Montana is historically a “tough” town. Unemployment and underemployment are common, and drinking, fighting and drug use are rampant. According to one physician, depression is the most common diagnosis at Butte’s Community Health Center. However, mental health issues among the elderly in Butte are under-addressed. According to professional literature, health outcomes are negatively affected if depression is not treated. Through raising awareness among members of the elderly community in Butte on mental health issues and available resources, this project sought to improve quality of life and health outcomes through treatment of depression.

Methods Used: Based on input from community health care providers and a thorough literature review, it was determined that the most effective way to raise awareness on depression among the community elderly was to address a group of caregivers at a bi-monthly caregiver support group held at the Belmont Senior Center. An informational brochure specific to the community of Butte outlining the signs and symptoms of depression and resources in the community was prepared to supplement the presentation.

Summary of Results: Thirteen caregivers attended the educational offering at the Belmont Senior Center co-hosted by a social worker. Participants were led through a self-reflection exercise to raise awareness of the symptoms of depression. The topic was very well-received. Several participants expressed gratitude that a forum had been created to discuss depression. The informational brochures were distributed. An electronic copy was provided to Belmont Senior Center and to Butte Community Health Center for further use.

Conclusions: This project helped to raise awareness of depression issues and to dispel some of the stigma surrounding depression. Hopefully, frank discussion of depression communicated that it is both acceptable and cathartic to discuss sensitive issues. This served to increase awareness among healthcare workers the importance of knowing the signs of depression for their own mental health and for increased overall health of the individuals they care for.

370 ANTIDEPRESSANT USE ASSOCIATED WITH MORTALITY AND CARDIO-VASCULAR OUTCOMES IN A VETERAN POPULATION

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Purpose of Study: Depression is common and newer antidepressants are increasingly prescribed. Unlike TCA, limited data exist on their safety profile. Atypical antipsychotics (AAP) are known to cause metabolic derangements and may contribute to poor CV outcomes. We sought to determine the pattern of antidepressant prescription in a VA population and association between use of different classes of antidepressants and CV outcomes.

Methods Used: Chart review was conducted on 17466 veterans. Those diagnosed with depression (n1136) were categorized into groups of SSRIs (n416), TCA (n51), NASSA (n41), NDRI (n67), SNRI (n35), SRA (n54) and controls on no antidepressant (n472). Patients on multi-antidepressant regimens were excluded. Chi square or ANOVA were used for comparison.

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Summary of Results: Mean age of the study population was 61 years with 90% males. Two third of the patients received antidepressants; SSRI being most common. Benzodiazepine use was more frequent in those already on antidepressants, especially SNRI and SSRI (P<0.0001). Concomitant AAP use was more common with SNRI, SSRI and SRA categories (P<0.0067). TCA group demonstrated highest all-cause mortality (P<0.0012). After adjusting for demographics, medications and co-morbidities, AAPs were associated with CVA/TIA (OR2.23, 95%CI 1.29-3.83, P<0.0036) and all-cause mortality (OR2.05, 95%CI 1.03-4.1, P=0.04) independent of age, BMI, smoking, CAD, and statin or SSRI use. NASSA use was associated with more prevalent CHF (OR3.26, 95%CI 1.029-10.38) independent of age, CAD, and statin or beta blockers use. SSRI use was significantly associated with lower all-cause mortality (OR0.37, 95%CI 0.19-0.71, P=0.0028) independent of age, BMI, smoking, CAD, statin or AAP use.

Conclusions: Our results favor early treatment of depression, preferably with an SSRI, to improve mortality. Adequate control of depression and stress reduction may improve self care of general health and medical issues and lower suicide risk. SSRI may confer its cardioprotective effects through platelet modulation but specific mechanisms require further investigation. AAPs should be used with caution in this population. Use of Mirtazapine in CHF patients with depression deserves further study.

371 THE TIMING HYPOTHESIS: A PARADIGM SHIFT IN CARDIOVASCULAR DISEASE PREVENTION
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Purpose of Study: Over the past decade, there has been no more controversy than that generated by the role of postmenopausal hormone therapy (HT) in the prevention of coronary heart disease (CHD). Beyond this distraction however, are the public health implications of the findings that the effect of HT on atherosclerosis progression appears to be determined by the stage of atherosclerosis.

Methods Used: Our sister randomized controlled trials (RCTs) WELL-HART and EPAT have shown the importance of timing of HT initiation. The differing outcomes of no HT effect on atherosclerosis progression in the WELL-HART cohort of women with symptomatic advanced atherosclerosis and a reduction in atherosclerosis progression in the EPAT cohort of women with early subclinical atherosclerosis may be related to the timing of HT intervention relative to the stage of atherosclerosis. Since age and atherosclerosis are inextricably linked, age and/or time-since-menopause likely serve as chronological markers for vascular age (stage of atherosclerosis) which is the ultimate determinate as to whether HT will be cardioprotective.

Summary of Results: This timing hypothesis or window of opportunity is strongly supported by cumulated RCTs. Discordance between the consistent reduction of CHD and overall mortality in observational studies and a null effect reported from RCTs is now understood to be likely due to 2 distinct populations of women. The subgroup of women randomized to HT in RCTs who are more representative of the women in observational studies (HT initiation within 6 years of menopause and/or when <60 years old) had reduced CHD and overall mortality, whereas women who were >10 years beyond menopause and/or older than 60 years of age when randomized to HT (who are not representative of the women in observational studies) showed no reduction in CHD risk or overall mortality. Broadening support for the timing hypothesis are accumulating data from other classes of estrogen receptor binding agents which exhibit the same beneficial effect as HT on CHD in young postmenopausal women, including our recently completed WISH study, a RCT of isoflavone soy protein supplementation.

Conclusions: The timing hypothesis, an important paradigm shift in how we view CHD interventions will be described in the context of HT and cardioprotection.

372 CORRELATES AND PREVALENCE OF URINARY INCONTINENCE AMONG OLDER, COMMUNITY-DWELLING CALIFORNIANS
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Purpose of Study: Understanding the correlates and prevalence of urinary incontinence (UI) becomes increasingly important as the older population in the US continues to grow. UI has been associated with an increased risk of nursing home admission, and it may serve as an important predictor of health. We sought to determine the correlates and prevalence of UI among older, community-dwelling Californians through the use of the California Health Interview Survey (CHIS).

Methods Used: CHIS is population-based, random digit dialing telephone survey which began in 2001 and is conducted biennially. The CHIS 2003 adult survey included one question regarding UI for Californians aged 65+:

“... In the past 30 days, have you been incontinent, that is unable to hold or control your urine more than once?” Survey results were analyzed for statistical significance with respect to demographics, general health status, co-morbidities, and health behaviors.

Summary of Results: 8,668 individuals aged 65+ responded. The overall prevalence of UI among those aged 65-69 was 15.4%, increasing to 25% among those aged 75+. Overall male and female prevalence was 14.5% and 25.4%, respectively. Significant associations were found with poor health (41.3% incontinent), legal blindness (32.7%), need for help with daily activities (47.4%), falls (37.8%), asthma (25.6%), diabetes (26.7%), heart disease (27.1%), hypertension (22.8%), stroke (32.2%), and BMI 30+ (27.7%). Walking was associated with lower levels of UI (17.4%). No significant association was found with smoking.

Conclusions: UI prevalence among older, community-dwelling Californians parallels that of other population-based surveys. CHIS demonstrated that general health status, co-morbidities, and health behaviors are correlated with incontinence, as are increasing age and female gender. CHIS data did not find a correlation between UI and smoking, an association that has been debated in prior studies.

373 HUMAN LENS IMAGING FOR EARLY DIAGNOSIS OF ALZHEIMER’S DISEASE
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Purpose of Study: The purpose of this study is to determine if morphological changes in the eye are useful indicators of Alzheimer’s Disease (AD). Positron Emission Tomography (PET) brain imaging is a reliable diagnostic measure of early or asymptomatic AD, but large scale radiological evaluations are costly. Beta amyloid plaques similar to those found in the brains of patients with AD may build up in the periphery of the lens creating supra nuclear cataracts. It is possible that these cataracts form in the early stages of AD before significant memory loss and mental impairment have occurred, thus providing a minimally invasive cost effective preclinical diagnostic measure of AD. In this study, we compared lens opacity and fluorodeoxy glucose (FDG) metabolism in the brain, in a small cohort of subjects, to determine whether protein buildup in the lens is a reliable preclinical diagnostic indication of AD.

Methods Used: Participants (n=16) underwent standard PET and customized slit lamp examinations. Glucose metabolism was assessed by measuring uptake of a radioactive tracer in the posterior cingulate gyrus, and lens opacity was calculated by measuring light scatter in the anterior lens using an infinity 2-1C camera and a Nikon FS-2 slit lamp. Cognitive test scores were used to classify subjects as having AD, mild cognitive impairment (MCI), or a normal control. Lens opacity and glucose metabolism data were normalized and compared across subjects.

Summary of Results: Participants with AD and MCI had significantly less glucose metabolism in their posterior cingulate gyri than control subjects (p<0.01) at all ages tested. Lens opacity did not correlate significantly with FDG metabolism when controlling for age differences. However, relative to baseline, lens opacity increased more rapidly with age in patients with MCI and AD compared to normal control subjects.

Conclusions: Due to the small sample population, a statistically significant correlation was not observed between FDG metabolism and lens opacity in AD, control, or MCI subjects. However, the rapid increase in lens opacity with age in subjects with MCI suggests the need to evaluate a larger population to further explore the utility of early AD diagnosis from a lens imaging approach.

Supported by EY 04542 from the NEI.
374
DIFERENTIAL EFFECTS OF EXOGENOUS INDUCED OXIDATIVE STRESS ON HUMAN SPERMATOZOA DNA INTEGRITY AND MOTILITY

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Purpose of Study: Sperm motility and sperm DNA integrity are important indicators for male fertility. While studies have shown that exposure to oxidative stress can negatively affect fertility by causing sperm DNA damage and by impairing sperm motility, the sequence of these two events has not yet been established. To address this question, our experiment aims to measure the effects of different levels of exogenous induced oxidative stress on sperm DNA integrity and motility.

Methods Used: Semen samples were collected from healthy donors. Highly motile spermatozoa were isolated via swim-out and incubated in different concentrations of hydrogen peroxide between 0 and 200 μM. Following incubation, spermatozoa motility was analyzed via IVOS computer analysis. Cell membrane integrity was assessed by staining cells with Trypan Blue dye and manually evaluating nucleus staining at 1000× magnification. Changes to DNA integrity were determined by using an alkaline DNA diffusion assay and AND. By manually differentiating between cells with damaged DNA and cells with intact DNA at 400× magnification.

Summary of Results: No change in progressive motility was observed from 0 μM to 12.5 μM H2O2 treatment. At 25 μM H2O2, the percentage of spermatozoa with progressive motility dropped to 80.8% of its original value and remained constant until 100 μM H2O2. All cells were completely immotile at 200 μM H2O2. At 6.25 μM H2O2 treatment the percentage of cells with intact DNA decreased to 87.9% of its original value and remained constant until 100 μM H2O2. At 200 μM H2O2 the percentage of cells with intact DNA decreased to 15% of its original value. No change in cell membrane integrity was observed at any concentration.

Conclusions: Our results show that with increasing exposure to exogenous induced oxidative stress, there is differential damage of first, decreased sperm DNA integrity and second, decreased sperm motility. Disruption of the cell membrane did not contribute to the observed effects. Since sperm DNA integrity becomes impaired at lower levels of oxidative stress than motility, our findings suggest that even spermatozoa with highly damaged DNA can exhibit normal motility. Therefore, there is a concern that such sperm potentially may fertilize an oocyte.

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KIKUCHI-FUJIMOTO LYMPHADENITIS

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Case Report: KW, a 35-year-old healthy Caucasian female, presented with a painful lump under her right arm. Ultrasound revealed several lymph nodes in the right axilla, with two dominant nodes measuring 13mm and 8mm. Both demonstrated normal fatty hilum and vascularity. Diagnostic mammogram demonstrated no breast masses. PET CT showed hypermetabolic nodes in the right axilla but no primary breast lesion or mediastinal lymphadenopathy. Kw was referred to oncology for management of presumed node positive breast cancer.

Examination including breast exam, was unremarkable except for palpable 10x20mm right axillary lymph node and additional small right axillary adenopathy. CBC, CMP, and serologic tumor markers were normal. LDH was 808 U/L. Biopsy demonstrated no breast masses. PET CT showed hypermetabolic nodes in the right axilla but no primary breast lesion or metastasis. Hematopathology consultation was requested. Upon review, this was not felt to represent malignancy but instead necrotizing lymphadenitis consistent with Kikuchi-Fujimoto Lymphadenitis.

KW did not undergo surgery or chemotherapy. At one month follow-up, she reported persistent tenderness in her right axilla and on exam she had persistently palpable nodes that were unchanged in size. She was treated with a short course of high dose steroids. At two month follow-up, she had no further tenderness and axillary nodes were no longer palpable.

Kikuchi-Fujimoto Lymphadenitis is a subacute necrotizing lymphadenopathy of unknown etiology characterized by histiocytic proliferation and lymph node necrosis. It affects mostly young Asian females and cervical lymph nodes. Adenopathy and fever are primary symptoms. For severe symptoms, corticosteroids are recommended. The disease resolves spontaneously over several weeks to six months. Recurrence of disease occurs in 2-5% of patients.

This case illustrates the importance of careful evaluation and expert pathology review of atypical cases of cancer presentation.

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CAN THE TIMED UP AND GO DEFINE SEVERITY OF FALL RISK?

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Purpose of Study: We sought to determine whether Timed Up and Go (TUG) times might reflect different patterns of fall risk factor profiles. While prior studies have established TUG cut-points for “low-risk” and “high-risk” groups, the relationship between TUG time and fall risk factor profiles has not been previously examined.

Methods Used: Patients from an outpatient fall prevention clinic in Seattle were enrolled in a prospective chart review study. Patients were sorted into low, medium, and high fall risk groups based on their TUG time (<9, 10-19, and ≥20 seconds, respectively) at their first clinic appointment. Nonparametric and t-tests were used to compare these groups on demographics, comorbidities associated with falling, modifiable fall risk factors, and fall-related healthcare use.

Summary of Results: Statistically significant differences were observed between the 3 groups in the percent with cognitive impairment (low-risk 0% vs. medium-risk 14% vs. high-risk 58%, P<0.01), coronary artery disease (0% vs. 19% vs. 17%, P<0.01), obesity (0% vs. 16% vs. 25%, P<0.01) and mean number of comorbidities (1 vs. 2 vs. 2 comorbid conditions, P=0.02). Non-significant trends across groups were noted for use of ≥4 medications, (63% vs. 76% vs. 83%), presence of a gait or balance disorder (75% vs. 89% vs. 92%), lower extremity weakness (63% vs. 70% vs. 83%), poor visual acuity (25% vs. 35% vs. 50%), and depression (25% vs. 35% vs. 50%). The medium- and high-risk groups were more likely to be prescribed a hypoglycemic medication and less likely to be taking a vitamin D supplement. Mean serum vitamin D levels tended to be lower among those in the high-risk group (32.7 vs. 31.6 vs. 23.0 ng/mL). Medium- and high-risk groups were more likely to have a fall-related emergency room visit within two years prior to their appointment (13% vs. 22% vs. 33%, P<0.05).

Conclusions: Both statistically significant differences and non-significant trends were seen between the three groups defined by TUG time. The TUG test is easy to administer, and fall risk factor profiles based on TUG time have relevance both for future fall prevention research as well as for clinicians and aging service providers seeking to match patients at risk for falling with the most appropriate fall prevention program.

Hematology and Oncology II

Concurrent Session

1:30 PM

Saturday, January 28, 2012

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HIGH BCL11B EXPRESSION IS CORRELATED WITH HIGH C-MYC EXPRESSION AND ANTI-APOPTOTIC PHENOTYPE IN MEDULLOBLASTOMA

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Purpose of Study: Medulloblastoma are a heterogeneous group of highly malignant brain tumors that most often affect children. Outcomes among children vary widely and C-MYC amplification is the single most important molecular indicator of poor prognosis. Here we analyzed gene expression in high MYC expressing tumors and compared these results to low MYC expressing controls to identify new therapeutic targets for high MYC expressing medulloblastoma.

Methods Used: Primary tumor samples were obtained from surgeries performed at The Children’s Hospital of Colorado. RNA extracted from these samples was profiled using whole genome microarrays. Differentially expressed genes were profiled using Ingenuity Systems pathway analysis software. The results of this analysis identified the leukemia associated zinc
Experiments were conducted using a microfluidic device, Purpose of Study: The real-time localization of P-selectin in platelets

Illing DA, Brodsky G, DiPaola J
University of Colorado School of Medicine, 

Summary of Results:
Methods Used:

Purposes of Study:
AND IN VIVO STUDIES
INHIBITION OF MAMMARY CANCER STEM CELL
MCSCs express low levels of Vitamin D receptor (VDR) and are resistant to

BCL11B expression blocked colony formation in both Daoy and ONS-76 as well as

SILENCE OF BCL11B BY SMALL INHIBITORY RNA EXPRESSION IN VITRO
Transfection with a MYC expressing plasmid increased BCL11B expression. 

Conclusion: Silencing of BCL11B expression resulted in significant decrease in sphere diameter (72.8+/-4.8%) as well as in
described above. It had no effect in the liver tumor model (p=.87).

Results: Host syndecan-4 inactivation increased survival
all three experimental settings involving the lung tumor model (p=.02,.11,.60). However, it had no effect in the liver tumor model (p=.97).

Conclusions: Syndecan-4 expression in the tumor microenvironment has
site-specific effects on tumor growth, ranging from inhibitory in the lung
parenchyma and subcutaneous shoulder to stimulatory in the mammary fat pad. Data from lungs harvested during tumor growth shows that despite size differences, the number of tumor nodules is not decreased. This suggests that

blood was drawn into C1/Citrate tubes, it was incubated with the fluorescent antibodies, and then recalled with CoCl2 and added to the microfluidic device. Sufficient CaCl2 was added to increase the final blood [Ca+++] by 2 or 20 mM, depending on experimental aim. The blood was drawn through the device, mounted on a glass slide with a strip of deposited fibrillar collagen. The slide with collagen was incubated with bovine serum albumin before the experiment to prevent activation of platelets by the slide. The blood wall shear rate in the device was a constant 100s-1, representing conditions found in large veins. In select experimental treatments, PPACK (D-phenylalanine-L-prolyl-L-arginine chloromethyl ketone), a direct thrombin inhibitor, and abciximab, a GP IIb/IIIa inhibitor, were added to blood to assess differential effects of activation pathways on P-selectin expression and localization.

Summary of Results: Platelet aggregates formed under higher [Ca++] resulted in small, string-like, aggregates with diffuse P-selectin expression throughout the aggregate in a pattern similar to a honeycomb. Platelet aggregates formed under lower [Ca++] were large, often rounded, and displayed P-selectin localization to the periphery of the forming aggregates; large P-selectin devoid areas were seen inside the aggregate. In low [Ca++] experiments, the addition of PPACK did not result in any significant changes in aggregate morphology or P-selectin localization. Addition of abciximab to the low [Ca++] experiment resulted in diffuse localization of P-selectin throughout the aggregate, similar to the results in the high [Ca++] case.

Conclusions: The results from these experiments indicate that platelet aggregate morphology and P-selectin localization is dependent on extracellular calcium concentration and GP IIb/IIIa signaling.

378 NITRIC OXIDE POTENTIATES VITAMIN D INDUCED INHIBITION OF MAMMARY CANCER STEM CELL PROLIFERATION: INSIGHTS FROM IN VITRO AND IN VIVO STUDIES
Singh R12, Hewison M2, Chun R2, Karam A2, Braga M2, Chaudhuri G2, Pererin SL2, 1Charles Drew University, Los Angeles, CA and 2David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Vitamin D signaling in mammary cancer stem cells (MCSCs), which are implicated in the initiation, progression and recurrence of breast cancer, is poorly understood. We have previously reported that MCSCs express low levels of Vitamin D receptor (VDR) and are resistant to vitamin D treatment. The goal of this study is to evaluate the potential of combination therapy using low dose of nitric oxide (NO) with 1,25(OH)2 vitamin D3 (D3) in vitro under mammosphere conditions as well as in vivo in xenograft model.

Methods Used: Mammospheres enriched in MCSCs were grown in serum-free medium using ultra-low attachment plates. Mammospheres were treated with various concentrations of D3 either alone or in combination with low dose of DETA NONOate, a NO-donor for 1-7 days. Photomicrographs were analyzed for their average sizes by Image Pro software. MCSCs were treated with small inhibitory RNA (siRNA) targeted against Map Kinase Phosphatase 1 (MKP-1). Protein levels were analyzed by immunofluorescence and western blot analysis. Mammospheres (1 x 10^5) isolated from MCF7 cells were injected into humanized fat pads in nude mice with various combinaisons and tumor volume was monitored using calipers after 1-8 weeks. Tumor volume was calculated from pi-based ellipsoid volume formula pi/6.length.width.height.

Summary of Results: NO treatment of mammospheres led to a significant induction of MKP1 and dephosphorylation of ERK1/2. This effect was antagonized by MKP1 siRNA. While there was no considerable difference in mammosphere sizes after D3 treatment alone, combination of NO with D3 resulted in significant decrease in sphere diameter (72.8+/-4.8%) as well as in
tumor volume (32.6+/-14.4%) in nude mice.

Conclusions: Deactivation of constitutively active ERK1/2 signaling mediated via NO may target key survival pathways in MCSCs. Combination therapy using D3 or its potent analogues with NO donors may be more effective in treatment of aggressive breast cancer.

379 P-SELECTIN LOCALIZATION IN PLATELET AGGREGATES FORMED UNDER FLOW
Illing DA, Brodsky G, DiPaola J University of Colorado School of Medicine, Aurora, CO.

Purpose of Study: The real-time localization of P-selectin in platelets formed under flow on a fibrillar collagen substrate was investigated.

Methods Used: Experiments were conducted using a microfluidic device, developed previously for analysis of platelet phenotypes under flow. The formation of platelet aggregates was observed in real-time using fluorescence microscopy with anti-CD41 and anti-P-selectin fluorescent antibodies. After

Pervin S 1,2
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Purpose of Study: The real-time localization of P-selectin in platelets

binding site specificity of the calcium channel blockers.</ref>
Purpose of Study: Cancer patients are increasingly using the internet to guide decision-making concerning their disease. Although there is a substantial amount of information available on the internet regarding breast cancer, there are no studies evaluating whether it is comprehensive enough to support patients’ decision making. The purpose of this study was to analyze the quality of online breast cancer information.

Methods Used: Using the meta-search engines Yippy and Dogpile, and the search engine Google, a list of 100 breast cancer websites was compiled. The websites were assessed for accountability, interactivity, organization, readability, and content using a previously validated structured rating tool. Inter-rater reliability was assessed.

Summary of Results: The majority of the breast cancer websites were administered by commercial businesses (47%) and non-profit organizations (33%). 86% of the websites disclosed ownership, sponsorship, and/or advertising. Only 34% of websites identified the author and 39% cited sources. The majority of the information was out of date and 27% of websites had updated their content within the last two years. The average readability was a grade 9 level. Almost all websites were completely accurate or mostly accurate. While 88% of the websites sufficiently covered breast cancer, only 18% addressed prognosis.

Conclusions: Although the assessed websites were mostly accurate there were significant deficits in authorship, attribution, and currency. Additionally, very few provided information regarding prognosis. These data can be used to counsel patients on the strengths and weaknesses of web-based breast cancer information and to empower patients to choose sites likely to enhance their personal knowledge.

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UNCOUPLING NF-KB SIGNALING FROM PRO-SURVIVAL AND PRO-METASTATIC ACTIVITIES IN BREAST CANCER CELLS

Ferguson JE, Gonzalez AM, Orlando RA

Purpose of Study: Activation of the NF-kB pathway promotes pro-survival and pro-metastatic behaviors of advanced stage breast tumors. Since curcumin (CUR) and resveratrol (RES) are known to inhibit NF-kB signaling in many cell types, we explored their potential therapeutic effects along with two RES-based analogs on NF-kB-dependent, tumor promoting behaviors using an ER-negative breast cancer cell line.

Methods Used: NF-kB activity in MDA-MB-231 cells was quantified using an NF-kB promoter-driven GFP reporter plasmid and flow cytometry. Tumor cell invasiveness was measured using Matrigel invasion chambers and measurements of urokinase (uPA) activity were made by zymography. Breast cancer cell proliferation was quantified by BrdU incorporation assays.

Summary of Results: Constitutive NF-kB activity was strongly inhibited by all compounds tested; RES-analogs, LD38 and LD55, showed improved inhibitory activity when compared with CUR and RES. CUR and RES (60 uM) reduced uPA expression in MDA-MB-231 cells by 60% and 20%, respectively. LD38 and LD55 had no significant effects on uPA expression. CUR and RES inhibited MDA-MB-231 cell invasion by 95% and 80%, respectively, LD38 and LD55 also showed significant anti-invasive activity with 50% inhibition. CUR and RES both demonstrated anti-proliferative activity with IC50 values of 15 μM and 70 μM, respectively; LD38 and LD55 had no effect on DNA synthesis. 5-FU inhibited MDA-MB-231 cell DNA synthesis in a dose dependent manner as expected (IC50, 25 μM). When 5-FU was titrated against CUR, no additional inhibitory effect was measured on DNA synthesis. However, CUR did confer a significant level of protection against 5-FU cytotoxicity (LD50 of 5-FU alone, 39 μM; LD50 of 5-FU and CUR, >100 μM).

Conclusions: Although CUR, RES and RES-based analogs are effective inhibitors of NF-kB activation, we found a differential effect on cell invasion with CUR, RES and RES-based analogs on NF-kB-dependent, tumor promoting signaling in many cell types, we explored their potential therapeutic effects along with two RES-based analogs on NF-kB-dependent, tumor promoting behaviors using an ER-negative breast cancer cell line.

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CHARACTERIZATION OF FALLOPIAN TUBE EPITHELIAL CELLS AS POSSIBLE PRECURSORS FOR SEROUS OVARIAN CANCER

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Purpose of Study: There are several hypotheses regarding the cells of origin for serous ovarian cancer. One hypothesis is that fallopian tube epithelial cells transform and translocate to the surface of the ovary or disseminate in the abdomen. To test this hypothesis it is essential to characterize the epithelial cell population of the fallopian tube. We hypothesize that stem cells of the fallopian tube epithelia may be the cell of origin for serous cancers. This study seeks to characterize the expression of selected cytokeratins, β-tubulin and PAX8 in order to detect terminally differentiated (ciliated and secretory cells), partially differentiated and undifferentiated (stem cells) of the fallopian tube epithelia.

Methods Used: Paraffin-embedded fallopian tube sections from four patients were dual-stained for combinations for Keratin 5 (K5), Keratin 8 (K8), β-tubulin and PAX8.

Summary of Results: Expression of K8 was found throughout the fallopian tube and detected in secretory and ciliated cells. We have detected a population of partially differentiated 20% of all cells that express β-tubulin only in the cytoplasm and low levels of nuclear PAX8. These cells may represent the transient amplifying cells of the fallopian tube. Both of these cell populations in the fallopian tube are of interest as potential cells of origin for serous epithelial ovarian cancer.

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REDUCED INCIDENCE OF EARLY INVASIVE FUNGAL INFECTION IN ALLOGENEIC TRANSPLANT PATIENTS FOLLOWING MICAFUNGIN PHYLPROLAXIS

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Purpose of Study: Invasive fungal infection (IFI) is a significant cause of morbidity in allogeneic stem cell transplant (HSCT) patients. The incidence of IFI in our HSCT patients using low dose amphotericin B (LDAB) (10mg/m2) during the neutropenic phase is 20%. This study was performed to determine whether an alteration in prophylaxis was effective in reducing the incidence of IFI. We also aimed to identify risk factors for IFI.

Methods Used: We performed a retrospective analysis of the 67 patients undergoing HSCT between January 2010 and June 2011 and compared the incidence and risk factors for IFI (EORTC criteria) to our historical controls (n=69). Patients with a prior history of IFI were excluded. Inpatients undergoing myeloablative or unrelated donor non-myeloablative transplantation received micafungin 100mg daily and outpatient, non-myeloablative transplant patients received oral fluconazole 200 mg daily. Prophylaxis was started on day +1 and was continued until absolute neutrophil count >0.5 X 109/L.

Summary of Results: We saw a significant decrease in the overall incidence of IFI (10/67;15%), with 5% proven/probable and 10% possible IFI. The median time to diagnosis of IFI was 78 days. 2 patients developed an IFI during the first 30 days post HSCT (20%), 4 patients between days 30 and 100 (40%) and 4 patients developed an IFI after day 100 (40%). 50% (5/10) of patients who developed an IFI have died compared to 9% of the patients in the no IFI group (5/57). Mortality due to IFI was 30% in the IFI group. A significant risk factor for developing an IFI was steroid refractory graft versus host disease (GVHD) with an incidence of 56% (5/9) compared to 7% in patients with GVHD who did not require second line therapy (p=0.01).

Conclusions: We show a reduction in early IFI in receiving micafungin prophylaxis. This appears attributable to a reduction in the rate of early (< day
385 DEFINING VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER
Brittain P, Kelly S, Garcia D University of New Mexico, Albuquerque, NM.

Purpose of Study: Venous thromboembolism (VTE) is an important cause of morbidity and mortality for patients with active cancer. The role of primary VTE prophylaxis for outpatients with cancer is undefined; if such prophylaxis is to be of clinical benefit, it must be targeted at the subgroup of cancer patients at highest risk.

This study aims to validate a previously published VTE risk assessment model for cancer patients on active treatment.

Methods Used: Out of 770 patients receiving treatment for a pervasive DVT or PE at the University of New Mexico Anticoagulation Clinic, 59 who had cancer and were receiving chemotherapy at the time of the index DVT/PE were identified. The included VTE events were not thought to be secondary to central lines or tumor related pressure effects. These patients were age-matched with controls who had the same tumor type, stage, and gender but no VTE history. Patients’ VTE risk scores were calculated according to the model derived by Khorana. The model assumes VTE risk increases with the number of risk factors present: anemia (hemoglobin <10), leukocytosis (WBC count >11×10^9/L), thrombocytosis (platelet count ≥350×10^9/L), obesity (BMI ≥35), and tumor type (gastric and pancreatic are highest risk). Only pre-chemotherapy complete blood count values were used. Patients who did not have a CBC within a year before receiving any treatment were excluded. A Fisher’s exact test was used to compare the prevalence among the high, medium, and low risk groups.

Summary of Results: 14 of the 96 patients scored in the high risk category. Of the 14, 10 (71%) experienced a VTE event, 4 (29%) did not (p=0.56).

Conclusions: For the cancer patients in this case-control study, a VTE risk-dictates that a prophylactic approach should be adopted for high risk patients.

386 64CU-LIPOSOMES VS. [18F]FLUORODEOXYGLUCOSE AS POSITRON EMISSION TOMOGRAPHY CONTRAST AGENTS IN THE MURINE MET-1 TUMOR MODEL
Wong A, Ormsby E, Zhang H, Seo JW, Ferrara K University of California, Davis, Davis, CA.

Purpose of Study: 64Cu-liposomes may be useful in PET imaging of tumors. [18F]FDG, the dominant clinical PET tracer, has difficulty finding tumors that are small, in patients with hyperglycemia, or that demonstrate variable FDG uptake. While [18F]FDG finds areas of high metabolic activity, LCLs collect in tumors due to the Enhanced Permeability and Retention effect of leaky vasculature and dysfunctional lymphatics. The Ferrara lab has developed efficient and stable lipid chelators (48 hour 64Cu-liposomes were 0.661 +/- 0.074 and 0.733 +/- 0.086 respectively). Tumor contrast ratios of [18F]FDG and 48 hour 64Cu-liposomes were 0.661 +/- 0.074 and 0.373 +/- 0.056 respectively.

Methods Used: 28 female FVB mice implanted with murine Met-1 tumors were imaged with [18F]FDG PET, 64Cu-Liposomes, and ultrasound. Mice were sacrificed following imaging and underwent necropsy, biodistribution, and histology of tumors.

Summary of Results: Tumors were followed for 48 hours with 64Cu-liposomes. Tumor size by 64Cu-liposomes correlated strongly with [18F]FDG, ultrasound, histology, and excised tumor size (R=0.84, 0.75, 0.88, and 0.80 respectively). Tumor contrast ratios of [18F]FDG and 48 hour 64Cu-liposomes were 0.661 +/- 0.074 and 0.373 +/- 0.056 respectively.

Conclusions: 64Cu-liposomes deserve further study as contrast agents in cancer imaging. We demonstrate the ability to track tumors over 48 hours, the ability to size tumors, and comparable contrast ratio of 64Cu and [18F]FDG.

387 DETECTION OF MESOTHELIOMA USING AUTOANTIBODY SIGNATURES
Thomas D, Zhao L, Zhang X, Zhong L, WesternU, Pomona, CA.

Purpose of Study: Malignant mesothelioma (MM) is an asbestos-induced, highly aggressive tumor, and its survival is highly stage dependent. Patients treated with the best available therapies have survived 13 to 18 months in some studies, and with only supportive care the median survival is about 9 months. Therefore, novel diagnostic strategies may improve the dismal prognosis and allow detection of MM at a stage when combined treatment involving surgery, chemotherapy, and radiation therapy might be effective. Measurement of autoantibodies to tumor proteins has been proven effective to extend the range of diagnostic markers of diseases. In this context we propose to translate the humoral immune response to cancer proteins into a valuable blood test for MM. The goal of this proposal is to develop a blood-based early detection assay using disease-associated autoantibodies as biomarkers for MM.

Methods Used: In this study, a T7 phage cDNA library was constructed using MM tumor tissues. This phage library was then biopanned with pooled MM and normal serum samples. After four cycles of biopanning, 4000 of these enriched phage tumor-associated antigens (TAs) were spotted onto nitrocellulose coated microarray slides. These slides were then tested with 100 normal individual serum and 100 MM patient serum samples group to develop classifiers for distinguishing patients from normal samples.

Summary of Results: So far 43 phage clones have been identified statistically significant (p < 0.01) in distinguishing patient from normal samples. These clones are being further analyzed by logistic regression and receiver operating characteristic (ROC) curve to identify the most accurate combinations for MM detection. Eventually these involved phage clones will be identified through PCR and sequencing.

Conclusions: Autoantibodies could be useful biomarkers for MM early detection.

388 OUTCOME OF RETROPERITONEAL SARCOMAS TREATED AT THE UNIVERSITY OF WASHINGTON

Purpose of Study: Retroperitoneal sarcomas represent roughly 10-15% of soft tissue sarcomas, a group which itself accounts for less than 1% of all solid tumors. There is a great deal of controversy regarding the best management of these malignancies, but surgical resection remains the mainstay of treatment providing the only means of cure. This retrospective study examined outcomes for patients following surgery and radiation or chemotherapy.

Methods Used: At the University of Washington between January 2000 and April 2011 was performed. Patient demographics, tumor characteristics, treatment modalities, tumor response rate, and survival data were obtained from the Sarcoma Unit database and patient chart. Univariable Cox regression models described survival (OS) and recurrence-free survival (RFS) by tumor grade, resection type, and histology.

Summary of Results: One hundred and three patients were identified. Median follow-up was 40.3 months (2-257.3). The male: female ratio was 49:54. Tumor grade was as follows, low (n=25), intermediate (n=30), high (n=28) and not available (n=20). Histological subtype: leiomyosarcoma (n=20), liposarcoma (n=60), solitary fibrous tumor (n=3) and other (n=20). Forty-five patients underwent complete microscopic resection (R0) and 39 underwent R1 resections (tumor cells <1 mm from margin). Median OS was
111 months and median RFS was 37 months. Patients with high grade tumors had significantly worse OS (p=0.0483, HR 2.539, 95%CI 1.108-5.030) and worse RFS (p=0.0180, HR 2.280, 95%CI 1.152-4.513), compared to those with low grade tumors. No significant difference in OS was observed between those with R0 and R1 resections. Similarly, no significant difference in OS or RFS was observed between the different histological subtypes. Of twenty nine tumors treated with neoadjuvant chemotherapy, 9 progressed, 14 had stable disease, 2 improved and 4 had an unknown response.

Conclusions: These data confirm that surgical resection is the mainstay of management for retroperitoneal sarcomas, with median OS of 111 months and RFS of 37 months. This study suggests that neoadjuvant chemotherapy has no role in the management of these patients.

389 LEARNING ONCOLOGY FROM AN INTEGRATED INTERDISCIPLINARY PERSPECTIVE


Purpose of Study: A deficit in oncology education exists for medical students in North America. Exposure to oncology in undergraduate medical programs occurs sporadically in a discipline-specific manner, limiting students from experiencing the unique interdisciplinary nature of oncology. Emerging evidence suggests that integrated clerkships, where students work with health care professionals to manage disease, improve learning outcomes. The goal of this project is to develop an integrated interdisciplinary oncology elective supplemented by online modules and virtual patients (VP).

Methods Used: The Kern approach to curriculum development was used. A needs assessment of 3rd year medical students was conducted which polled interest levels for an integrated oncology clerkship and elicited preferences for educational material delivery. In 2008, following survey analysis, elective development began. To supplement clinical experiences, online modules complimented by branching-logic VP cases have been written and published. VP cases have been created using Vue, Open Labyrinth and Articulate. Software tools have been evaluated for the ability to analyze data from the online modules for education research.

Summary of Results: The needs assessment showed high interest in an integrated oncology clerkship supplemented by online learning: 50% (41/82) of students surveyed had not interacted with cancer patients during clerkship and 52% (51/82) felt their ability to discuss oncology issues with patients was poor or fair. 80% (65/82) felt that online modules would enhance learning. The modules for lung, prostate, breast and colorectal cancer along with their associated VP cases have been written, reviewed, and published online. Jasper iReports have been used to analyze use of the website. The integrated elective will be piloted in 2011.

Conclusions: The gaps in oncology education are addressed by the needs-based development of an integrated oncology clerkship that is complimented with online module components. Supplemental VP cases offer a unique learning opportunity where students practice clinical reasoning and experience the consequences of their decisions in a safe environment. Additional research will be done to determine the educational benefits of an integrated elective.

390 A NOVEL CASE OF DIAMOND-BLACKFAN ANEMIA WITH A 2Q11.2 CHROMOSOMAL DELETION

Fisher R, Clark RD, Bedros AA Loma Linda University, Loma Linda, CA.

Purpose of Study: To investigate the genetic cause of congenital anemia in a 6 month old child with features of Diamond-Blackfan anemia, which included severe macrocytic anemia, forearrow anomalies and thumb anomalies.

Methods Used: Cytogenetics, Comparative Genomic Hybridization, Fluorescence In-Situ Hybridization, DNA Sequencing.

Summary of Results: A child with a negative family history for Diamond-Blackfan anemia was found to have a large deletion at 2q11.2 by cGH. Gene sequencing for the genes known to cause Diamond-Blackfan anemia was normal. This observed deletion implicates several candidate genes in the deleted region as the cause of this child’s phenotype.

Conclusions: All gene mutations and deletions associated with the Diamond-Blackfan anemia phenotype discovered to date are ribosomal protein genes acting in an autosomal dominant manner by causing haploinsufficiency. The finding of a previously unreported gene deletion which includes a ribosomal protein gene in the deleted region likely identifies a new genetic cause of Diamond-Blackfan anemia.

Immunology and Rheumatology II

Concurrent Session

1:30 PM
Saturday, January 28, 2012

391 EXPOSURE TO ATTENUATED TOXOPLASMA GONDI AND SURFACE PROTEIN SAG1 BLOCKS THE DEVELOPMENT OF TH2-MEDIATED ASTHOMATIC AIRWAY INFLAMMATION

Lee S1,2, Arizabalaga G2,1, Miura T2,1 1University of Washington School of Medicine, Seattle, WA and 2University of Idaho, Moscow, ID.

Purpose of Study: Asthma is a respiratory disease characterized by acute bronchoe constriction and alveolar airway obstruction caused by a Th2-mediated hypersensitivity-type reaction to environmental allergens. Infection by Toxoplasma gondii has been shown to elicit a polarized Th1 cell-mediated response, effectively suppressing the Th2 response potentiating an asthmatic attack. The purpose of this study was to determine if exposure to either an attenuated strain of T. gondii (ATG) or its surface protein, SAG1, results in the suppression of Th2-mediated airway inflammation in allergen-sensitized mice.

Methods Used: Ovalbumin-allergen sensitized mice were separated into two experimental groups. One was exposed to the ATG, the other group was exposed to SAG1. Mice were administered ATG or SAG1 on days 3-7 by intraperitoneal (IP) injection. Mice from each group were then challenged with allergen either one week or one month post-vaccination. After sacrifice, lung lavage was collected for cytokine and cytological analysis. Two groups of control mice were also sacrificed and analyzed. For the purposes of evaluating the magnitude of allergic response, eosinophilia was quantified utilizing cell differentiating-logic VP and compared between groups.

Summary of Results: At one week post-exposure, in mice exposed to IP ATG, the eosinophilic increase associated with allergen challenge was markedly dampened when compared to unexposed mice. ATG exposed mice showed an eosinophil increase to 9.9% from a non-exposed baseline of 0.6%, compared with 40.4% in the corresponding control group. Mice receiving nasal SAG1 and challenged after one week witnessed an increase in eosinophilia from 2.6% at baseline to 30.4%. This is roughly half the response observed in unexposed, asthmatic mice, which was 56%.

Conclusions: ATG administered IP significantly reduced Th2-mediated allergic eosinophilia in mice for a period lasting at least one week. This protective effect was lost after one month. This effect was not seen in mice exposed to the ATG nasally. One-week challenged mice receiving SAG1 saw some protection as seen in contrast to asthmatic-control mice. One-month SAG1 mice were not protected from allergen-induced lung inflammation.

392 DECREASED INTRACELLULAR AND EXTRACELLULAR PRODUCTION OF THE HELPER 1 CYTKINE IL-17 BY CORD BLOOD MONONUCLEAR CELLS MAY CONTRIBUTE TO NEONATAL INFECTIONS

Caron J1, La Pine TR1,2, Augustine NH3, Martins TB3, Yost CC2, Hill HR1,2,3 1University of Utah, Salt Lake City, UT; 2University of Utah, Salt Lake City, UT and 3ARUP Institute, Salt Lake City, UT.

Purpose of Study: Human neonates and immunocompromised hosts are uniquely susceptible to severe and overwhelming bacterial and fungal infections. Defective neonatal polymorphonuclear leukocyte (PMN) activation and movement contribute to this increased susceptibility. The T helper 1 (Th1) lymphocytes produce cytokines. Following stimulation and intracellular transcription these cytokines are secreted extracellularly to affect target tissues. Th1 cytokines interleukin 17 (IL-17), has been described to act on fibroblasts and endothelial cells to recruit PMNs to sites of microbial invasation. Here, we examine cord blood monocytic cells in culture, production of IL-17 and measure intracellular IL-17 compared to adult controls.

Methods Used: Whole blood was collected from adults and umbilical cord blood from term deliveries. Mixed MMCs were isolated and stimulated with phytohemagglutinin (PHA), group B streptococcus (GBS) or E. coli, and then incubated for 24 hours in tissue culture medium. IL-17 production was
measured utilizing Luminex multianalyte technology. Phorbol myristate acetate (PMA) stimulated intracellular IL-17 production was measured by flow cytometry.

**Summary of Results:** In response to stimulation with PHA, GBS, or E.coli, IL-17 production was significantly diminished in cord blood. PHA (cord n=14, mean=0.2 pg/mL; adult n=16, mean=455 pg/mL; p=0.023). GBS (cord n=10, mean=0.2 pg/mL; adult n=12, mean=10.9 pg/mL; p=0.004). E. coli (cord n=10, mean=0.0 pg/mL; adult n=12, mean=12.5 pg/mL; p=0.001). Flow cytometry results demonstrate decreased PMA stimulated intracellular IL-17 production in the cord blood cells compared to cells from adults (cord n=6; MFI=0.0%; adult n=5;MFI=13.9%; p<0.01).

**Conclusions:** IL-17 has a profound effect on the immune response to bacterial and fungal infections. For instance, IL-17 production is markedly deficient in autosomal dominant Hyper IgE (Job Syndrome) patients who suffer recurrent bacterial and candida infections. This study is the first to describe defective production of intracellular and extracellular IL-17 by neonatal MMCs; which may contribute to the human neonates increased susceptibility to microbial infections.

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**THE TRANSCRIPTION FACTOR ZF521 REGULATES MAST CELL DEVELOPMENT**

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**Purpose of Study:** Mast cells are primarily known for their role in immunoglobulin E (IgE)-associated immune responses in allergic reactions. However, mast cells also participate in host defense during innate and adaptive immune responses and in chronic inflammatory diseases. Although mast cells have diverse functions in innate immunity, little is known about transcriptional regulation and the signaling pathways that lead to their distinct roles. The transcription factor Zinc-finger protein 521 (Zfp521) plays an important role in the differentiation of hematopoietic cells including B lymphocytes and erythrocytes. Because mast cells also express Zfp521 at high levels, we sought to elucidate the role of Zfp521 in mast cell development.

**Methods Used:** The Zfp521ko/ckoMcpt5-Cre mouse model was created to study the role of Zfp521 in mast cells. This model deletes coding sequences of Zfp521 genes using the Cre/loxP recombination system under the control of the mast cell protease (Mept)-5 promoter. The ‘floxed’ functional copy of Zfp521 is excised by Cre recombine specifically in mast cells, but not in other tissues that express Zfp521. Flow cytometry was performed on cells isolated from the peritoneal cavity of Zfp521ko/ckoMcpt5-Cre mice to examine the effect of Zfp521 inactivation in the mast cell population.

**Summary of Results:** Zfp521ko/ckoMcpt5-Cre mice exhibited as few as 25% of normal numbers of mast cells. Mast cell development is likely impeded in bone marrow precursors, which reduces their differentiation into mature mast cells in peripheral tissues. Current research is enumerating mast cells in the intestinal mucosa and culturing bone marrow-derived mast cells for analysis of specific gene expression and function.

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**IDENTIFICATION OF CD40 LIGAND AND ICOS DEFECTS IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES**

Martins TB1, Augustine NH1,2, Kumanovics A1,2, Hill HK1,2 1ARUP Laboratories, Salt Lake City, UT and 2University of Utah School of Medicine, Salt Lake City, UT.

**Purpose of Study:** Hyper IgM syndrome (HIGM) and common variable immunodeficiency (CVID) are two primary immunodeficiencies characterized by IgG deficiency. In HIGM, IgG and IgA deficiency are combined with normal or high IgM levels due to Ig class switching deficiency. In CVID, the IgA and IgM levels can be low or normal making the differential diagnosis difficult. Defects in CD40 ligand (CD40L) expression on T cells are most often the cause of HIGM, while partial CD40L deficiency has been described in CVID. Inducible T-cell costimulator (ICOS) is a costimulatory molecule expressed on activated T cells which has been found defective in some CVID patients. The purpose of this study was to determine CD40L and ICOS expression in HIGM and CVID patients.

**Methods Used:** We developed a quantitative flow cytometric assay for determining CD40L and ICOS expression on stimulated and unstimulated T cells using whole blood. Expression of these two molecules was then examined on T cells obtained from two male HIGM and 19 CVID (13 female, 6 male) patients, as well as 13 related family members, which were compared to healthy controls.

**Summary of Results:** CD40L expression was absent in both HIGM patients and one female CVID patient. An additional 4 CVID patients (1 male, 3 female) showed half normal CD40L expression compared to healthy controls. No deficiencies were found for ICOS expression in any of the HIGM or CVID patients.

**Conclusions:** This assay should be useful as an aid in the diagnosis of HIGM and CVID patients, for screening family members as potential carriers, and in the investigation of co-stimulatory functions of T cells.

**HEMATOPOIETIC CHANGES DURING MYCOBACTERIAL INFECTION IN ZEBRAFISH**

Levitte S1, Ramakrishnan L1,2,3 1University of Washington, Seattle, WA; 2University of Washington, Seattle, WA and 3University of Washington, Seattle, WA.

**Purpose of Study:** Mycobacterium tuberculosis (Mtib) infection in humans can result in a range of phenotypes, from resistance to progressive and severe disease. An infection model to study the mechanisms underlying this phenomenon has been developed using zebrafish and Mycobacterium marinum (Mm), a close genetic relative of Mtib. Previous studies identified mutations that change the abundance of inflammatory mediators, resulting in susceptibility to Mm and Mtib infection. Furthermore, studies in humans have found that disrupting the balance between erythropoiesis and myelopoiesis result in susceptibility to mycobacteria. This study investigates whether altering hematopoietic pathways in zebrafish leads to Mm susceptibility, and takes the first steps in describing alterations in normal hematopoiesis during the course of Mm infection.

**Methods Used:** Wild-type zebrafish larvae were infected by microinjection into the caudal vein. Morpholino oligonucleotides (MOSs) were injected at the 1-4 cell stage to disrupt gene function. Results were gathered by microscopy and imaging of infections or by RT-PCR to assess transcript abundance.

**Summary of Results:** Zebrafish lacking the transcription factor gata1 had increased numbers of macrophages (~2x) and neutrophils (~10x) but did not display increased susceptibility to infection over wild type. Furthermore, levels of the gata1 transcript decreased over the course of wild type infection. Confocal microscopy of Mm granulomas showed that while more neutrophils were present in gata1 morphants, it was unclear if they were taking part in granuloma formation. RT-PCR analysis of 6 genes involved in hematopoiesis and myelopoiesis identified several genes involved in myelopoiesis and erythropoiesis are induced during Mm infection.

**Conclusions:** To date no studies have investigated the effect of increased myeloid effector cells during Mm infection. The lack of a susceptibility or resistance phenotype in gata1 morphants compared to wild type could be explained by decreased expression of genes that limit myeloid cell number during wild type infection. This hypothesis is currently being tested. Finally, this study demonstrated that hematopoiesis undergoes significant changes during the course of infection that merit further investigation.

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**CYCLOSPORINE TO TREAT SEVERE URTICARIA AND ABDOMINAL PAIN DUE TO ANTIBODIES TO IgE RECEPTOR**

Wang KY, Roberts RL UCLA, Los Angeles, CA.

**Case Report:** Rationale: Urticaria and abdominal pain due to antibodies to the IgE Fc receptor in children with oral cyclosporine.

Methods: We described 2 children with urticaria due to IgE antibodies. The urticaria only responded to prednisone. She was also treated with cyclosporine. The first patient started to develop severe, painful urticaria and abdominal pain at 5 years. Work-up showed no evidence of antibodies (IgE 58 IU/ml) but positive for antigenic antibody (1:320) and thyroid antibodies. The urticaria only responded to prednisone. She was then treated with cyclosporine. The second patient developed severe urticaria and severe abdominal pain at 14 years. She also...
had a low IgE (38 IU/ml) but positive for ANA (1:160). The lesions only responded to daily prednisone (25 mg/daily). She also had antibodies to IgE receptor (64%).

Results: The first patient was started on cyclosporine (initially 150 mg daily) and we were able to taper off completely the prednisone within 2-3 months. The urticarial lesions completely resolved as did the abdominal pain.

The second patient was also started on cyclosporine (175 mg/day) and we were able to taper her prednisone to zero without the recurrence of urticaria in 3 months. Her abdominal pain also resolved.

Conclusion: Children with severe urticaria due to antibodies to IgE receptor went into complete remission with oral cyclosporine. Their abdominal pain also resolved with cyclosporine, suggesting that the pain could have also been due to the antibodies to IgE receptor which may have caused local abdominal pain by histamine release in the gut.

Neonatal – Pulmonary II
Concurrent Session
1:30 PM
Saturday, January 28, 2012

397 ACTIVATION OF WNT SIGNALING BY LUNG MESENCHYMAL STROMAL CELLS IN A RODENT PERINATAL VITAMIN D DEFICIENCY MODEL OF CHILDHOOD ASTHMA
Gorman C, Villarreal P, Anthony S, Sakurai R, Torday J, Rehan VK

Purpose of Study: Vitamin D deficiency during the perinatal period leads to altered pulmonary structural development, predisposing to airway hyperresponsiveness. Though the effects of vitamin D deficiency on alveolar type II cells and lipofibroblasts have been relatively well-characterized, its effect on lung mesenchymal stromal cells (LMSC), a cell type known to be critically important in chronic lung diseases such as asthma is not known. We hypothesized that Vitamin D deficiency during lung development activates Wnt signaling and down-regulates PPARy expression by LMSCs, driving them to a myogenic phenotype.

Methods Used: 4 weeks prior to pregnancy, Sprague-Dawley rats were started on the following 4 dietary regimens, which were continued through pregnancy and lactation i) No cholecalciferol added diet ii) 250 IU/kg iii) 500 IU/kg or iv) 1000 IU/kg cholecalciferol added groups. After delivery, at postnatal day 21, the pups were killed and the lung tissue was collected and processed to culture LMSC following standard methods. Using qRT-PCR, Western blotting, immunostaining, and triglyceride uptake assay, passage 2-3 cells were used for molecular and functional characterization under basal conditions, and following adipogenic or myogenic induction.

Summary Results: By flow cytometry, >95% of cells were CD45neg, CD105neg, Stro-1pos, and CD45pos, indicating their undifferentiated mesenchymal phenotype. Compared to the vitamin D-added groups, with vitamin D deficiency there was activation of Wnt signaling (increased LEF-1 and p-Bcatenin) and suppression of PPARy signaling (decreased PPARy and leptin expression), accompanied by an enhanced myogenic phenotype (increased cSMA, fibronectin, and vimentin expressions), under basal conditions and following adipogenic or myogenic induction. 500 IU/kg cholecalciferol supplementation most effectively blocked the effects of perinatal vitamin D deficiency.

Conclusions: These data further support the concept that in the developing lung, VEGF-R2, are reduced in the immature lung by prolonged MV. Another family of pro-angiogenic molecules is the ephrin family (ephrin ligands and eph receptors). Eph receptors are implicated in angiogenesis in the lung. EphA2 receptor, for example, affects angiogenesis by activating migration of endothelial cells and their assembly into capillaries. Whether the ephrin/eph family of receptor tyrosine kinase ligands/receptors is down-regulated in the lung of chronically ventilated preterm neonates is not known. We hypothesized that prolonged MV decreases ephrin ligands and eph receptors in the lung of preterm lambs.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV or nasal high-frequency ventilation (nasal HFV) (n=4 each) for 21d. We used nasal HFV as the positive gold standard for outcome. Frozen lung tissue was analyzed by immunoblot for ephrinB1 ligand as well as EphA2, A3, and A4 receptors.

Summary of Results: MV for 21d did not affect protein abundance of ephrinB1 ligand in the lung compared to nasal HFV for 21d. On the other hand, MV for 21d significantly reduced protein abundance of EphA2 (~20%; p<0.05), A3 (~50%; p=0.05), and A4 (~75%; p<0.05) receptors in the lung compared to nasal HFV for 21d. Eph receptors were immunolocalized in mesenchymal cells in the walls of distal airspaces.

Conclusions: We conclude that MV for 21d decreases Eph receptor expression in the lung of preterm lambs. Decreased amounts of angiogenic receptors (VEGFR2 and EphB2, R2 and Ephins) may reflect fewer angiogenic progenitor cells. We speculate that replacement of angiogenic progenitor cells may be an approach to facilitate capillary growth in the lung of preterm neonates that require prolonged support by MV.

398 MECHANICAL VENTILATION DECREASES EPHA2, A3, A4 IN THE LUNG OF CHRONICALLY VENTILATED PRETERM LAMBS
Weinlander E2, Alvord J1, Wimmer J1, Houston B1, Dong L1, Dahl MJ1, McKnight RA1, Null DM3, Yoder BA1, DiGeronimo R2, Lane RH1, Albertine KH1

University of Utah, Salt Lake City, UT and 2Lawrence University, Appleton, WI.

Purpose of Study: Prolonged mechanical ventilation (MV) of preterm neonates leads to alveolar simplification. An element of simplification is less thickened alveolar walls that contain accumulations of interstitial cells. A hypothesis is that MV for 21d decreases Eph receptors in the lung compared to nasal HFV for 21d. We measured protein abundance of EphrinB1 ligand as well as EphA2, A3, and A4 receptors.

Methods Used: Preterm (PT) neonates who develop neonatal chronic lung disease (CLD) frequently have long-term, recurrent respiratory problems such as airways hyperreactivity and recurrent respiratory infections. The underlying mechanisms leading to these long-term consequences are unknown. To begin to investigate potential mechanisms, we modified our PT lamb model of neonatal CLD to deliver the preterm lambs earlier in gestation, wean them from mechanical ventilation (MV), and let them recover for ~3 months, which is equivalent to ~2 years postnatal age in humans. We recently showed that long-term consequence of brief ventilation support is persistently thickened alveolar walls that contain accumulations of interstitial cells. A family of molecules that direct developmental progression of interstitial cells to endothelial cells is the ephrin family (ephrin ligands and eph receptors). We hypothesized that ephrin ligands and eph receptors in the lung are altered in former MV PT lambs.

Methods Used: Pregnant ewes were given dexamethasone before delivery of PT lambs (~128d gestation; term ~130d). The PT lambs were intubated, given surfactant, managed by MV for 3d, weaned from ventilation support, and lived for 10-11wk more (PT weaned; n=6). Control lambs were born at term gestation (~3 wk after the PT lambs were delivered) and lived for 8-wk more (T+8wk control; n=6). Lambs were fed ewe’s colostrum and milk. Lung tissue was analyzed by immunoblot for ephrinB1 ligand as well as EphA2, A3, and A4 receptors.

Summary of Results: Protein abundance of ephrinB1 ligand in the lung did not change in former MV PT lambs compared to control lambs. In contrast, protein abundance of EphA2 (~30%; p=0.05) and A3 (~30%; p<0.05) remained greater in former PT lambs. Eph receptors were immunolocalized in interstitial cells in alveolar walls.

Conclusions: Eph receptors are persistently increased in interstitial cells in the lung of former MV PT lambs. We speculate that this increase may reflect delayed developmental progression of interstitial cells into capillary endothelial cells.

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HYPEROXIA INDUCES ALVEOLAR HYPOPLASIA THROUGH CHANGES IN ADENOSINE RECEPTOR EXPRESSION IN NEWBORN MICE

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Purpose of Study: To determine the impact of hyperoxia exposure on adenosine receptor expression during alveolar development in newborn mice.

Methods Used: Newborn mice from timed-pregnant dams were divided into 4 experimental groups: 1) saline normoxia (FiO2 21%); 2) saline hyperoxia (FiO2 0.80); 3) caffeine normoxia; and 4) caffeine hyperoxia. Starting at P1, pups were treated with daily i.p. injection of saline or adenosine antagonist, caffeine (20 mg/kg, 10 mg/kg daily caffeine citrate), under constant normoxia or hyperoxia conditions. Animals were sacrificed at P15 to collect BAL and lung tissue for mRNA, protein, and histological analysis.

Summary of Results: Hyperoxia-exposed pups showed poorer weight gain compared to normoxia controls. Lung histology also exhibited larger alveolar airspaces with reduced radial alveolar counts in hyperoxia groups when compared to normoxia controls (p < 0.05). Pups exposed to hyperoxia had a significant decrease in adenosine receptor (A1 and A3) receptor expression as demonstrated by immunofluorescence and quantitative PCR (p < 0.05). In contrast, A1 and A3 receptor expression decreased markedly during hyperoxia. Finally, caffeine treatment decreased A1 and A3 receptor expression in normoxia while decreasing A2A receptor expression during hyperoxia alone.

Conclusions: A2A and A1/A3 receptors exhibit different roles in regulating alveolar formation during hyperoxia exposure in developing mouse lungs. Our findings further suggest that caffeine adversely impacts alveolar development under hyperoxic conditions in this animal model.

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SIPAP AND CPAP PROVIDE EQUIVALENT SUPPORT IN LOW BIRTH WEIGHT INFANTS WITH RESPIRATORY DISTRESS

Lampard A1,2, Plum B3, Meyers P1, Worwa C1,2, Mammel MC1,2

1Children’s Hospitals and Clinics of MN - St. Paul, St. Paul, MN and 2University of Minnesota, Minneapolis, MN.

Purpose of Study: Compare effects of bi-phasic continuous positive airway pressure (SiPAP) versus standard continuous positive airway pressure (CPAP) in low birth weight infants (LBW) with respiratory distress.

Methods Used: Non-blinded, randomized cross-over study of 20 LBW infants on CPAP for >24 hours and requiring FiO2 0.25 - 0.5 at study entry. Patients were randomized to CPAP followed by SiPAP, or the opposite sequence, for four alternating 60-minute periods. Mean airway pressures and oxygen saturations were targeted similarly in both modes. Transcutaneous carbon dioxide (TCO2) values, pulse oximetry, and vital signs were monitored throughout the study. A 3-channel pneumogram documented apneic, bradycardic, and desaturation events. Pneumogram results and physiologic data from the last 20 minutes of each block were analyzed by paired 2-tailed t-test. P<0.05 was significant.

Summary of Results: Average patient weight was 1310 grams (±733) and FiO2 was (0.36) ±0.04 at study entry. There were no significant differences in heart rate (HR), oxygen saturations (SaTs), TCO2 values, respiratory rate (RR), or FiO2 (See Table 1). Infants had significantly lower diastolic (DBP) and mean blood pressures (MBP) on CPAP versus SiPAP. No significant differences in prolonged (>20 seconds) apnea, bradycardia or desaturation events were noted between the two modes.

Conclusions: When targeted at the same mean airway pressure, SiPAP has no evidence for significant clinical benefit over the use of conventional CPAP for treatment of respiratory distress in the low birth weight population.

Clinical Data Comparisons

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<tr>
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<th>CPAP</th>
<th>SIPAP</th>
<th>p-value</th>
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<tr>
<td>HR</td>
<td>168.2 (±12.2)</td>
<td>167.3 (±12.1)</td>
<td>0.5</td>
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<tr>
<td>SaTs</td>
<td>87.4 (±2.9)</td>
<td>87.3 (±3.8)</td>
<td>0.98</td>
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<tr>
<td>TCO2</td>
<td>54 (±7.1)</td>
<td>55.2 (±6.4)</td>
<td>0.91</td>
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<tr>
<td>RR</td>
<td>67.9 (±9.5)</td>
<td>67.6 (±9.9)</td>
<td>0.7</td>
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<td>FiO2</td>
<td>35.1 (±4.8)</td>
<td>29.4 (±4.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>SDB</td>
<td>68.4 (±10.4)</td>
<td>69.8 (±10.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>DBP</td>
<td>42.5 (±7.4)</td>
<td>45.1 (±8.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>MBP</td>
<td>52.2 (±9.3)</td>
<td>50.4 (±9.5)</td>
<td>0.61</td>
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<tr>
<td>Apnea</td>
<td>0.4 (±1.1)</td>
<td>1.0 (±0.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.63 (±0.2)</td>
<td>0 (±0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Desaturation</td>
<td>2.7 (±4.4)</td>
<td>2.9 (±5.0)</td>
<td>0.67</td>
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INTRAUTERINE GROWTH RESTRICTION INCREASES LUNG NITRIC OXIDE SYNTHASE ACTIVITY AT BIRTH AND DELAYS ONSET OF RIGHT VENTRICULAR HYPERTROPHY IN FEMALE BUT NOT MALE RATS

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Purpose of Study: Intrauterine growth restriction (IUGR) increases the incidence of pulmonary hypertension (PH) in newborns and adults. Both neonatal and adult forms of PH are associated with decreased nitric oxide synthase (NOS) activity. Normal vascular growth requires NOS activity at critical periods during development. Abnormal pulmonary vascular growth may predispose IUGR offspring to PH. We have shown that IUGR male rats develop right ventricular hypertrophy, a marker of elevated pulmonary vascular pressures, sooner than IUGR female rats. Whether IUGR alters age- and gender-specific levels of the endothelial (eNOS) and inducible (iNOS) NOS isoforms and total NOS activity in IUGR rat lungs is not known. We hypothesize that IUGR will decrease NOS protein and activity in male but not female rat lungs at birth.

Methods Used: IUGR was induced in pregnant Sprague-Dawley rats by bilateral uterine artery ligation at day e19 of a 21.5 day gestation. Pups were surgically delivered at e21. Pup lungs were harvested at postnatal days (P) 0, P21, and P100. Whole-lung eNOS and iNOS protein levels and total NOS activity were measured.
Summary of Results: IUGR decreased whole-lung eNOS protein levels and increased iNOS protein levels in male and female rats at P0. IUGR had no effect on whole-lung total NOS activity in males but increased activity in females at P0. IUGR decreased whole-lung eNOS and iNOS protein levels in males and had no effect in females at P21. IUGR increased whole-lung total NOS activity in males and females at P21. IUGR decreased whole-lung eNOS protein levels in males and increased levels in females at P120. IUGR had no effect on iNOS protein levels in males or females at P120. IUGR had no effect on whole-lung total NOS activity in males or females at P120.

Conclusions: IUGR affects NOS protein levels and activity differently in male and female rat lungs. Contrary to our hypothesis, NOS activity was not decreased in male lungs at birth but was increased in females. We speculate that increased whole-lung NOS activity at birth may be protective against early development of PH in IUGR females.

404 PULMONARY FUNCTION, OXYGEN CONSUMPTION, AND EXHALED NITRIC OXIDE MEASURES FOR EXTREMELY LOW BIRTH WEIGHT, HEAVIER PRETERM, AND TERM CHILDREN

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Purpose of Study: To assess the impact of preterm birth on childhood pulmonary function and oxygen consumption measurements. Secondary objective is to assess levels of exhaled nitric oxide in preterm versus term children and relationship to clinical findings.

Methods Used: Pulmonary function and treadmill exercise testing were performed at 12-15 years of age after obtaining medical history for 39 children born in 1993-95 who had been enrolled in a neurodevelopmental preterm follow-up program, including 12 extremely low birth weight (ELBW), 18 heavier preterms (HPT), and 9 born at term with normal birth weight (NBW). Exhaled nitric oxide (FeNO) levels were determined prior to exercise testing by utilizing NIOX Flex® or NIOX Mino®. Testing results were compared between groups using univariate analysis with P <0.05 significance.

Summary of Results: Mean BW and GA were significantly different per study protocol (ELBW 674±83 g, 24.7±1.3 wk; HPT 195±278, 33.2±1.7; NBW 3661±770, 38.9±0.2). Pulmonary function results did not differ between groups, although ELBW children tended to be lowest (FEV1, 97%±18, 103%±15, 107%±13; FEV2−50, 87%±28, 98%±26, 103%±25, P=3). Mean VO2max also did not differ between groups (38.8±41.2; 43±14 mL/kg/m) and the percents of infants with VO2max <35 were not different. 33 children had FeNO measurements, which were significantly higher in males (15.5±6.3 and 10.7±7.1 ppb, P=0.08) but not different by BW category (10.2±9, 15.2±16, 10.4±6, P=0.11). 3 children, all former preterm, had high FeNO (>20 ppb). The other preterm children had intermediate FeNO (16-20 ppb); however, FeNO did not correlate with VO2max or PFTs.

Conclusions: These findings show no differences in pulmonary function and oxygen consumption measurements between ELBW, heavier preterm, and term children born in the 1990s. Findings vary from previous studies and suggest improved pulmonary outcomes and exercise capacity for even extremely preterm infants born in the past decade. The preliminary data on pulmonary function and oxygen consumption measurements. Secondary objectives include comparisons of FeNO measurements between groups utilizing NIOX Flex® or NIOX Mino®. Testing results were compared between groups using univariate analysis with P <0.05 significance.

406 IUGR’S EFFECTS OF HYPOTHALAMIC OREXIN AND MELANIN CONCENTRATING HORMONE EXPRESSION IN YOUNG ADULT MICE

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Purpose of Study: Intrauterine growth restriction (IUGR) with rapid postnatal catch-up growth predisposes towards early onset of obesity. Rapid postnatal catch-up may originate from increased food intake. Food intake is regulated centrally by the hypothalamus. Two hypothalamic orexigenic neuropeptides that have received little attention after IUGR are orexin and melanin concentrating hormone (MCH). We hypothesize that IUGR mouse offspring will consume more food per day after weaning from lactation and have increased hypothalamic orexin and MCH mRNA levels at postnatal day 60 (P60).

Methods Used: IUGR was induced via maternal thromboxane A2-analog infusion in the last week of C57BL/6J mouse gestation. Sham operated dams acted as controls. IUGR offspring weighed 15% less at birth. Sham and IUGR offspring were cross-fostered to unmanipulated dams and weaned to standard mouse chow at P21. IUGR males exhibited catch-up growth at P28. IUGR females exhibited catch-up growth at P77. We measured food intake from P21 to P60. We measured hypothalamic orexin and MCH mRNA levels at P60 via quantitative real-time RT-PCR.

Summary of Results: IUGR offspring consumed similar amounts of food compared to their gender-matched sham offspring from P21 to P60 (0.18±0.04 grams of food/gm of body weight/day in IUGR males vs. 0.19±0.05 in sham males; 0.20±0.06 in IUGR females vs. 0.19±0.04 in sham females, n=9-11/group). IUGR elicited a trend towards decreased hypothalamic orexin and MCH mRNA levels in males only at P60 (72±8% and 76±8% respectively in IUGR males vs. 100: 12% and 100: 18% respectively in sham males, n=6/group).

Conclusions: Despite consuming the same amount of food as sham males, young adult IUGR males showed decreased hypothalamic orexin and MCH mRNA levels. This discordance between food intake and hypothalamic expression suggests that IUGR males may have disrupted food intake regulation. Activity is also regulated by orexin and MCH. Having decreased hypothalamic orexin and MCH expression additionally suggests that IUGR males may have decreased activity. Collectively, these two mechanisms may

Neuroscience II

Concurrent Session

1:30 PM Saturday, January 28, 2012

405 INTRAUTERINE GROWTH RESTRICTION INCREASES ESTROGEN RECEPTOR ALPHA PROTEIN LEVELS IN THE CA1 AND CA3 REGIONS OF THE MALE RAT HIPPOCAMPUS

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Purpose of Study: Intrauterine growth restriction (IUGR) predisposes to impaired neurodevelopmental outcomes in humans and in the rat, particularly in males. This impaired neurodevelopment is related to hippocampal dysfunction and increased hippocampal apoptosis. Hippocampal apoptosis results from estrogen which mediates its effects via estrogen receptors α and β. IUGR reduces hippocampal levels of the estrogen synthesizing enzyme aromatase, local hippocampal estrogen levels and total hippocampal estrogen receptor mRNA levels in male rats. However, the effect of IUGR on hippocampal estrogen receptor protein levels on discrete regions of the male rat hippocampus is not known. Based on this background, we hypothesized that IUGR will reduce estrogen receptor levels in discrete regions of the male rat hippocampus.

Methods Used: IUGR was induced in Sprague-Dawley rats by bilateral uterine artery ligation at e19.5. C-section was done at e21 (term). Newborn rats were perfused, brains dissected, fixed and embedded. Frozen whole brain sections of hippocampi were triple immunofluorescent stained for DAPI, NeuN and either estrogen receptor α or β. Confocal microscopy was used to image the sections which were then analyzed and quantified using ImageJ software.

Summary of Results: Contrary to our hypothesis, IUGR increased estrogen receptor α protein levels two-fold in the CA1 and CA3 regions of the male rat hippocampus. No effect was seen on estrogen receptor protein α levels in the dentate gyrus. No effect was seen on estrogen receptor β levels in any hippocampal region.

Conclusions: We conclude that IUGR affects estrogen receptor levels in the male rat hippocampus in a region and receptor specific manner. We speculate that the increase in estrogen receptor α levels is a homeostatic response to the decrease in local hippocampal estrogen levels. To determine whether estrogen signaling downstream from the receptor is affected, we will examine the effects of IUGR on estrogen receptor phosphorylation and co-immunoprecipitation of estrogen receptor with transcription factors. Reduction in estrogen signalling in the hippocampus would be reflected by decreased estrogen phosphorylation and decreased transcription factor binding to estrogen receptors.
account for the faster catch-up growth seen in UGR males. We speculate that the disrupted hypothalamic orexin and MCH expression predisposes IUGR males to an earlier onset of obesity.

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THE INCIDENCE OF ZURICH CONCUSSION GUIDELINES USE IN SPORTS MEDICINE IN IDAHO AND WASHINGTON
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Purpose of Study: The guidelines for concussion screening and management constantly change to accommodate for new evidence-based information. The purpose of this study was to determine the knowledge, use, and perceptions of the current standardized guidelines, known as the Zurich guidelines, by physicians and athletic trainers in Washington and Idaho, to determine what barriers exist to implementing these guidelines in clinic, and inquire about ways in which the current guidelines may be improved.
Methods Used: Surveys were produced for each study group to gather data regarding the knowledge, use, and perception of the Zurich guidelines. Reliability and validity of the tools were established and the surveys were sent and collected via e-mail, fax, post-mail, and by hand. Responses were analyzed using SPSS 18 statistical software.
Summary of Results: 46 physicians and 61 athletic trainers responded to the survey. Both groups stated that they were more than “somewhat familiar” with the Zurich guidelines (physician: X = 3.36 ± 0.77, athletic trainer: X = 3.33 ± 0.96). Despite the majority of respondents stating that they use the guidelines (physician: 86.7%, athletic trainer: 71.7%), and agreeing that they are quality guidelines (physician: X = 5.20 ± 0.77, athletic trainer: X = 5.26 ± 0.64), 73.7% of physicians and 73.6% of athletic trainers stated that they deviate from the guidelines. 81.0% of physicians and 83.6% of athletic trainers stated that family history of brain injuries may improve concussion management. Lack of knowledge or experience using the guidelines was cited as the greatest barrier to clinical implementation (physician: X = 2.40 ± 1.51, athletic trainer: X = 3.00 ± 1.08).
Conclusions: Future studies should investigate the areas of the guidelines from which clinicians are deviating and what causes them to deviate. Specific patient outcomes studies should investigate clinical situations in which the guidelines are adhered to and deviated from to help determine the effectiveness of the guidelines. Lastly, in order to continually improve concussion management guidelines, more biomedical and translational research investigating a potential genetic link to concussion susceptibility, as well as other concussion screening and management methods, is necessary.

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THE DORSAL MEDIAL HYPOTHALAMUS MEDIATES PAIN HYPERSENSITIVITY INDUCED BY CHRONIC STRESS
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Purpose of Study: Stress and pain are closely linked through common neural circuits, as reflected in the dual effects of stress on pain thresholds: acute, intense stress decreases sensitivity to pain via neural pathways in the midbrain and brainstem, whereas prolonged but less severe stress causes increased sensitivity to pain (hyperalgesia) through yet unknown pathways. Prolonged stress also increases heart rate, blood pressure, and core temperature, all mediated by the hypothalamus. Direct stimulation of the dorsal mediolateral region of the hypothalamus (DMH) in anesthetized rats reproduces these physiological stress responses and also increases pain sensitivity. The goal of these experiments was to identify a neural pathway by which prolonged stress produces hyperalgesia in awake, behaving rats.
Methods Used: Awake Sprague-Dawley rats were stressed using a period of restraint combined with a low-flow stream of air directed at the face (30 min). Mechanical pain thresholds were measured before and after the stress paradigm. To assess the role of the DMH in this stress-induced hyperalgesia, a cannula was stereotactically implanted to allow direct microinjections into the area. To inactivate DMH neurons, the GABA agonist musimol was injected prior to the stress paradigm. To activate DMH neurons in the absence of imposed stress, the GABA antagonist bicuculline was injected. An injection of artificial cerebrospinal fluid was used as a control.
Summary of Results: Mild, prolonged stress lowered mechanical pain thresholds compared to baseline. Inhibiting DMH neural activity attenuated stress-induced hyperalgesia, showing that the DMH mediates this behavior. In unstrained rats DMH activation with bicuculline was sufficient to induce hypersensitivity to pain.
Conclusions: The increased sensitivity to pain resulting from mild, chronic stress is mediated by the DMH. Further studies are needed to map the neurotransmitter-specific projections to and from the DMH to elucidate other neural circuits by which the DMH modulates pain and stress responses. These results further our understanding of the interplay between chronic stress and pain, and highlight how relieving stress may be an important part of treating chronic pain.

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SYSTEMIC INFLAMMATION INHIBITS LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN-1 MEDIATED CLEARANCE OF AMYLOID-ß FROM BLOOD: IMPLICATIONS FOR ALZHEIMER'S DISEASE
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Purpose of Study: Alzheimer's disease (AD) is a neurodegenerative disease characterized by the formation of amyloid plaques containing amyloid-β (Aβ) in brain parenchyma. Neurons produce Aβ constitutively. In normal physiology low density lipoprotein receptor-related protein-1 (LRP-1) transports Aβ from brain across the blood-brain barrier (BBB) into blood (efflux). Aβ is then taken up by peripheral organs (primarily liver) for degradation. LRP-1 mediates liver uptake of Aβ from blood. It has been proposed that Aβ in blood may also contribute to Aβ accumulation in brain, thus liver uptake may play a significant role in maintaining brain Aβ homeostasis. Lipopolysaccharide (LPS)-induced inflammation recapitulates many components of this aspect of the AD phenotype, and evidence suggests oxidative modification (adding 3-nitrotyrosine (3-NT) and 4-hydroxy-2-nonenal (4-HNE)) inhibits BBB LRP-1. We tested whether systemic inflammation inhibits liver LRP-1 and peripheral Aβ uptake by the same proposed mechanism.
Methods Used: We injected young CD-1 mice with intraperitoneal LPS (control: saline) to induce inflammation, and then injected radiolabeled albumin and Aβ intravenously. Blood, liver and kidney were collected at various time points. Aβ/albumin uptake and serum clearance were assessed by gamma counting. Exposure time was calculated with multiple-time regression analysis. Liver LRP-1 expression and liver protein carbonyl were determined by dot blot. 3-NT and 4-HNE modifications on liver LRP-1 were assayed with Western blot.
Summary of Results: LPS treatment significantly increased liver protein carbonyl, liver LRP-1 expression and 4-HNE modification on liver LRP-1. 3-NT modification on liver LRP-1 increased 38.8%. LPS significantly inhibited serum Aβ clearance as well as the rate of liver and kidney Aβ uptake.
Conclusions: These findings support the hypothesis that oxidative modification on LRP-1 in liver increases circulating Aβ, which has been shown to increase brain Aβ concentration and contribute to amyloid plaque formation, hallmarks of Alzheimer's disease pathology.

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AMINO-TERMINAL CLEAVAGE OF APOLIPOPROTEIN E4 IN ALZHEIMER’S DISEASE
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Purpose of Study: Alzheimer’s disease (AD) currently afflicts 5.6 million people in the US, a number predicted to increase to 16 million by 2050. While advancements have been made in our understanding of AD, these growing numbers reflect a need for further investigation of the underlying cellular and molecular basis of disease. Since the discovery of an association between the apolipoprotein E4 (ApoE4) allele and an increased risk of AD, ongoing work has been aimed at elucidating the mechanism. Preferential cleavage of the ApoE4 isoform relative to other polymorphic forms appears to be significant, as the resulting fragments are associated with hallmarks of AD including increased accumulation of amyloid plaques and neurofibillary tangles (NFTs). To further understand the role of ApoE4 proteolysis in AD, the purpose of this work was to investigate a previously unexplored amino-terminal cleavage event. We hypothesized that the resulting fragment would associate with amyloid plaques and NFTs in vivo in an ApoE isoform-specific manner.
Methods Used: A novel antibody to an amino-terminal ApoE4 cleavage fragment (nApoE4CF) was applied to frontal cortex brain tissue from eight neuropathologically confirmed cases of AD and evaluated by immunohistochemistry or immunofluorescence. Double-labeling experiments were performed to assess co-localization to amyloid plaques and NFTs. Western blot analysis was used to evaluate the in vitro proteolysis of ApoE4.

Summary of Results: A significantly higher number of nApoE4CF labeled NFTs was observed in AD cases with the ApoE4 allele (ApoE 3/3 = 5.5±4.5, ApoE 4/4 = 30.1±6.8, p<0.05). No co-localization to amyloid plaques was observed. Western blot analysis demonstrated the nApoE4CF antibody is specific to the predicted 19 kDa amino-terminal fragment and does not recognize full length ApoE4. Surprisingly, this fragment was identified by Western blot in both control and proteolytically digested recombinant ApoE4, suggesting bacterial protease activity during purification.

Conclusions: The ApoE4 amino-terminal cleavage fragment localizes to NFTs in the AD brain, with the greatest number of NFTs observed in AD cases with the ApoE4 allele. Further study is needed to identify the protease responsible for the amino-terminal cleavage event.

411 THE EFFECT OF TBR1 ON INTERNEURON MIGRATION IN MICE

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Purpose of Study: Developmental diseases such as autism may be associated with defects in cortical neuronal migration, a critical process in brain development. Many post-mitotic projection neurons in the cortex express the transcription factor Tbr1, which is thought to signal interneurons to migrate to the cortex. The hypothesis of this study is that knocking out Tbr1 inhibits migration of interneurons.

Methods Used: Mice were used as the model. Tbr1 knock out (n=3) and wild type (n=1) P0 mice brains were taken. They were sectioned into 12-micron, sagittal sections. The slides were blocked with goat serum, stained with a rabbit anti-Dlx, goat anti-rabbit, and counterstained with DAPI. Dlx marked interneurons red and DAPI marked nuclei blue. Images were analyzed to determine cell densities of interneurons in levels of the cortex (10 bins).

Summary of Results: A 20 percent reduction in cortical interneuron cell density was seen in P0 Tbr1 knock out mice compared with wild type mice (from 640 to 517 cells/mm2). Both the wild type and knock out P0 mice had a large portion of the cells in the most superficial layer of the cortex (bin 10), but there was a shift of the other large portion of cells in cortical plate of the wild type (bins 5-6) to a more superficial level (bins 7-8) in the knock out mice.

Conclusions: Tbr1 knock out in post mitotic cortical projection neurons resulted in fewer interneurons migrating to the cortex during development. These interneurons that did migrate to the cortex migrated to the incorrect cortical layer. These results show that Tbr1 affects the migration of cortical interneurons in mice and suggest that Tbr1 is an important transcription factor in brain development.
(p=0.008), there was no significant increase after reconstruction for the AC-CC technique (p=0.133). Neither technique showed a significant increase in S-I translation after reconstruction (p=0.076, p=0.881). When the difference in translation between the post-reconstruction state and the intact state was compared between the two techniques, the coracoid cerclage technique demonstrated significantly greater A-P translation than the AC-CC technique (p=0.007). There was no difference in S-I translation between the two techniques (p=0.053).

Load to failure testing: Ultimate load, deformation at ultimate load, and energy absorbed at ultimate load were significantly greater after AC-CC reconstruction than after coracoid cerclage reconstruction (p < 0.05). Yield load, deformation at yield load, energy absorbed at yield load, and stiffness were not significantly different (p > 0.05).

Conclusions: Our novel AC-CC reconstruction resulted in increased stability and stronger load to failure characteristics than the coracoid cerclage reconstruction.

414 IATROGENIC RADIATION EXPOSURE TO PATIENTS WITH EARLY ONSET SPINE AND CHEST WALL DEFORMITIES

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Purpose of Study: Children with Thoracic insufficiency syndrome (TIS) undergo extensive evaluations to characterize their deformity and subsequent respiratory impacts. This study quantifies total ionizing radiation exposure, in units of millisieverts (mSv), to these children during the course of their treatment with a Vertically Expandable Prosthetic Titanium Rib (VEPTR), a device to correct spinal deformity for patients with TIS.

Methods Used: We retrospectively studied 62 children who had VEPTR surgical treatment for TIS at our center from 2001-2011. We reviewed all x-rays, CT scans, nuclear medicine studies, fluoroscopy evaluation, and MRI related to treatment for all patients. Epochs of treatment were time of initial evaluation to end of initial surgery and each subsequent epoch was marked by another surgical intervention. Radiation exposure from plain radiographs and V/Q scans were calculated from reference values and applied to each study. Direct radiation exposure for CTs since 2007 was calculated and reported as mSv using the method of Allelo and Phillips from the variables of dose length product (DLP), kilovoltage peak (KVP), phantom, and age at time of study. Fluoroscopy exposures were directly calculated from the dose area product (DAP) multiplied by the conversion factor 0.2 mSv per Gy cm².

Summary of Results: The 62 children had a total of 447 procedures. There were a total of 290 CT scans, 4293 x-rays, 147 MRI scans, and 134 V/Q scans. Average radiation exposure up to initial surgery was 33.7 mSv. The average exposure/epoch for subsequent surgical treatments was 5.2 mSv (2.9 to 13.8 mSv). Fluoroscopy accounted for 60% and CT scans 25% of total radiation exposure.

Conclusions: Average background radiation exposure in the US is estimated to be 3.6 mSv/year. The mean exposure for this group was markedly elevated at 34 mSv prior to any surgery and 10 mSv/year with an average of 2 surgeries/year. Fluoroscopy and CT scans account for 85% of radiation exposure in this cohort of patients. The results of this study suggest the need to reconsider the quantity and type of imaging studies used to characterize thoracic deformities over the course of treatment with a VEPTR device.

415 LOCAL SOFT TISSUE INTERPOSITION APPROACH TO THUMB CARPOMETACARPAL ARTHRITIS

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Purpose of Study: Osteoarthritis (OA) of the thumb carpometacarpal (CMC) joint is a common condition affecting one in four people over the age of 45. Sequelae include pain and limitation of thumb motion, which can lead to significant impairment of daily living. The purpose of this study is to describe the primary surgeon’s (MSM) technique for the surgical treatment of thumb CMC arthritis using local soft tissue interposition, as well as to compare the results of this technique with his previous technique, using a palmaris longus autograft.

Methods Used: A retrospective review of patients over a seven-year period from January 2003 to December 2009 was performed. Inclusion criteria were all patients over the age of 18 who were surgically treated for arthritis of the thumb CMC joint by the primary surgeon (MSM) with either palmaris longus interposition (Group A) or local soft tissue interposition (Group B). There were 60 patients and 67 surgeries performed in Group A and 62 patients and 71 surgeries in Group B. The mean preoperative and postoperative grip strength and pinch strength were calculated for both groups. The complication rate for each group was calculated. Patients were asked to return for a follow-up visit to assess long-term outcomes. Patients completed a Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and underwent testing for grip strength, pinch strength, and first web distance.

Summary of Results: In both the retrospective chart review and long term follow up there was no difference between the groups in any of the measured outcomes. The overall complication rate for Group A was 5.9% (4 patients). Three of the four patients required reoperation. The overall complication rate for Group B was 2.80% (2 patients).

Conclusions: Tendon harvest is not necessary for the successful treatment of thumb CMC arthritis and is associated with a higher complication rate. Utilizing local soft tissue as the interposition graft, eliminates the need for tendon harvest and the morbidity associated with the harvest. It also compares well with the principle investigator's previous treatment of thumb basal joint arthritis utilizing the palmaris longus. We recommend the use of local soft tissue interposition in treatment of thumb CMC joint arthritis and recommend its use as an alternative to tendon interposition.

416 QUANTITATIVE ASSESSMENT OF SCALENE MUSCLE BLOCK IN THE DIAGNOSIS OF THORACIC OUTLET SYNDROME

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Purpose of Study: Thoracic outlet syndrome (TOS) results from the compression of the subclavian vessels and/or brachial plexus between the clavicle, scalene muscles, and the first rib. It is associated with fatigue, pain, and paresthesias in the upper extremity. Anterior scalene muscle block (ASMB) is reported by Gage (1939) for the assessment of patients with TOS. The author notes temporary relief of symptoms in patients when local anesthetic is injected into the muscle for temporary paralysis. It is thought that a paralyzed scalene muscle lowers the first rib and thereby decompresses the neurovascular bundle between the rib and clavicle. Sanders (1991) provides compelling statistics for positive surgical outcome in those patients who report substantial symptomatic improvement after an ASMB. However, objective measurement of functional improvement in response to ASMB is not reported. The purpose of the study is to provide quantifiable data of symptomatic improvement in patients after the block procedure to enable an evidence-based medical decision-making process.

Methods Used: Patients (n=34) with a clinical diagnosis of TOS were tested on a BTE Work Simulator before and after a unilateral ASMB. Three tests were used for evaluation of ipsilateral arm: (1) a push-pull test performed repetitively while gripping a bar with the forearm at waist level, (2) an overhead test performed repetitively to move a bar up and down with the arm abducted to 90° and forearm flexed to 90°, and (3) a flexion/extension activity of the fingers against a gripping tool with the shoulder abducted 90° and forearm flexed 90° (Roos’ test). The tests continued until fatigue. The work produced (inch-pound-degrees), duration of the test (seconds) and power generated were captured.

Summary of Results: All patients (n=34) expressed symptomatic relief after the ASMB. An average increase of 93%, 108%, and 104% for test 1, 2, and 3, respectively, was observed in the work produced after administration of ASMB (p<0.001). Statistically significant improvements in the time-to-fatigue and calculated power were also observed.

Conclusions: ASMB is routinely used to assess symptomatic improvement for diagnosis of suspected TOS patients. BTE Work Simulator allows us to objectively identify and measure changes in patients’ work data following an ASMB.

417 OPTIMIZING THE DETECTION OF LIMBAL EPITHELIAL STEM CELLS USING IN VIVO CONFOCAL SCANNING LASER MICROSCOPY

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Purpose of Study: Limbal stem cell deficiency (LSCD) is an eye condition that leads to severe ocular surface opacity, causing discomfort, vision loss, and ultimately, complete blindness if left untreated. In vivo confocal microscopy (ICM) is a relatively new technique that can visualize microstructure at the single cell level in patients with LSCD and limbal stem cell transplant donors. We aim to optimize the detection of regions within the normal limbus that have a high concentration of undifferentiated limbal stem cells using ICM.

Methods Used: Human sclerocorneal tissues were obtained from healthy donors and divided into six regions. Images of each region were taken using the Heidelberg Retina Tomograph III Cornea Module at three locations: anterior, middle and posterior limbus. The limbal epithelial layer was then isolated from each of the six regions and cultured on growth-arrested NIH 3T3 feeder layers. Colony forming efficiency (CFE) was assessed after 14 days. Total RNA was extracted from colonies and reverse transcribed to cDNA. Quantitative real-time PCR was performed on cDNA to detect the mRNA expression level of putative stem cell markers and house-keeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Summary of Results: Confocal laser scanning microscopy reveals proposed stem cell niche, the limbal palisades of Vogt (POV), as well as regions with a high density of limbal epithelial cells but an absence of the POV. The average CFE of the regions with visible POV is lower (p<0.05) than the average CFE for the regions with a high density of visible epithelial cells but without POV. QRT-PCR data also reveals that sections without the POV had a slightly higher expression (p=0.07) of putative stem cell marker ABCG2 and a significantly lower (p<0.05) expression of the differentiation marker K12 compared to the regions with POV.

Conclusions: Our preliminary data indicates that regions along the corneal surface with a high density of putative stem cells can be visualized using confocal scanning laser microscopy. In addition, these findings show that undifferentiated limbal stem cells may be found outside the POV. Therefore, the POV may not be the sole target niche for obtaining limbal stem cells for transplantation.

418 THE LONG-TERM OUTCOMES OF BARRETT’S ESOPHAGUS IN PATIENTS TREATED WITH LAPAROSCOPIC ANTI-REFLUX SURGERY

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Purpose of Study: The incidence of esophageal adenocarcinoma is more rapidly increasing than any other cancer in the United States. Barrett’s esophagus (BE) - the replacement of the normal squamous epithelium of the distal esophagus with specialized intestinal metaplasia, caused by chronic gastro-esophageal reflux disease (GERD) - is a risk factor for this type of cancer. Laparoscopic anti-reflux surgery (LARS) treats GERD by recreating the barrier between the esophagus and stomach; by eliminating the reflux, LARS may change the natural course of BE. The purpose of this study is to determine whether LARS can lead to long-term histological regression of BE and control of GERD.

Methods Used: We performed a retrospective review of medical records to identify patients with BE who underwent LARS at our institution at least three years ago. Patients were sent a questionnaire to evaluate long-term changes in post-operative GERD symptoms. Follow-up data included endoscopy findings, histology, pH studies, and manometry studies. Histological regression was defined as either change to a lower grade or disappearance of BE. Follow-up time varied widely depending on the patient’s preference and what had been indicated by the surgeon. Patients were asked to rate their heartburn and regurgitation on a scale of 1 to 10, where 10 was worst. Patients were then asked to rate their satisfaction with the procedure on a scale of 1 to 10, where 10 was best.

Summary of Results: Twenty and fifteen patients met the inclusion criteria. Twenty-two patients completed the post-operative questionnaire, and 14 patients returned the post-operative questionnaire. The overall average improvement in heartburn and regurgitation was 5.4 (range 2 to 9) and 6 (range 2 to 9), respectively.

Conclusions: LARS was associated with both physiologic and symptomatic control of GERD in patients with BE. In addition, and perhaps as a result, LARS was also associated with long-term histological regression of BE in 30% of patients.

419 LONG-TERM CLINICAL AND SURGICAL OUTCOMES OF INTRACRANIAL MENINGIOMAS PATIENTS RECEIVING GROSS AND SUBTOTAL RESECTION

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Purpose of Study: Meningiomas are the second most common primary CNS neoplasm and are commonly benign and slow growing. While gross total resection has been associated with improved survival, complete surgical resection can be difficult given poor tumor accessibility and proximity to sensitive structures. We review our institution’s long-term experience with meningiomas to compare outcomes and complications associated with gross (GTR) and subtotal resection (STR).

Methods Used: We reviewed all patients with meningiomas treated at Ronald Reagan UCLA Medical Center from 1996 to 2009. Inclusion criteria included 1) histopathologically confirmed primary intracranial meningioma, 2) GTR or STR performed at UCLA, 3) follow up ≥2 years. Surgical and clinical outcomes of GTR vs. STR were analyzed.

Summary of Results: 106 of 203 patients receiving surgical resection met our inclusion criteria. There were 41 males and 65 females and the average age was 54 at presentation. There were 84 WHO grade I (79%), 19 WHO grade II (18%) and 3 WHO grade III (3%) meningiomas. Average follow-up was 61.2 years (range: 24 to 172 months). Of the 72 patients undergoing GTR, 5 (7%) received radiotherapy. Of the 34 patients with STR, 19 (56%) received radiotherapy. Overall survival for both groups was 100%. Compared to STR, GTR was associated with improved 3-yr PFS (92.5% vs. 75%, p=0.062) and 5-yr PFS (92.5% vs. 62.5%, p=0.002). However, GTR was correlated with increased complications (11% vs. 2.9%, p=0.26). This difference was not statistically significant. Reported complications include hematoma (2), surgical site infections (2), CSF leak (2), venous infarcts (2), and venous thrombosis (1).

Conclusions: Overall, meningiomas are slow growing tumors with a good prognosis and surgical resection can offer excellent rates of tumor control. Although GTR is associated with longer PFS and should be the goal when feasible, these findings suggest that a more aggressive surgical approach is correlated with increased risk for surgical complications.

420 DYNAMIC MECHANICAL ANALYSIS OF FIBROBLAST SEEDED SCAFFOLDS AND ITS APPLICATION TO LIGAMENT RECONSTRUCTION

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Purpose of Study: There are disadvantages and complications seen with currently used biologic grafts for ligament reconstruction. For these reasons, engineered ligaments composed of an individual’s own extracellular matrix (ECM) producing cells has been proposed as a mechanism for ligamentous reconstruction. The goal of this project was to determine the effect of ECM deposition on the mechanical properties of human foreskin fibroblast (HFF)-seeded polycaprolactone (PCL) scaffolds exposed to basic fibroblast growth factor (bFGF) and/or uniaxial cyclic strain in vitro.

Methods Used: Nanofibrillar PCL scaffolds were analyzed via Dynamic Mechanical Analysis (DMA) in order to show the effect of cellular proliferation and ECM deposition on scaffold stiffness (storage modulus) and polymer deformation. PCL was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol to produce 11% PCL solutions and then electrospun into fibrous mats. Scaffolds (n=20) were divided into 5 groups; unseeded scaffold, HFF only, HFF+bFGF, HFF+ strain, and HFF+bFGF+strain. Strained groups were placed in a bioreactor and subjected to uniaxial strain at 0.2 Hz for 12 days. At Day 12, the storage modulus of each scaffold was determined using DMA and ECM deposition was analyzed using a type I collagen immunostain.

Summary of Results: Microscopy demonstrated that strained scaffolds were devoid of cells while those not strained showed significant proliferation and collagen deposition. Furthermore, DMA showed that strained scaffolds had decreased stiffness when compared to both unstrained HFF-seeded scaffolds and unseeded PCL controls. Unstrained HFF-seeded scaffolds with
and w/o bFGF showed increased stiffness in comparison to unseeded controls implying that the extensive collagen deposition enhanced the stiffness of the scaffold.

**Conclusions:** The decreased stiffness seen in strained scaffolds can be due to a number of factors; stress induced apoptosis of HFF’s, HFF detachment and/or permanent mechanical deformation of the PCL polymer. Ultimately, this experiment showed that seeding HFF’s on PCL scaffolds enhances the mechanical properties of the polymer via collagen deposition but leaves the question of how strain affects HFF activity unanswered.

421 NISSEN FUNDOPLICATION LIMITS DISEASE PROGRESSION IN PATIENTS WITH CONCURRENT IDIOPATHIC PULMONARY FIBROSIS AND GASTROESOPHAGEAL REFLUX

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**Purpose of Study:** Idiopathic Pulmonary Fibrosis (IPF) is an interstitial lung disease characterized by a radiographic appearance of usual interstitial pneumonia with honeycombing and an irreversible decline in pulmonary function. Microaspiration of esophageal refluxate in the context of gastro-esophageal reflux disease (GERD) in patients with IPF has been shown to significantly contribute to their pulmonary decline. It has thus been postulated that steps taken to mitigate such reflux may have a significant role in stabilizing the pulmonary decline of patients with IPF. The purpose of this study was to demonstrate that patients with concurrent IPF and GERD who undergo Nissen fundoplication as an anti-reflux measure show a stabilization of pulmonary function when compared to those patients treated medically.

**Methods Used:** We performed a chart review of 129 patients with concurrent diagnoses of IPF and GERD. Subjects were grouped into four study arms: A control group of IPF patients without active GERD who received no anti-reflux therapy, a group of IPF patients receiving medical therapy which controlled their GERD, confirmed by 24-hour esophageal pH testing, a group of IPF patients with uncontrolled GERD despite medical therapy, and a group of IPF patients who underwent Nissen Fundoplication and also received medical therapy.

Pulmonary function test results were used as a measure of disease progression over the course of each patient’s history. A linear regression was then performed using that data, and an R value was extracted representing the rate of decline for that patient. Averaging these R values within the respective groups provided a mean rate of decline for each study arm.

**Summary of Results:** IPF patients who underwent Nissen fundoplication experienced a lower rate of pulmonary decline than their peers, with a rate of decrease of 0.016%/mo (-0.046%), of their baseline pulmonary capacity per day while the two medical therapy groups experienced declines of 0.029%/mo (-0.0023), and 0.037% respectively.

**Conclusions:** Nissen fundoplication limits the disease progression of IPF in the setting of GERD.

422 INTEGRIN SIGNALING AND OSTEOGENESIS IN HUMAN MESENCHYMAL STEM CELLS CULTURED IN 2D AND 3D CONDITIONS

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**Purpose of Study:** It has been previously demonstrated that cells cultured on two-dimensional (2D) surfaces exhibit different osteogenic properties from those in three-dimensional (3D) scaffolds. The aim of this study was to evaluate signaling pathways in response to the changes in culture conditions and their role in the regulation of the osteogenesis in human mesenchymal stem cells (hMSCs). We examined the expression of several integrin subunits in hMSCs cultured on 2D surfaces, 3D poly-L-lactide-co-glycolide (PLGA) and 3D type I collagen scaffolds. We further investigated the activation of downstream mechanotransducers focal adhesion kinase (FAK) and extracellular related kinase (ERK1/2) and its effect on osteogenesis in hMSCs.

**Methods Used:** 200,000 hMSCs were seeded onto 2D plates, 3D PLGA scaffolds, and 3D type I collagen scaffolds and cultured in osteogenic medium. Gene expression of integrin subunits α1, α-ν, β1- and β-3 as well as osteogenic markers ALP, β-CBFa-1, BSP and OCN were measured by RT-PCR at days 1, 4, and 7. Phosphorylation of FAK and ERK1/2 was measured by western blots on days 1, 4 and 7 samples.

**Summary of Results:** Western blot analysis revealed a decrease in FAK and ERK1/2 activation in the type I collagen cultures compared to the 2D and PLGA cultures. In addition, osteogenesis appeared hindered in the hMSCs cultured in type I collagen scaffolds compared to cells in 2D and PLGA scaffolds as demonstrated by lower levels of CBFa-1 and BSP expression. The differences in expression of the tested integrins are not significant enough to support a direct correlation between activation of a particular subunit and phosphorylation of FAK at this time.

**Conclusions:** The differences observed in FAK and ERK1/2 activation and osteogenesis among the three systems confirms that hMSCs are highly responsive to modifications of their environment such as changes in composition or stiffness of the biomaterial used. Furthermore, the decreased activation of both FAK and ERK1/2 in the type I collagen cultures suggests a possible link between Integrin/FAK/ERK signaling and osteogenic differentiation. Evidence is currently being generated.

423 MIDLINE CERVICAL CLEFTS: A RARE ANATOMIC ANOMALY

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**Purpose of Study:** Midline cervical clefts (MCC) are rare congenital abnormalities thought to occur from abnormal fusion of the branchial arches at the midline. Closure types range from multiple z-plasties for larger defects to w-plasties to primary closure for mild soft tissue deficiencies. We present a case series of midline cervical cleft repairs.

**Methods Used:** Review of an ongoing case series of midline cervical clefts repaired by the chief of pediatric otolaryngology at our institution.

**Summary of Results:** Three of the four cases received opposing z-plasties of the platysma in hopes of improving definition of the cervicomental angle as primary closure in the vertical or horizontal plane could result in unacceptable scarring or contracture. The fourth case had a mild soft tissue deficiency, and was closed primarily. He is currently being followed to determine if his cervicomental profile is as well defined as the other three patients in our series.

**Conclusions:** The efficacy of the platysma z-plasty is debatable. In our case series, the overall lateral cervicomental profile were improved in all three patients who received the z-plasty. Scarring in the horizontal plane of the z-plasty is excellent, though hypertrophic scarring is more common at the oblique closures. Although no consensus exists regarding optimal surgical management of MCC, opposing z-plasties of the subcutaneous tissue and the platysma appear to improve the cervicomental contour of our patients, and should be considered when planning surgical reconstruction.

424 DISSEMINATION OF TOBACCO CONTROL GUIDELINES TO A SPECIALTY CARE SETTING: A UROLOGIC PERSPECTIVE

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**Purpose of Study:** Tobacco use is causal or contributory in many urologic diseases including cancers of the bladder, kidney, and prostate, as well as erectile dysfunction. Continued tobacco use after diagnosis negatively impacts disease-specific outcomes and treatment effectiveness. Yet, tobacco screening was infrequently occurring in a regional VA Urology clinic.

**Methods Used:** An EMR-based tobacco screening template was designed in accordance with the VA’s Clinical Practice Guidelines for the Management of Tobacco Use. The template was instituted for all new patient encounters beginning January 2010. Performance measures included the proportion of patients asked about tobacco use, advised to quit, and assisted with smoking cessation stratified by provider type and the tobacco-relatedness of the urologic diagnoses.

**Summary of Results:** For the six consecutive months ending June 2010, 1315 veterans were seen on a consultation basis in the urology clinic. The EMR-based template was used by providers 60% of time. Attending physicians
utilized the template in 14% of consultations, resident physicians in 64%, and nurse practitioners in 96% (p < 0.001).

In 38% of encounters, patients were actively smoking. All patients smoking were advised to quit with 37% opting to initiate a cessation strategy. Of those actively smoking at consultation, 59% had been referred to the Urology clinic for a tobacco-related disease process. Patients with a tobacco-related disease process were more likely to initiate a cessation strategy than those without (44% vs. 28%, respectively, p = 0.03).

Conclusions: Our data suggest that the Urology clinic may be fertile ground for implementation of an evidence-based tobacco initiative. More than one-third of patients screened were smoking at the time of consultation. 40% of active smokers opted to initiate a cessation strategy at the time of their clinical encounter, those patients with a tobacco-related disease process more likely to do so. As utilization varied by provider type, identification of provider-level facilitators and barriers to tobacco screening in the specialty care setting is worthy of additional study.

425 ASSESSING NOVEL METHODS IN FACIAL RECONSTRUCTION: ELECTROMECHANICAL RESHAPING
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Purpose of Study: To compare electromechanical reshaping (EMR) to techniques that have been reported in the reshaping of structural frameworks of the face: thermforming and selective enzymatic methods.

To determine effective EMR dosimetry parameters for shape change and cell viability in the ex-vivo rabbit costal cartilage model.

Methods Used: Rabbit costal cartilages (n=12) were secured in a jig that recreated the shape of the rabbit auricle framework. Finite element modeling was used to determine the initial electrode geometry, polarity, spacing, and pilot dosimetry parameters. Porcine cartilage (n=21) was first utilized to narrow the range of possible dosing parameters. Parametric analysis was performed to determine the effect of voltage and application time on tissue shape change. A reduced parameter set of voltage-time pairs were identified. Next, rabbit rib cartilage was reshaped varying voltage and application time to identify the lowest parameters to produce acceptable shape change mimicking native auricular cartilage. Acceptable qualitative shape change was determined on a five point Likert scale with one-way general linear analysis of variance (ANOVA). Confocal microscopy with Live/Dead Cell viability analysis and histology determined the degree of injury.

A review of laser, radiofrequency, and enzymatic ex-vivo cartilage reshaping in animal and clinical applications of auricular, costal, and septal reshaping was conducted.

Summary of Results: The minimum acceptable deformation of rabbit costal cartilage was found at 4V 3min. Viability analysis at 4V 3min demonstrated cell injury extending 2 mm away from each electrode with viable cells found between the electrodes. Limitations to laser and radio-frequency reshaping includes uncontrolled heating, loss of chondrocyte viability, and the need for optimization of thermoforming parameters.

Conclusions: The EMR parameters of 4V 3minutes demonstrates appropriate shape change that resembles the native auricle with viable cells adequate for clinical evaluation. Relative to thermforming, EMR is low-cost and has the ability to confine tissue injury to stress concentrated areas.

Surgical Procedures
Concurrent Session
1:30 PM
Saturday, January 28, 2012

426 UTILITY OF PRE-PROCUREMENT BEDSIDE LIVER BIOPSY IN THE EXTENDED CRITERIA LIVER DONOR
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Purpose of Study: Management of marginal donors by the organ procurement organization (OPO) can result in a significant financial loss if no organs are transplanted. The Indiana OPO has utilized pre-procurement bedside liver biopsies of high-risk donors, obtained by the on-site coordinator in the intensive care unit, to determine the utility of pursuing donation.

Methods Used: All bedside liver biopsies obtained over a 3-year period were reviewed. Study variables included: indication, results, taking the case to the operating room (OR), and transplantation. All biopsies were reviewed at a single center.

Summary of Results: 110 donors underwent biopsy. Primary indications: hepatitis C+ (21%), alcohol abuse (20%), elevated liver function enzymes (16%), age (14%), and obesity (14%). Biopsy results demonstrated a potentially transplantable liver in 66% of cases, all of whom were taken to the OR (34% ruled out). Of all biopsied livers, 46% were transplanted. Of all donors taken to the OR, 70% of liver grafts were transplanted.

Conclusions: Routine training of coordinators and use of bedside biopsy may lead to significant OPO cost savings where the donor case may be closed at an earlier stage if the liver is found to be non-transplantable.
Methods Used: All corneal ablations were performed using the VISX Star Eximer Laser System set to a custom PTK protocol. PTK diameter was 6.5 mm, total ablation depth was 60 μm, and target fluence was 160 mJ/cm² per procedure. Corneal plume samples were generated from intact adult bovine eyes using one series of ten PTK procedures and filtered through High-Glucose DMEM under vacuum. Experimental media conditions included unexposed complete media, plume-filtered complete media, air-filtered complete media, and lipopolysaccharide in complete media. RAW264.7 cells were exposed to experimental media in triplicate. To quantify various cytokines in cell culture media, supernatant collected at various time points was analyzed using ELISA.

Summary of Results: Media containing Lasik plume particles did not induce a statistically significant difference in the amount IL-6 and TNFα released as compared to negative controls in RAW264.7 cells (p=0.05). Data from repeated exposures is still pending. Currently, the cytokine response of mouse and human pulmonary cells repeatedly exposed to Lasik plume particles is being analyzed. Additionally, the particulate contents of all experimental media samples are being quantified at this time.

Conclusions: We expect to identify significantly higher levels of cytokines released from mouse and human pulmonary cells, and RAW264.7 cells, repeatedly exposed to Lasik plume particles as compared to negative controls. We also expect to identify a unique population of plume particles roughly 0.22 μm in diameter within Lasik plume-filtered media samples.

429 PREEMPTIVE ANALGESIA AND KETOROLAC FOR PERIOPERATIVE PAIN MANAGEMENT IN PEDIATRIC GENERAL SURGERY PATIENTS
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Purpose of Study: Ketorolac is a non-steroidal anti-inflammatory agent that is used as an anti-pyretic and for pain relief. The post-operative use of Ketorolac has been shown to reduce the amount of narcotics necessary for adequate pain control. Narcotic use is associated with respiratory depression, nausea, vomiting and allergic reactions. Ketorolac is associated with a low risk of bleeding and renal dysfunction. In this study, we will review adequacy of pain relief and side effects in children that received preemptive analgesia (intra-operative local and/or caudal epidural anesthesia) and post-operative Ketorolac. These results will be compared to children that received preemptive analgesia and post-operative narcotics. We postulate that there are fewer post-operative complications and earlier return of bowel function in children that received preemptive analgesia and Ketorolac.

Methods Used: This study is a case-matched retrospective chart review of children ages 0-18 who received general pediatric surgery between October 2007 and January 2011. For both groups of patients, the study will review the type of intra-operative preemptive analgesia, total post-operative dosages of Ketorolac and narcotics, adequacy of post-operative pain relief, incidence of post-operative nausea and vomiting, time of resumption of a normal diet, duration of post-operative oxygen requirement, and the incidence of respiratory distress, clinical bleeding and renal dysfunction.

Summary of Results: Data Collection in progress.

Conclusions: We hypothesize that children who receive preemptive in-traoperative analgesia with concomitant postoperative ketorolac have a decreased need for narcotic pain management without significant increase in complications due to NAID use. We also hypothesize that patients who have preemptive analgesia and ketorolac also experienced decreased complications due to narcotic use.

430 RADIATION EXPOSURE DURING CENTRAL VENOUS LINE INSERTION IN PEDIATRIC ONCOLOGY PATIENTS: COMPARISON OF OUT OF HOURS AND IN HOURS SURGERY
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Purpose of Study: Evidence suggests an increased morbidity for patients with non-emergent surgical conditions who are operated on “out of hours” (OOH) compared to “in hours” (IH). Children diagnosed with cancer are an OOH group. With IRB ethics approval, all CVL insertions that were performed between October 2006 and January 2010 were reviewed. IH was defined as Monday-Friday 0745-1530. The proportion of OOH compared to IH was tabulated and OOH subgroup categorized: Term 1(1530-1800), Term 2(1800-2300), Term 3(2300-0745), and Term 4(weekends and holidays 0745-1530). Fluoroscopy radiation time as well as the total doses were compared between OOH and IH CVL insertions. Data was analyzed with a Mann Whitney-U test.

Summary of Results: There were 266 patients who altogether underwent 311 CVL insertions. The average patient age was 8 years. 145 procedures (47%) were performed IH, with mean fluoroscopy dose of 109 mgY·cm² and mean fluoroscopy time of 11 seconds. 166 procedures (53%) were performed OOH, with mean dose of 190 mgY·cm² and mean time of 11 seconds.

There were 38 (12%) Term 1, 42 (13%) Term 2, 8 (3%) Term 3 and 78 (25%) Term 4 OOH procedures with mean (median) fluoroscopy doses and times of 87 (33.5) mgY·cm² and 8 seconds, 154 (31.4) mgY·cm² and 6 seconds, 378 (101.4) mgY·cm² and 20 seconds, and 139 (34) mgY·cm² and 8 seconds respectively. Overall, comparing the radiation exposure times, IH CVL insertions were significantly longer than OOH (p=0.02), however there was no significant difference in radiation dose between IH and OOH groups. When IH was compared to OOH Term 3, radiation dose was increased (p=0.07).

Conclusions: The majority of CVL insertions performed in oncology patients in our center are performed outside of standard working hours. Radiation exposure time is significantly longer in IH procedures, however there is a trend to increased radiation exposure in the patients operated on between 2300-0745.

431 ENDOSCOPIC FOREHEAD CYST REMOVAL: A CASE SERIES
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Purpose of Study: Masses and tumors localized in the craniomaxillofacial area cause undesirable aesthetic malformations. For many years, endoscopic surgery has been utilized in the craniomaxillofacial area to hide incisional scars in an aesthetic manner. However, endoscopic forehead osteoma removal has only recently been described within the last 15 years in several case reports. Here we describe the results of 8 cases performed within the last 10 years at our institution to remove forehead masses with this endoscopic technique.

Methods Used: Patient charts and operative reports of the cases of endoscopic forehead surgery were reviewed and surgical technique was described.

Summary of Results: Four patients with forehead osteomas, 2 patients with forehead lipomas, 1 patient with a forehead schwannoma and 1 patient with a forehead cyst secondary to a giant cell reaction received endoscopic excisions by the chief of facial plastic surgery at our institution. All seven patients had good cosmetic outcomes, with no post-operative complications. Endoscopic surgery has revolutionized facial aesthetic surgery. Endoscopic excision of forehead osteomas, lipomas, and other masses is a safe, feasible, and reliable method of removing forehead masses while hiding the incision in the hairline.

432 ULTRASOUND-GUIDED ASPIRATION AND INJECTION OF INTRANEURAL GANGLION CYST WITHIN THE PERONEAL NERVE
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Case Report: INTRODUCTION/PURPOSE: Intraneural ganglia cysts are rare non-neoplastic cysts caused by the accumulation of thick mucinous fluid within the epineurium of peripheral nerves. Cysts often arise from adjacent structures, and in the case of the peroneal nerve, they may be due to osteoarthritis of the proximal tibiofibular joint. The cysts often compress adjacent nerve fascicles, commonly resulting in paresthesias, pain, weakness, muscle denervation, and atrophy. Surgical decompression of the cysts is the current standard of care but is associated with frequent recurrence. More aggressive surgery has been reported involving removal of the proximal fibula.
METHODS: A 64 year old man presented with a 4 month history of progressively deteriorating left foot drop and paresthesia. Peroneal nerve pathology was suspected and an MRI scan confirmed the typical features of a peroneal intraneural ganglion cyst associated with osteoarthritus of the proximal tibiofibular joint. The cyst was identified extending proximally from the deep branch of the nerve along the course of the common peroneal nerve, and through the popliteal fossa as far as the distal sciatic nerve. Ultrasound guided percutaneous aspiration of the intraneural cyst was performed under local anesthetic at multiple levels removing thick gelatinous material typical for this condition. For this reason corticosteroid was injected into the nerve and also into the adjacent proximal tibial-fibular joint. The patient tolerated the procedure well, did not suffer any immediate adverse effects and returned home immediately afterwards. He will be followed for relief of symptoms, adverse effects and to establish long term recovery of the paralysis.

RESULTS/CONCLUSION: Peroneal intraneural ganglion cyst was successfully aspirated under ultrasound guidance, and at the same time both the myotendinous and adjacent joint were successfully injected with steroid as an outpatient. This percutaneous therapy may obviate the need for aggressive surgery.

434 NOVEL USE OF A PORTABLE POSITRON EMISSION PROBE IN INTRAOPERATIVE LOCALIZATION OF PERSISTENT ADRENOCORTICAL CARCINOMA

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Purpose of Study: A 13-year-old girl presented with a 1-year history of virilization, voice deepening and acne. Her workup revealed elevated serum testosterone levels and a right adrenal mass with intracaval tumor thrombus that was evident on ultrasound and CT scanning. A PET scan showed increased positron avidity in the primary tumor, without evidence of metastatic disease.

The patient underwent right adrenalectomy and inferior vena cava ligation with extraction of intravascular tumor. Pathology was consistent with adrenocortical carcinoma. Her serum testosterone levels returned to normal and a right adrenal mass with intracaval tumor thrombus was identified at the retrocaval area adjacent to the right adrenal bed, without an identifiable mass.

Methods Used: A PET detector from IntraMedical Imaging was used for intraoperative tumor localization. Following iv administration of labeled FDG, the patient underwent laparotomy and tissue interrogation with a hand held probe within a sterile sheath. Several areas of impalpable increased avidity were detected and excised from the retrocaval area. One of these specimens contained a 0.3 cm specimen of adrenocortical carcinoma. Postoperative PET scanning demonstrated persistent avidity suggesting that a complete resection was not achieved; however, the patient remains clinically well with no detectable mass by CT or MRI.

Summary of Results: Intraoperative PET image guidance is expected to play an increasingly important role in the diagnosis and treatment of malignant disease. Specifically, it may be helpful in identifying tissue that has difficult-to-establish margins, or cannot be localized with certainty using other conventional imaging modalities. Such technology can be applied by multidisciplinary groups including oncologists, surgeons, and interventional radiologists. Like any new application, careful, reflective experience is required to ensure that new technology is introduced safely and evaluation of outcomes proves its effectiveness.

Conclusions: The persistence of a PET positive lesion after an apparently successful resection underscores the challenges in interpreting and treating tumors which are PET “positive”, but CT or MRI “negative”.

434 SURGICAL RESECTION OF PEDIATRIC CEREBELLAR AstrocytomAs

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Purpose of Study: Optimal treatment for low grade cerebellar astrocytomas (LGCA) in children is gross total resection (GTR). When only subtotal resection is achieved, the long-term outcomes are still excellent, but further surgery may be required for tumour progression. A study of children with LGCA prior to 1992 at our institution showed a 98% rate of GTR, but a concerning incidence of resection related permanent neurological dysfunction. The purpose of this study was to determine: (1) rate of GTR of LGCA since 1992 and (2) frequency of neurologic injury caused by the surgical resection. We hypothesized that the philosophy of the surgeons changed after the prior study, such that there would be fewer GTRs but also fewer permanent neurologic deficits caused by surgical resection.

Methods Used: Retrospective review of the hospital records of children with LGCA was performed. Pre- and post-operative CT/MR scans were reviewed by a pediatric neuroradiologist to assess extent of resection. We evaluated the following primary outcomes:(1) incidence of GTR, defined as GTR according to both the surgeon and post-operative CT/MR scans;(2) incidence of new neurologic deficits still present at 1 year. The 2 primary outcomes were compared with the outcomes prior to 1992 using Chi-Square analysis. A p value < 0.05 was considered significant.

Summary of Results: There were 54 LGCA between 1992 and 2010. GTR was achieved in 40 (74%) compared to 43 of 44 (98%) prior to 1992 (p < 0.005). 23 (43%) patients had worsening of pre-operative neurologic deficits and 21(39%) had one or more new post-operative deficits. There was incomplete recovery of surgery related neurologic deficits at least follow-up 1 year or more after surgery in 5 of 54 (9%) compared to 16% in the prior era, but this difference was not statistically significant (p=0.30).

Conclusions: The rate of GTR for LGCA has decreased since our previous study, but this has resulted in a trend to a lower rate of permanent neurologic deficit caused by surgery. Subtotal resection may be the treatment of choice when the surgeon thinks GTR is likely to cause more neurologic dysfunction.

435 DEMOGRAPHIC STUDY OF HIP ARTHROSCOPY

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Purpose of Study: Hip arthroscopy has become an alternative to open hip arthrotomy for the treatment of many disorders. Indications for hip arthroscopy continue to evolve as outcome data becomes available. As with all new procedures, there is little data on current practice patterns of orthopedic surgeons. The purpose of this study is to investigate current trends in arthroscopy of the hip across time, gender, age and regions in the US.

Methods Used: Patients who underwent hip arthroscopy were identified using the PearlDiver Patient Records Database, a national database of insurance records during years 2004-2009. The codes were also run in combination with LGCA was performed. Pre- and post-operative CT/MR scans were reviewed by a pediatric neuroradiologist to assess extent of resection. We reviewed the following primary outcomes:(1) incidence of GTR, defined as GTR according to both the surgeon and post-operative CT/MR scans;(2) incidence of new neurologic deficits still present at 1 year. The 2 primary outcomes were compared with the outcomes prior to 1992 using Chi-Square analysis. A p value < 0.05 was considered significant.

Summary of Results: There were 54 LGCA between 1992 and 2010. GTR was achieved in 40 (74%) compared to 43 of 44 (98%) prior to 1992 (p < 0.005). 23 (43%) patients had worsening of pre-operative neurologic deficits and 21(39%) had one or more new post-operative deficits. There was incomplete recovery of surgery related neurologic deficits at least follow-up 1 year or more after surgery in 5 of 54 (9%) compared to 16% in the prior era, but this difference was not statistically significant (p=0.30).

Conclusions: The rate of GTR for LGCA has decreased since our previous study, but this has resulted in a trend to a lower rate of permanent neurologic deficit caused by surgery. Subtotal resection may be the treatment of choice when the surgeon thinks GTR is likely to cause more neurologic dysfunction.

Summary of Results: 3,447 patients were identified who underwent hip arthroscopy between 2004 and 2009. The number of procedures increased significantly over the study period from 188 hip arthroscopy performed in 2004 compared to 1,076 in 2009 (P<0.001). More than one CPT code was frequently used for each patient and the most common combination of CPT codes identified was "hip arthroscopy with debridement" with "hip arthroscopy with synovectomy." No difference was found in the gender of patients undergoing hip arthroscopy in the database were identified. Factors identified for each patient included gender, age group, and region in the United States. Statistical analysis was performed to determine trends over the study time period.

Summary of Results: 3,447 patients were identified who underwent hip arthroscopy between 2004 and 2009. The number of procedures increased significantly over the study period from 188 hip arthroscopy performed in 2004 compared to 1,076 in 2009 (P<0.001). More than one CPT code was frequently used for each patient and the most common combination of CPT codes identified was "hip arthroscopy with debridement" with "hip arthroscopy with synovectomy." No difference was found in the gender of patients undergoing hip arthroscopy compared to the overall gender distribution in the database as 52.9% of patients undergoing hip arthroscopy were female and 47.1% were male (P=0.38). The greatest number of procedures was performed in patients aged 45-49, accounting for 15.8% of procedures over the study period. With regard to region, more procedures were performed in the West than North, South, or East (P<0.001).

Conclusions: Hip arthroscopy has become an important tool in the treatment of hip disorders. Our study demonstrates an significant increase in the number of hip arthroscopies performed between 2004 and 2009. Hip arthroscopy was performed more commonly in middle aged patients and no
significant gender differences were observed. Further outcome studies are needed to ensure hip arthroscopy evolves as a safe and effective way to manage hip pathology.

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COMPARISON OF SURGICAL AND NON-SURGICAL TREATMENTS FOR CONGENITAL MICROPHTHALMIA
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Purpose of Study: Microphthalmia is a developmental defect in which the eye is abnormally small at birth. Current treatments for microphthalmia aim to promote growth of the bony orbit and the surrounding soft tissues, as well as remediate facial asymmetry. Until now, there has not been long-term follow-up of patients who have undergone treatment for microphthalmia. The purpose of this study is to compare the long-term outcomes of patients who had surgical interventions with patients who had more conservative, less invasive treatments.

Methods Used: The medical records of seventeen patients with unilateral congenital microphthalmia were retrieved. Patients were divided into two groups. The non-surgical group was composed of nine patients whereas eight patients were in the surgical group. Pre-op and a post-op images were collected for each patient. Facial measurements including fissure height, fissure length, distance between the lateral canthus and nasal ala, and distance between the medial canthus and the nasal ala were taken for each patient. Percent asymmetry was calculated by comparing the measurements in the microphthalmic side of the face with the measurements in the normal side of the face. Treatment outcome was calculated by comparing the delta asymmetry between the pre-op image post-op image. Paired t tests were used to compare the percent asymmetry before and after treatment.

Summary of Results: Facial asymmetry did not improve significantly in either the surgical group or non-surgical group. When comparing the surgical and non-surgical groups’ change in asymmetry, the p-value was .187 for fissure height, .316 for fissure length, .186 for lateral canthus to nasal ala, and .112 for medial canthus to nasal ala.

Conclusions: Neither non-surgical nor surgical intervention for microphthalmia provide significant reduction in asymmetry in four facial measurements.

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TRENDS IN SURGICAL UTILIZATION AND ASSOCIATED PATIENT OUTCOMES IN THE TREATMENT OF ACOUSTIC NEUROMA
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Purpose of Study: The emergence of stereotactic radiosurgery has provided an alternative to traditional surgical excision in the treatment of acoustic neuromas. In our study, we investigate the recent trends in surgical volume and associated patient outcomes in the treatment of this neoplasm.

Methods Used: A retrospective analysis was carried out using the Nationwide Inpatient Sample database from 1998 to 2007. Patients with a primary diagnosis of benign neoplasm of cranial nerve VIII that underwent excision were included. Univariate and multivariate models were then used to evaluate trends of outcomes over time.

Summary of Results: A total of 4829 cases were admitted for surgery between 1998 and 2007. At large-volume hospitals, surgical caseload declined progressively from 337 to 287 cases (a 14.8% decrease) between 1998 and 2007. From 1999 to 2007, this decline followed a near-linear pattern (R=0.88) with a decrease of 21 cases per year. Surgical caseload changes at medium and small-volume hospitals were less pronounced based on linear regression analyses. While mortality has remained low (average: 0.32%, SD: 0.24), the overall odds of non-routine discharge and complications increased mildly over time. Yearly increments in the risk of non-routine discharge (Odds Ratio, OR 1.13, p<.0001) and complications (Odds Ratio, OR 1.06, p=.05) have been observed even after adjusting for hospital volume and patient comorbidities.

Conclusions: A fifteen percent decrease in surgical caseload was observed at large-volume hospitals between 1998 and 2007, with a 21 case per year decline between 1999 and 2007. Similar declines were not observed at medium and small-volume hospitals. A possible explanation for this trend includes increased utilization of stereotactic radiosurgery at these large hospitals. While mortality rates have remained consistently low, a small increase in the risk of complications and non-routine discharges is associated with the decline in surgical utilization. Further investigation is warranted to determine the cause(s) of increased morbidity and, correspondingly, the future roles of surgery and stereotactic radiosurgery in treating acoustic neuromas.