Sladen Libraries
Great Research · Great Care · Start Here
Henry Ford Hospital
Henry Ford Macomb Hospital
Henry Ford Wyandotte Hospital
2799 W Grand Blvd
Detroit, MI 48202
313 916-2550, 313 874-4730 Fax
sladen@hfhs.org
henryfordconnect.com/sladen
M-Th 8:00a-7:30p, F 8:00a-5:00p

Henry Ford Health System Publication List – March 2016

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health System personnel. Searches were conducted in PubMed, Embase, Web of Science, and Google Scholar during the beginning of April, and then imported into EndNote for formatting.There are 115 unique citations listed this month. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health System authors.

Click the "Full Text" link to view the articles to which Sladen Library provides access. If the full-text of the article is not available, you may request it through ILLiad by clicking on the "Article Request Form," or calling us at 313-916-2550. If you would like to be added to the monthly email distribution list to automatically receive a PDF of this bibliography, or you have any questions or comments, please contact Angela Sponer at asponer1@hfhs.org. Click here to notify us of your published work.

Allergy and Immunology

Brown KR, Zabel RA, Calatroni A, Visness C, Sivaprasad U, Matsui E, West JB, Makhija MM, Gill MA, **Kim H**, Kattan M, Pillai DK, Gern JE, Busse WW, Togias A, Liu AH, and Khurana Hershey GK. Endotypes of difficult-to-control asthma in inner city children differ by race *J Allergy Clin Immunol* 2016; 137(2):AB177. PMID: Not assigned. Abstract

K.R. Brown, Cincinnati Children's Hospital Medical Center, Cincinnati, United States

RATIONALE: Blood neutrophils, eosinophils, and serum cytokine levels were assessed in an inner-city pediatric asthmatic population to identify endotypes of childhood asthma severity. We hypothesized that in addition to blood neutrophils and eosinophils, serum cytokines would significantly contribute to the definition of Difficult-to-Control asthma endotypes in African American and non-African American patients. METHODS: Blood neutrophils, blood eosinophils, and 38 serum cytokine levels determined by luminex assay were measured in a sample of 365 asthmatic children (6-17 years) enrolled in the Asthma Phenotypes in the Inner City study. Patients were classified as Easy-to-Control or Difficult-to- Control based on their dose of controller medication over one year. A multivariate variable selection procedure, stratified by race, was used to select cytokines associated with Difficult-to-Control versus Easy-to-Control asthma, adjusting for age, sex, blood eosinophils, and blood neutrophils. RESULTS: In African Americans, 11 cytokines contributed to asthma severity (n=235), while only IL-5 was significant in non-African Americans (n=130). In African Americans, GRO, IL-8, and IL-17A were positively associated with Difficult-to-Control asthma, while IL-4 and IL-13 were positively associated with Easy-to-Control asthma. CONCLUSIONS: In an inner city pediatric population, serum cytokines significantly contributed to the definition of Difficult-to-Control asthma endotypes in African Americans, and to a lesser extent in non-African Americans, suggesting that inflammatory responsesmay differ by race. Mixed responses characterizedby Th2 and Th17 cytokines were most associated with asthma severity in African Americans. Accordingly, treatment regimens that specifically target inflammatory pathways characteristic of asthma severity in African Americans may be beneficial in treating this at risk population.

Allergy and Immunology

Cajigal S, **Peterson EL**, **Wells KE**, **Zoratti EM**, **Lanfear DE**, Seibold M, Rajesh K, Burchard EG, and **Williams LK**. Asthma control test composite score may not be superior to assessments of rescue inhaler use for predicting severe asthma exacerbations *J Allergy Clin Immunol* 2016; 137(2):AB207. PMID: Not assigned. Abstract

S. Cajigal, Division of Allergy and Clinical Immunology, Henry Ford Health System, Detroit, United States

RATIONALE: Current U.S. guidelines recommend the Asthma Control Test (ACT) for assessing disease control and selecting treatment. The ACT was initially validated based on concurrence with specialist opinion. The goal of this study was to prospectively assess the ACT and its component questions for their utility in predicting severe exacerbations. METHODS: Study individuals were participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) and had the following characteristics: age ≥18 years, physician diagnosis of asthma, and membership in a health system serving southeastern Michigan. Participants underwent a baseline evaluation that included the ACT. Severe asthma exacerbations, defined as the need for oral steroids, emergency room visit, or inpatient admission, were identified prospectively using pharmacy claims and patient encounters. Receiver-operator curves were used to assess predictive utility, and the area under the curve (AUC) was used for comparisons. RESULTS: Two hundred thirty two (23.4%) of the 990 participants experienced an

asthma exacerbation in the 6 months following their baseline evaluation. The ACT composite score had an AUC of 0.675. With the exception of the rescue inhaler use question, the composite ACT score was significantly better in predicting exacerbations when compared to the 4 other ACT questions. Pharmacy records of concurrent SABA MDI use were equally predictive of exacerbation when compared to the composite ACT score. CONCLUSIONS: Our study demonstrates that while the ACT is predictive for exacerbations, the composite score may not be superior to assessing SABA rescue use alone when predicting risk of serious asthma exacerbations.

Allergy and Immunology

Esquivel AT, Busse WW, Calatroni A, Gergen PJ, Grindle K, Gruchalla RS, Kattan M, Kercsmar C, Khurana Hershey GK, **Kim H**, Lebeau P, Liu AH, Szefler SJ, Teach SJ, Pongracic JA, West JB, Wildfire J, and Gern JE. Omalizumab decreases rates of cold symptoms in Inner-City children with allergic asthma *J Allergy Clin Immunol* 2016; 137(2):AB87. PMID: Not assigned. Abstract

A.T. Esquivel, University of Wisconsin, Madison, United States

RATIONALE: Omalizumab can reduce virus-induced asthma exacerbations, however little is known about its effects on colds. Our previous data show that omalizumab treatment reduces duration of viral detection, and that omalizumab can improve interferon/antiviral responses. Thus, we hypothesized that omalizumab treatment would decrease weeks with symptomatic upper respiratory illnesses. METHODS: The Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study was a randomized trial of guidelines-based asthma care vs. add-on fluticasone boost vs. add-on omalizumab in 478 asthmatic children (6-17 years) from low-income census tracts. Cold symptom scoring sheets were collected weekly over the 4-month treatment period during the fall seasons of 2012 or 2013. Colds were identified as increased symptoms (runny nose, stuffy nose, sneezing, cough, sore throat) compared to baseline. Adjusted illness rates (colds per sample) by treatment arm were calculated using an over-dispersed Poisson regression. RESULTS: In total, 5873 cold assessments were completed and 1034 (18%) symptomatic illnesses were detected. Rates of colds (per sample) were significantly reduced (p=0.01) in participants treated with add-on omalizumab (0.15, n=259) compared to guidelines-based asthma care alone (0.20, n= 89), a decrease of 27%. Interestingly, this reduction was seen across asthma treatment steps, with the same rate of reduction observed in children with moderate vs. severe persistent asthma. Fluticasone boost had no significant effect on cold rates (0.17, n=130). CONCLUSIONS: Omalizumab significantly decreases rates of cold symptoms in children with allergic asthma. These findings indicate that IgE contributes to the frequency and/or duration of upper respiratory illnesses in this population.

Allergy and Immunology

Liu AH, Babineau DC, Zabel RA, **Zoratti EM**, Pongracic JA, O'Connor GT, Wood RA, Khurana Hershey GK, Kercsmar C, Gruchalla RS, Kattan M, Teach SJ, Arbes Jr SJ, Gergen PJ, Togias A, Visness C, and Busse WW. Identification of pathways to asthma severity in inner-city children *J Allergy Clin Immunol* 2016; 137(2):AB10. PMID: Not assigned. Abstract

A.H. Liu, Children's Hospital Colorado, University of Colorado, School of Medicine, Aurora, United States

RATIONALE: Pathways describing how host and environmental factors lead to asthma severity have not been well defined in inner-city children. METHODS: Nine sites in the NIAID-funded Inner City Asthma Consortium enrolled 717 children aged 6-17 years with asthma. Subjects were evaluated every two months for one year, with adjustments in asthma and rhinitis management made at each visit. An overall measure of asthma severity was defined using longitudinalmeasures of asthma symptoms, exacerbations and treatment. Twenty-two other variables measured at baseline or longitudinally were used to define 8 domains: allergic sensitization, blood eosinophils and exhaled nitric oxide (Eos/FeNO), lung function, Vitamin D, stress, obesity, exposure to tobacco smoke (ETS), and rhinitis severity. A conceptual model of how these domains act through different pathways to explain asthma severity was tested using structural equation models. RESULTS: This analysis included 579 participants with rhinitis who completed at least 4 follow-up visits. In an allergy pathway to asthma severity, allergic sensitization strongly affected Eos/FeNO ($p<0.001$); and Eos/FeNO was indirectly associated with asthma severity via lung function and rhinitis severity ($p<0.001$).Additionally, ETS, lung function and rhinitis severity were directly associated with asthma severity ($p<0.004$). ETS was also indirectly associated with asthma severity via lung function ($p<0.001$). Our complete pathways model accounted for 50.9% of the variance in asthma severity. CONCLUSIONS: This is the first study to identify specific pathways and their relative contributions to asthma severity in inner-city children with asthma and rhinitis, providing a strategic blueprint of pathogenesis and prioritized targets for preventive interventions.

Allergy and Immunology

Luria CJ, **Sitarik AR**, **Havstad S**, **Wegienka GR**, **Kim H**, **Zoratti EM**, **Joseph CLM**, and **Andrea Cassidy B**. Association between asthma symptom scores and increased perceived stress and trait anxiety in asthmatic adolescents *J Allergy Clin Immunol* 2016; 137(2):AB11. PMID: Not assigned. Abstract

C.J. Luria, Division of Allergy and Clinical Immunology, Henry Ford Health System, Detroit, United States

RATIONALE: The relationship between asthma symptoms and perceived stress and trait anxiety is not well understood. METHODS: Adolescents ages 14-17 years were recruited to examine the effect of stress on health measures. They were included in the present analysis if they reported current asthma, defined as self-reported cliniciandiagnosed asthma plus one or more episodes of asthma in the past year. Asthma symptoms were assessed on a 7-point Likert scale using six asthma control questionnaire items targeting nocturnal awakening due to asthma, symptoms upon awakening, activity limitation, shortness of breath, time spent wheezing, and short-acting bronchodilator (SABA) use. Stress was measured using the perceived stress scale (PSS), and trait anxiety was measured using the State-Trait Anxiety Inventory. Linear regression was used to associate asthma symptoms with PSS and trait anxiety. RESULTS: Of 335 adolescents recruited, 38 (11.3%) reported current asthma. Four of the six asthma symptom assessments had significant associations with PSS: symptoms upon awakening (β54.8, p-value<0.001), nocturnal awakening due to asthma (β54.47, p<0.001), activity limitation (β52.78, p=0.005), and shortness of breath (β51.73, p=0.014). These associations remained significant after adjusting for gender, race, and BMI percentile. Time spentwheezing and SABA use were not significantly associated with PSS. Trait anxiety had significant associations with nocturnal awakening (β59.28, p=0.002) and symptoms upon awakening (β58.74, p=0.002). CONCLUSIONS: Asthma symptoms are associated with increased perceived stress and trait anxiety. Asthmatic adolescents may represent a population that is particularly vulnerable to perceived stress and anxiety, highlighting the importance of considering these factors in asthma counseling.

Allergy and Immunology

Pongracic JA, Zabel RA, Babineau DC, **Zoratti EM**, O'Connor GT, Wood RA, Khurana Hershey GK, Kercsmar C, Gruchalla RS, Kattan M, Teach SJ, Arbes Jr SJ, Busse WW, Gergen PJ, Togias A, Visness C, and Liu AH. Characteristics that distinguish difficult-to-control asthma in inner-city children *J Allergy Clin Immunol* 2016; 137(2):AB8. PMID: Not assigned. Abstract

J.A. Pongracic, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, United States

RATIONALE: Because a significant proportion of inner-city children are only partially responsive to guidelines-directed asthma therapy, we sought to identify the clinical characteristics that distinguish difficult-to-control asthma. METHODS: The Inner City Asthma Consortium enrolled children aged 6-17 years with asthma. After baseline assessment, participants had bi-monthly guidelines-based asthma management visits over one year. Difficult-to-control asthma (DCA) versus Easy-to-control asthma (ECA) were defined as daily controller therapy with inhaled fluticasone >500mcg +/-LABA versus <100mcg assigned on at least 4 visits, respectively. Forty-one baseline variables were used to compare DCA and ECA using univariate analyses. A variable selection algorithm was used to determine the most relevant features of DCA versus ECA. Generalized additive mixed-effects models were used to describe seasonal variation of symptoms, lung function, and exacerbations. RESULTS: Of the 619 participants, 40.9% had DCA and 37.5% had ECA. DCA was characterized by persistently low lung function, more frequent exacerbations in the spring and fall as well as greater daytime and nocturnal symptoms in the fall and winter. Of the 41 variables, FEV1 bronchodilator reversibility (BDR) was the most important characteristic distinguishing DCA. The other dominant features of DCA, in order of importance, included: FEV1/FVC ratio, rhinitis medication score, FEV1% predicted, rhinitis symptom score, mold sensitization, and total serum IgE. CONCLUSIONS: The phenotypic characteristics of DCA in inner-city children include seasonal loss of asthma control, BDR, persistently low lung function, rhinitis severity and atopy. These findings suggest that baseline assessment of BDR and allergy-related factors, including rhinitis, may predict future DCA.

Allergy and Immunology

Zoratti EM, Zabel RA, Babineau DC, Pongracic JA, O'Connor GT, Wood RA, Khurana Hershey GK, Kercsmar C, Gruchalla RS, Kattan M, Teach SJ, Arbes Jr SJ, Visness C, Busse WW, Gergen PJ, Togias A, and Liu AH. Levels of allergy cluster with asthma severity in inner-city children *J Allergy Clin Immunol* 2016; 137(2):AB103. PMID: Not assigned. Abstract

E.M. Zoratti, Henry Ford Health System, Detroit, United States

RATIONALE: Phenotypic characterization of asthma among urban youth is lacking. Using unsupervised clustering techniques, we identified distinct asthma phenotypes in inner-city children who received one year of guidelines-based asthma management. METHODS: Nine sites in the NIAID-funded Inner City Asthma Consortium enrolled 717 children aged 6-17 years with mild to severe asthma. Data were collected at baseline and every 2 months for 1 year. Hierarchical cluster analysis was performed in participants completing >4 follow-up visits. Clusters were generated using 52 baseline characterization variables plus 12 longitudinal clinical variables reflecting lung function, asthma symptoms, exacerbations and controller treatment over 1 year. Univariate comparisons were used to determine distinguishing characteristics among clusters. RESULTS: 616 participants were eligible for analysis (58% male, 64% Black non-Hispanic, 29% Hispanic, 7% other). Four distinct clusters were characterized by differences in indicators of asthma severity, including level of controller therapy, prednisone use, bronchial hyper-responsiveness and lung function. Laboratory and clinical indicators of allergy were increased in the phenotypes with higher asthma severity. The cluster reflecting the most severe asthma included the highest proportions of self-reported eczema (77%) and food allergy (62%), along with the highest serum total IgE levels (geometric mean 763 kU/L), number of allergic sensitizations (median 15 of 20 allergens evaluated), exhaled nitric oxide levels (geometric mean 27.4 ppb), and peripheral blood eosinophil counts (median 400/microliter). CONCLUSIONS: Severe asthma phenotypes among inner city children exhibit high levels of allergy. Treatment and environmental control of allergy may be particularly important for optimal management of asthma in this population.

Behavioral Health

Miller-Matero LR, **Dykuis KE**, **Albujoq K**, **Martens K**, **Fuller BS**, **Robinson V**, and **Willens DE**. Benefits of integrated behavioral health services: The physician perspective *Fam Syst Health* 2016; 34(1):51-55. PMID: 26963777 Full Text

Department of Behavioral Health, Henry Ford Health System.
Department of Internal Medicine, Henry Ford Health System.

INTRODUCTION: There are benefits of integrating a behavioral health specialist in primary care; however, little is known about the physicians' perspectives. The purpose of this study was to explore primary care physicians' beliefs regarding the benefits of integrated care for both patients and themselves. METHOD: Fifteen senior staff physicians and 78 residents completed surveys regarding their opinions of referring to a psychologist in a patient-centered medical home. RESULTS: The top reasons that physicians believed their patients followed through with a visit with an integrated psychologist included that they recommended it (79.5%) and that patients can be seen in the same primary care clinic (76.9%). The overwhelming majority of physicians were satisfied with having access to an integrated psychologist (97.4%). Physicians believed that integrated care directly improves patient care (93.8%), is a needed service (90.3%), and helps provide better care to patients (80.9%). In addition, physicians reported that having an integrated psychologist reduces their personal stress level (90.1%). CONCLUSION: Primary care physicians may be motivated to integrate behavioral health services into their clinics knowing that other physicians believe that it directly and indirectly improves patient care and physician stress. (PsycINFO Database Record

Cardiology / Cardiovascular Research

Al-Mallah MH, Qureshi WT, **Keteyian SJ**, **Brawner CA**, **Alam M**, Dardari Z, Nasir K, and Blaha MJ. Racial differences in the prognostic value of cardiorespiratory fitness (Results from the Henry Ford Exercise Testing Project) *Am J Cardiol* 2016;PMID: 26976790. Full Text

Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan; Department of Medicine, Wayne State University, Detroit, Michigan; King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King ABdulAziz Cardiac Center, Ministry of National Guard, Health Affairs, Riyadh, Kingdom of Saudi Arabia. Electronic address: mouaz74@gmail.com.
Wake Forest University School of Medicine, Winston Salem, North Carolina.
Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan.
Johns Hopkins Ciccarone Center for Preventive Cardiology, Baltimore, Maryland.

The aim of this analysis was to determine whether racial differences exist in the prognostic value of cardiorespiratory fitness (CRF) in black and white patients undergoing stress testing. We included 53,876 patients (mean age 53 +/- 13, 49% women) from the Henry Ford Exercise Testing project free of established coronary disease or heart failure who completed a maximal exercise test from 1991 to 2009. Patients were followed for a mean duration of 11.5 years for all-cause mortality, ascertained by linkage with the Death Master File. Follow-up over mean 6.2 years was also available for incident myocardial infarction. Multivariate Cox proportional hazards regression models were used adjusting for demographic variables, risk factors, medications, and reason for stress test referral, including formal interaction testing by race (black vs white). Black patients (n = 16,725) were younger (54 +/- 13 vs 52 +/- 13, p

<0.001) but had higher prevalence of hypertension (73% vs 57%, p <0.001) and obesity (28% vs 21%, p <0.001). On average, black patients achieved a lower CRF compared with whites (8.4 vs 9.5 metabolic equivalents, p <0.0001). A graded increase in mortality risk was noted with decreasing CRF for both black and white patients. In multivariate Cox regression, CRF was a predictor of both myocardial infarction and mortality, with no significant interaction between race, fitness, and outcomes (all interaction terms p >0.10). CRF is a strong predictor of all-cause mortality in both white and black patients, with no significant interaction observed between race, fitness, and outcomes.

Cardiology / Cardiovascular Research
Ananthasubramaniam K, **Garikapati K**, and **Williams CT**. Progressive left ventricular hypertrophy after heart transplantation: Insights and mechanisms suggested by multimodal images *Tex Heart Inst J* 2016; 43(1):65-68. PMID: Not assigned. Full Text

K. Ananthasubramaniam, Heart and Vascular Institute, Henry Ford Hospital, Detroit, United States

Immunosuppression is the typical measure to prevent rejection after heart transplantation. Although rejection is the usual cause of cardiac hypertrophy, numerous other factors warrant consideration. Calcineurin inhibitors rarely cause hypertrophic cardiomyopathy; the few relevant reports have described children after orthotopic kidney or liver transplantation. We present the case of a 73-year-old woman, an asymptomatic orthotopic heart transplantation patient, in whom chronic immunosuppression with prednisone and cyclosporine apparently caused a phenotype of hypertrophic cardiomyopathy. The natural course of her midapical hypertrophy was revealed by single-photon-emission computed tomography, positron-emission tomography, and 2-dimensional echocardiography. Clinicians and radiographers should be alert to progressive left ventricular hypertrophy and various perfusion patterns in heart transplantation patients even in the absence of underlying coronary artery disease. Toward this end, we recommend that advanced imaging methods be used to their fullest extent.

Cardiology / Cardiovascular Research
Cajigal S, **Peterson EL**, **Wells KE**, **Zoratti EM**, **Lanfear DE**, Seibold M, Rajesh K, Burchard EG, and **Williams LK**. Asthma control test composite score may not be superior to assessments of rescue inhaler use for predicting severe asthma exacerbations *J Allergy Clin Immunol* 2016; 137(2):AB207. PMID: Not assigned. Abstract

S. Cajigal, Division of Allergy and Clinical Immunology, Henry Ford Health System, Detroit, United States

RATIONALE: Current U.S. guidelines recommend the Asthma Control Test (ACT) for assessing disease control and selecting treatment. The ACT was initially validated based on concurrence with specialist opinion. The goal of this study was to prospectively assess the ACT and its component questions for their utility in predicting severe exacerbations. METHODS: Study individuals were participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) and had the following characteristics: age ≥18 years, physician diagnosis of asthma, and membership in a health system serving southeastern Michigan. Participants underwent a baseline evaluation that included the ACT. Severe asthma exacerbations, defined as the need for oral steroids, emergency room visit, or inpatient admission, were identified prospectively using pharmacy claims and patient encounters. Receiver-operator curves were used to assess predictive utility, and the area under the curve (AUC) was used for comparisons. RESULTS: Two hundred thirty two (23.4%) of the 990 participants experienced an asthma exacerbation in the 6 months following their baseline evaluation. The ACT composite score had an AUC of 0.675. With the exception of the rescue inhaler use question, the composite ACT score was significantly better in predicting exacerbations when compared to the 4 other ACT questions. Pharmacy records of concurrent SABA MDI use were equally predictive of exacerbation when compared to the composite ACT score. CONCLUSIONS: Our study demonstrates that while the ACT is predictive for exacerbations, the composite score may not be superior to assessing SABA rescue use alone when predicting risk of serious asthma exacerbations.

Cardiology / Cardiovascular Research
Cheruvu C, Precious B, Naoum C, Blanke P, Ahmadi A, Soon J, Arepalli C, Gransar H, Achenbach S, Berman DS, Budoff MJ, Callister TQ, **Al-Mallah MH**, Cademartiri F, Chinnaiyan K, Rubinshtein R, Marquez H, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Shaw LJ, Kaufmann PA, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Chang HJ, Min JK, and Leipsic J. Long term prognostic utility of coronary CT angiography in patients with no modifiable coronary artery disease risk factors: Results from the 5 year follow-up of the CONFIRM International Multicenter Registry *J Cardiovasc Comput Tomogr* 2016; 10(1):22-27. PMID: 26719237. Full Text

Department of Radiology, University of British Columbia, Vancouver, BC, Canada.
Department of Medicine, University of British Columbia, Vancouver, BC, Canada.

Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA.
Department of Medicine, University of Erlangen, Erlangen, Germany.
Department of Imaging, Cedars Sinai Medical Center, Los Angeles, CA, USA.
Department of Medicine, Harbor UCLA Medical Center, Los Angeles, CA, USA.
Tennessee Heart and Vascular Institute, Hendersonville, TN, USA.
Department of Medicine, Wayne State University, Henry Ford Hospital, Detroit, MI, USA.
Cardiovascular Imaging Unit, Giovanni XXIII Hospital, Monastier, Treviso, Italy.
William Beaumont Hospital, Royal Oaks, MI, USA.
Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal.
Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.
Capitol Cardiology Associates, Albany, NY, USA.
Department of Medicine, Walter Reed Medical Center, Washington, DC, USA.
Division of Cardiology, Deutsches Herzzentrum Munchen, Munich, Germany.
Medizinische Klinik I der Ludwig-Maximilians-Universitat Munchen, Munich, Germany.
Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA.
University Hospital, Zurich, Switzerland.
Baptist Cardiac and Vascular Institute, Miami, FL, USA.
Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria.
Seoul National University Hospital, Seoul, South Korea.
Department of Clinical Sciences and Community Health, University of Milan, Centro Cardiologico Monzino, IRCCS, Milan, Italy.
Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea.
Department of Radiology, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA.
Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada. Electronic address: jleipsic@providencehealth.bc.ca.

BACKGROUND: Coronary computed tomography angiography (coronary CTA) can prognosticate outcomes in patients without modifiable risk factors over medium term follow-up. This ability was driven by major adverse cardiovascular events (MACE). OBJECTIVE: Determine if coronary CTA could discriminate risk of mortality with longer term follow-up. In addition we sought to determine the long-term relationship to MACE. METHODS: From 12 centers, 1884 patients undergoing coronary CTA without prior coronary artery disease (CAD) or any modifiable CAD risk factors were identified. The presence of CAD was classified as none (0% stenosis), mild (1% to 49% stenosis) and obstructive (>/=50% stenosis severity). The primary endpoint was all-cause mortality and the secondary endpoint was MACE. MACE was defined as the combination of death, nonfatal myocardial infarction, unstable angina, and late target vessel revascularization (>90 days). RESULTS: Mean age was 55.6 +/- 14.5 years. At mean 5.6 +/- 1.3 years follow-up, 145(7.7%) deaths occurred. All-cause mortality demonstrated a dose-response relationship to the severity and number of coronary vessels exhibiting CAD. Increased mortality was observed for >1 segment non-obstructive CAD (hazard ratio [HR]:1.73; 95% confidence interval [CI]: 1.07-2.79; p = 0.025), obstructive 1&2 vessel CAD (HR: 1.70; 95% CI: 1.08-2.71; p = 0.023) and 3-vessel or left main CAD (HR: 2.87; 95% CI: 1.57-5.23; p = 0.001). Both obstructive CAD (HR: 6.63; 95% CI: 3.91-11.26; p < 0.001) and non-obstructive CAD (HR: 2.20; 95% CI: 1.31-3.67; p = 0.003) predicted MACE with increased hazard associated with increasing CAD severity; 5.60% in no CAD, 13.24% in non-obstructive and 36.28% in obstructive CAD, p < 0.001 for trend. CONCLUSIONS: In individuals being assessed for CAD with no modifiable risk factors, all-cause mortality in the long term (>5 years) was predicted by the presence of more than 1 segment of non-obstructive plaque, obstructive 1- or 2-vessel CAD and 3 vessel/left main CAD. Any CAD, whether non-obstructive or obstructive, predicted MACE over the same time period.

Cardiology / Cardiovascular Research

Cooper LB, Mentz RJ, Sun JL, Schulte PJ, Fleg JL, Cooper LS, Pina IL, Leifer ES, Kraus WE, Whellan DJ, **Keteyian SJ**, and O'Connor CM. Psychosocial factors, exercise adherence, and outcomes in heart failure patients: Insights from heart failure: A controlled trial investigating outcomes of exercise training (HF-ACTION) *Circ Heart Fail* 2015; 8(6):1044-1051. PMID: 26578668. Full Text

From the Duke Clinical Research Institute (L.B.C., R.J.M., J.-L.S., P.J.S., C.M.O'C.), and Department of Medicine (L.B.C., R.J.M., W.E.K., C.M.O'C.), Duke University School of Medicine, Durham, NC; Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD (J.L.F., L.S.C., E.S.L.); Division of Cardiology, Albert Einstein College of Medicine, Bronx, NY (I.L.P.); Division of Cardiology, Jefferson Medical College, Philadelphia, PA (D.J.W.); and Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI (S.J.K.). lauren.b.cooper@duke.edu.

From the Duke Clinical Research Institute (L.B.C., R.J.M., J.-L.S., P.J.S., C.M.O'C.), and Department of Medicine (L.B.C., R.J.M., W.E.K., C.M.O'C.), Duke University School of Medicine, Durham, NC; Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD (J.L.F., L.S.C., E.S.L.); Division of Cardiology, Albert Einstein College of Medicine, Bronx, NY (I.L.P.); Division of Cardiology, Jefferson Medical College, Philadelphia, PA (D.J.W.); and Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI (S.J.K.).

BACKGROUND: Psychosocial factors may influence adherence with exercise training for heart failure (HF) patients. We aimed to describe the association between social support and barriers to participation with exercise adherence and clinical outcomes. METHODS AND RESULTS: Of patients enrolled in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), 2279 (97.8%) completed surveys to assess social support and barriers to exercise, resulting in the perceived social support score (PSSS) and barriers to exercise score (BTES). Higher PSSS indicated higher levels of social support, whereas higher BTES indicated more barriers to exercise. Exercise time at 3 and 12 months correlated with PSSS (r= 0.09 and r= 0.13, respectively) and BTES (r=-0.11 and r=-0.12, respectively), with higher exercise time associated with higher PSSS and lower BTES (All P<0.005). For cardiovascular death or HF hospitalization, there was a significant interaction between the randomization group and BTES (P=0.035), which corresponded to a borderline association between increasing BTES and cardiovascular death or HF hospitalization in the exercise group (hazard ratio 1.25, 95% confidence interval 0.99, 1.59), but no association in the usual care group (hazard ratio 0.83, 95% confidence interval 0.66, 1.06). CONCLUSIONS: Poor social support and high barriers to exercise were associated with lower exercise time. PSSS did not impact the effect of exercise training on outcomes. However, for cardiovascular death or HF hospitalization, exercise training had a greater impact on patients with lower BTES. Given that exercise training improves outcomes in HF patients, assessment of perceived barriers may facilitate individualized approaches to implement exercise training therapy in clinical practice. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00047437.

Cardiology / Cardiovascular Research

Handy CE, Desai CS, Dardari ZA, **Al-Mallah MH**, Miedema MD, Ouyang P, Budoff MJ, Blumenthal RS, Nasir K, and Blaha MJ. The association of coronary artery calcium with noncardiovascular disease: The multi-ethnic study of atherosclerosis *JACC Cardiovasc Imaging* 2016;PMID: 26970999. Full Text

The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland.
Heart and Vascular Institute, Henry Ford Hospital, Detroit, Michigan.
Minneapolis Heart Institute and Minneapolis Heart Institute Foundation, Minneapolis, Minnesota.
Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California.
The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland; Center for Healthcare Advancement & Outcomes, Baptist Health South Florida, Miami, Florida; Department of Medicine, Herbert Wertheim College of Medicine, Florida International University, Miami, Florida; Department of Epidemiology, Robert Stempel College of Public Health, Florida International University, Miami, Florida.
The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland. Electronic address: mblaha1@jhmi.edu.

OBJECTIVES: This study sought to determine if coronary artery calcium (CAC) is associated with incident noncardiovascular disease. BACKGROUND: CAC is considered a measure of vascular aging, associated with increased risk of cardiovascular and all-cause mortality. The relationship with noncardiovascular disease is not well defined. METHODS: A total of 6,814 participants from 6 MESA (Multi-Ethnic Study of Atherosclerosis) field centers were followed for a median of 10.2 years. Modified Cox proportional hazards ratios accounting for the competing risk of fatal coronary heart disease were calculated for new diagnoses of cancer, pneumonia, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), deep vein thrombosis/pulmonary embolism, hip fracture, and dementia. Analyses were adjusted for age; sex; race; socioeconomic status; health insurance status; body mass index; physical activity; diet; tobacco use; number of medications used; systolic and diastolic blood pressure; total and high-density lipoprotein cholesterol; antihypertensive, aspirin, and cholesterol medication; and diabetes. The outcome was first incident noncardiovascular disease diagnosis. RESULTS: Compared with those with CAC = 0, those with CAC >400 had an increased hazard of cancer (hazard ratio [HR]: 1.53; 95% confidence interval [CI]: 1.18 to 1.99), CKD (HR: 1.70; 95% CI: 1.21 to 2.39), pneumonia (HR: 1.97; 95% CI: 1.37 to 2.82), COPD (HR: 2.71; 95% CI: 1.60 to 4.57), and hip fracture (HR: 4.29; 95% CI: 1.47 to 12.50). CAC >400 was not associated with dementia or deep vein thrombosis/pulmonary embolism. Those with CAC = 0 had decreased risk of cancer (HR: 0.76; 95% CI: 0.63 to 0.92), CKD (HR: 0.77; 95% CI: 0.60 to 0.98), COPD (HR: 0.61; 95% CI: 0.40 to 0.91), and hip fracture (HR: 0.31; 95% CI: 0.14 to 0.70) compared to those with CAC >0. CAC = 0 was not associated with less pneumonia, dementia, or deep vein thrombosis/pulmonary embolism. The results were attenuated, but remained significant, after removing participants developing interim nonfatal coronary heart disease. CONCLUSIONS: Participants with elevated

CAC were at increased risk of cancer, CKD, COPD, and hip fractures. Those with CAC = 0 are less likely to develop common age-related comorbid conditions, and represent a unique population of "healthy agers."

Cardiology / Cardiovascular Research
Hencken L, **To L**, **Ly N**, and **Morgan JA**. Serotonin syndrome following methylene blue administration for vasoplegic syndrome *J Card Surg* 2016; 31(4):208-210. PMID: 26934199. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan.
Department of Cardiology, Henry Ford Hospital, Detroit, Michigan.
Department of Cardiac Surgery, Henry Ford Hospital, Detroit, Michigan.

Methylene blue (MB) has been used for additional blood pressure support in patients who develop severe, refractory vasoplegia; however, MB can induce serotonin syndrome, especially when used in conjunction with other serotonergic agents. We describe a case of serotonin syndrome in a patient who received MB for vasoplegic syndrome after left ventricular assist device implantation and discuss its presentation and management.

Cardiology / Cardiovascular Research
Kupsky DF, **Alaswad K**, and **Rabbani BT**. A rare case of aspergillus pericarditis with associated myocardial abscess and echocardiographic response to therapy *Echocardiography* 2016;PMID: 27009593. Full Text

Heart and Vascular Institute, Henry Ford Hospital System, Detroit, Michigan.

Myocardial abscess is an extremely rare entity and is often deadly in nature. We present a case of a patient with recent orthotopic liver transplant, on immunosuppression, who presented with cardiac tamponade due to Aspergillus fumigatus pericarditis and associated myocardial abscess. The diagnosis was made based on computed tomography imaging, culture of pericardial fluid for Aspergillus, and transthoracic echocardiography. The patient received antifungal therapy with clinical improvement and documented reduction in abscess size based on repeat echocardiogram. Aspergillus myocardial abscess is an extremely rare diagnosis but should be considered in an immunosuppressed patient presenting with pericardial effusion or ventricular mass.

Cardiology / Cardiovascular Research
Meredith IT, Tanguay JF, Kereiakes DJ, Cutlip DE, Yeh RW, Garratt KN, Lee DP, Steg PG, **Weaver WD**, Holmes DR, Jr., Brindis RG, Trebacz J, Massaro JM, Hsieh WH, and Mauri L. Diabetes mellitus and prevention of late myocardial infarction after coronary stenting in the randomized dual antiplatelet therapy study *Circulation* 2016;PMID: 26994121. Full Text

Monash Heart and Monash University, Melbourne, Australia.
Montreal Heart Institute, Universite de Montreal, Montreal, Quebec, Canada;
The Christ Hospital Heart and Vascular Center and The Lindner Center for Research and Education, Cincinnati, OH.
Beth Israel Deaconess Medical Center, Boston, MA; Harvard Clinical Research Institute, Boston, MA; Harvard Medical School, Boston, MA.
Harvard Clinical Research Institute, Boston, MA; Harvard Medical School, Boston, MA; The Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Boston, MA.
Lenox Hill Hospital, New York, New York.
Stanford University, Stanford, CA.
Universite Paris-Diderot, INSERM U-1148, Hopital Bichat, Departement Hospitalo-Universitaire Fibrosis, Inflammation, and Remodeling, Assistance Publique-Hopitaux de Paris, Paris, France; National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London, United Kingdom.
Henry Ford Medical Group, Detroit, MI.
Mayo Clinic, Rochester, MN.
Institute for Health Policy Studies, University of California, San Francisco, CA;
Jan Pawel II Hospital Krakow, Krakow, Poland.
Harvard Clinical Research Institute, Boston, MA; Boston University School of Public Health, Boston, MA.
Harvard Clinical Research Institute, Boston, MA; 6Harvard Medical School, Boston, MA; Brigham and Women's Hospital, Boston, MA lmauri1@partners.org.

BACKGROUND: -Patients with diabetes mellitus (DM) are at high risk for recurrent ischemic events after coronary stenting. We assessed the effects of continued thienopyridine among patients with DM participating in the Dual Antiplatelet Therapy (DAPT) Study as a prespecified analysis. METHODS AND RESULTS: -After coronary stent

placement and 12 months treatment with open-label thienopyridine plus aspirin, 11648 patients free of ischemic or bleeding events and who were medication compliant were randomized to continued thienopyridine or placebo, in addition to aspirin, for 18 more months. After randomization, patients with DM (N=3391), compared with patients without DM (N=8257), had increased composite outcome of death, myocardial infarction (MI), or stroke (6.8% vs. 4.3%, P<0.001), and increased death (2.5% vs. 1.4%, P<0.001), and MI (4.2% vs. 2.6%, P<0.001). Among patients with DM, comparing continued thienopyridine versus placebo, rates of stent thrombosis were 0.5% vs. 1.1%, P=0.06; and MI, 3.5% vs. 4.8%, P=0.058, and among patients without DM the rates were 0.4% vs. 1.4%, P<0.001 (stent thrombosis, p interaction=0.21) and 1.6% vs. 3.6%, P<0.001 (MI, p interaction=0.02). Bleeding risk with continued thienopyridine was similar amongst patients with or without DM (interaction P=0.61). CONCLUSIONS: -In patients with DM, continued thienopyridine beyond 1-year after coronary stenting is associated with reduced risk of MI, although this benefit is attenuated when compared with patients without DM. Clinical Trial Registration Information-ClinicalTrials.gov. Identifier: NCT00977938.

Cardiology / Cardiovascular Research

Shafiq A, **Brawner CA**, **Aldred HA**, **Lewis B**, **Williams CT**, **Tita C**, **Schairer JR**, **Ehrman JK**, **Velez M**, **Selektor Y**, **Lanfear DE**, and **Keteyian SJ**. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project *Am Heart J* 2016; 174:167-172. PMID: 26995385. Full Text

St Luke's Mid America Heart Institute, University of Missouri, Kansas City, MO. Electronic address: shafiqa@umkc.edu.
Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI.

BACKGROUND: Although cardiopulmonary exercise (CPX) testing in patients with heart failure and reduced ejection fraction is well established, there are limited data on the value of CPX variables in patients with HF and preserved ejection fraction (HFpEF). We sought to determine the prognostic value of select CPX measures in patients with HFpEF. METHODS: This was a retrospective analysis of patients with HFpEF (ejection fraction >/= 50%) who performed a CPX test between 1997 and 2010. Selected CPX variables included peak oxygen uptake (VO2), percent predicted maximum oxygen uptake (ppMVO2), minute ventilation to carbon dioxide production slope (VE/VCO2 slope) and exercise oscillatory ventilation (EOV). Separate Cox regression analyses were performed to assess the relationship between each CPX variable and a composite outcome of all-cause mortality or cardiac transplant. RESULTS: We identified 173 HFpEF patients (45% women, 58% non-white, age 54 +/- 14 years) with complete CPX data. During a median follow-up of 5.2 years, there were 42 deaths and 5 cardiac transplants. The 1-, 3-, and 5-year cumulative event-free survival was 96%, 90%, and 82%, respectively. Based on the Wald statistic from the Cox regression analyses adjusted for age, sex, and beta-blockade therapy, ppMVO2 was the strongest predictor of the end point (Wald chi(2) = 15.0, hazard ratio per 10%, P < .001), followed by peak VO2 (Wald chi(2) = 11.8, P = .001). VE/VCO2 slope (Wald chi(2)= 0.4, P = .54) and EOV (Wald chi(2) = 0.15, P = .70) had no significant association to the composite outcome. CONCLUSION: These data support the prognostic utility of peak VO2 and ppMVO2 in patients with HFpEF. Additional studies are needed to define optimal cut points to identify low- and high-risk patients.

Center for Health Policy and Health Services Research

Ahmedani BK, **Peterson EL**, **Wells KE**, **Henein F**, and **Williams LK**. Long-term management of low back pain with opioids and non-steroidal anti-inflammatory drugs in a health system *Am J Prev Med* 2016;PMID: 26970664. Full Text

Henry Ford Health System, Detroit, Michigan. Electronic address: bahmeda1@hfhs.org.

Center for Health Policy and Health Services Research

Nerenz DR. Challenges in moving to "pay for outcomes" *J Ambul Care Manage* 2016; 39(2):122-124. PMID: 26945294. Full Text

Director, Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Michigan.

Center for Health Policy and Health Services Research

Rajesh K, Cho SH, Min JY, Kang J, Chan W, Kim DY, Oh S, Torgerson D, Del Mar Del-Pino-Yanes M, Hu D, Sen S, Huntsman S, Eng C, Farber HJ, Rodriguez-Cintron W, Rodriguez-Santana J, Serebrisky D, Thyne S, Borrell L, **Williams LK**, Seibold M, Burchard EG, and Avila PC. PAI-1, early life infections and asthma risk, exacerbations, and reduced lung function *J Allergy Clin Immunol* 2016; 137(2):AB178. PMID: Not assigned. Abstract

K. Rajesh, Pediatric Allergy, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, United States

RATIONALE: Plasminogen activator inhibitor-1 (PAI-1) is induced in airways by virus and may mediate asthmatic airway remodeling. We sought to evaluate if PAI-1 genetic variants and early life lower respiratory infections jointly affect asthma risk. METHODS: We included Latino children aged 8-21 years (1736 subjects with physician-diagnosed asthma and 1747 healthy controls) from five U.S. centers and Puerto Rico after excluding subjects with incomplete clinical or genetic data. We evaluated the independent and joint effects of a PAI-1 gain of function polymorphism and Respiratory Syncytial Virus (RSV) or other lower respiratory infections (LRI) within the first 2 years of life on asthma risk, asthma exacerbations and lung function. RESULTS: RSV infection (9.9, 95%CI 4.9-20.2) and other LRI (9.1, 95% CI 7.2-11.5) were independently associated with asthma, but PAI-1 genotype was not. There were joint effects on asthma risk for both genotype-RSV (OR 17.7, 95% CI 6.3-50.2) and genotype-LRI (OR 11.7, 95% CI 8.8-16.4). A joint effect of genotype-RSV resulted in a 3.1-fold increased risk for recurrent asthma hospitalizations. In genotype-respiratory infection joint effect analysis, FEV1 % predicted, FVC % predicted, and FEV1/FVC % predicted were further reduced in the genotype-RSV group (β -7.2, 95% CI -10.3 - -4.2; β -5.7, 95% CI -8.7 - -2.7; and β -1.9, 95% CI -3.7 - -0.2 respectively). CONCLUSIONS: A genetic variant of PAI-1 together with early life LRI such as RSV bronchiolitis is associated with an increased risk of asthma, morbidity, and reduced lung function in this Latino population.

Center for Health Policy and Health Services Research

Wells KE, **Cajigal S**, **Peterson EL**, **Ahmedani BK**, Kumar R, **Lanfear DE**, Burchard EG, and **Williams LK**. Assessing differences in inhaled corticosteroid response by self-reported race-ethnicity and genetic ancestry among asthmatic subjects *J Allergy Clin Immunol* 2016;PMID: 27016472. Full Text

Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich. Electronic address: kewells1@aol.com.
Department of Internal Medicine, Henry Ford Health System, Detroit, Mich.
Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich.
Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Mich.
Department of Pediatrics, The Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Ill.
Department of Bioengineering & Therapeutic Sciences, University of California San Francisco, San Francisco, Calif; Department of Medicine, University of California San Francisco, San Francisco, Calif.
Department of Internal Medicine, Henry Ford Health System, Detroit, Mich; Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Mich.

BACKGROUND: Inhaled corticosteroids (ICSs) are the preferred treatment for achieving asthma control. However, little is known regarding the factors contributing to treatment response and whether treatment response differs by population group. OBJECTIVE: We sought to assess behavioral, sociodemographic, and genetic factors related to ICS response among African American and European American subjects with asthma. METHODS: Study participants were part of the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE). The analytic sample included asthmatic subjects aged 12 to 56 years with greater than 12% bronchodilator reversibility and percent predicted FEV1 of between 40% and 90%. Participants received 6 weeks of inhaled beclomethasone dipropionate. The primary measure of ICS response was a change in Asthma Control Test (ACT) score; the secondary measure was a change in prebronchodilator FEV1. Adherence was measured with electronic monitors. Genetic ancestry was estimated for African American participants by using genome-wide genotype data. RESULTS: There were 339 study participants; 242 self-identified as African American and 97 as European American. Baseline ACT score, percent predicted FEV1, degree of bronchodilator response, and ICS adherence were significantly associated with ICS response. A baseline ACT score of 19 or less was useful in identifying those who would respond, as evidenced by the significant dose-response relationship with ICS adherence. Neither self-reported race-ethnicity among all participants nor proportion of African ancestry among African American participants was associated with ICS responsiveness. CONCLUSIONS: Our findings suggest that baseline lung function measures and self-reported asthma control predict ICS response, whereas self-reported race-ethnicity and genetic ancestry do not.

Dermatology

Boguniewicz M, Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL, **Stein Gold LF**, Zaenglein AL, Hughes MH, Zane LT, and Hebert AA. Efficacy and safety of crisaborole topical ointment, 2%, a novel, nonsteroidal, topical, anti-inflammatory, phosphodiesterase inhibitor in 2 phase 3 studies in children and adults with mildto-moderate atopic dermatitis *J Allergy Clin Immunol* 2016; 137(2):AB397. PMID: Not assigned. Abstract

M. Boguniewicz, National Jewish Health, Denver, United States

RATIONALE: Phosphodiesterase 4 (PDE4) enzyme is overexpressed in inflammatory cells of patients with atopic dermatitis (AD); this leads to disease exacerbation. Here, we present safety and efficacy from 2 multicenter, double-blind, vehicle-controlled phase 3 studies of identical design in patients with mild-to-moderate AD (NCT02118766 and NCT02118792) treated with the novel, nonsteroidal, topical, anti-inflammatory investigational PDE4 inhibitor Crisaborole Topical Ointment, 2%. METHODS: Patients ≥2 years old with mild-to-moderate AD were randomized 2:1 to receive crisaborole or vehicle twice daily with evaluation on Days 8, 15, 22, and 29. Primary and secondary efficacy endpoints analyzed AD disease severity with the Investigator's Static Global Assessment (ISGA). Supportive efficacy endpoints examined time to improvement in pruritus, severity of pruritus, and signs of AD. RESULTS: Studies 1 and 2 enrolled 503:256 and 513:250 crisaborole/ vehicle patients, respectively. At Day 29, more crisaborole-treated patients achieved ISGA success than those treated with vehicle (study 1: 32.8% vs 25.4%, P=0.038; study 2: 31.4% vs 18.0%, P<0.001) with a greater percentage of “almost clear/1” or “clear/0” ISGA scores (study 1: 51.7% vs 40.6%, P=0.005; study 2: 48.5% vs 29.7%, P<0.001). Success in ISGA and improvement in pruritus were achieved earlier with crisaborole than vehicle (P<0.001 vs vehicle). A greater proportion of crisaborole-treated patients achieved success for all clinical signs of AD by Day 29. Treatment-related adverse events were infrequent, transient, and mild/ moderate in severity. CONCLUSIONS: Two Phase 3 studies demonstrate that Crisaborole Topical Ointment, 2%, represents a novel, safe, and efficacious treatment for children and adults with mild-to-moderate AD.

Dermatology

Gordon SC, **Porto DA**, and **Kerr HA**. Asymptomatic papules on the lateral aspects of the hands and feet *J Am Acad Dermatol* 2016; 74(4):e55-56. PMID: 26979365. Full Text

Department of Dermatology, Henry Ford Health System, Detroit, Michigan. Electronic address: scgordon4@gmail.com.
Department of Dermatology, Henry Ford Health System, Detroit, Michigan.

Dermatology

Kircik L, Sung JC, **Stein-Gold L**, and Goldenberg G. United states food and drug administration product label changes *J Clin Aesthet Dermatol* 2016; 9(1):39-48. PMID: 26962391. Full Text

Mount Sinai Medical Center, New York, New York; Indiana University School of Medicine, Indianapolis, Indiana; Physicians Skin Care PLLC, Louisville, Kentucky;
The Icahn School of Medicine at Mount Sinai, Department of Dermatology, New York, New York;
Department of Dermatology, Henry Ford Medical Center, Detroit, Michigan.

Once a drug has been approved by the United States Food and Drug Administration and is on the market, the Food and Drug Administration communicates new safety information through product label changes. Most of these label changes occur after a spontaneous report to either the drug manufacturing companies or the Food and Drug Administration MedWatch program. As a result, 400 to 500 label changes occur every year. Actinic keratosis treatments exemplify the commonality of label changes throughout the postmarket course of a drug. Diclofenac gel, 5-fluorouracil cream, imiquimod, and ingenol mebutate are examples of actinic keratosis treatments that have all undergone at least one label revision. With the current system of spontaneous reports leading to numerous label changes, each occurrence does not necessarily signify a radical change in the safety of a drug.

Dermatology

Kouba DJ, **LoPiccolo MC**, Alam M, Bordeaux JS, Cohen B, Hanke CW, Jellinek N, Maibach HI, Tanner JW, Vashi N, Gross KG, Adamson T, Begolka WS, and Moyano JV. Guidelines for the use of local anesthesia in office-based dermatologic surgery *J Am Acad Dermatol* 2016;PMID: 26951939. Full Text

Toledo Clinic Facial Plastics and Dermatology, Toledo, Ohio.
Toledo Clinic Facial Plastics and Dermatology, Toledo, Ohio; Department of Dermatology, Henry Ford Health System, Detroit, Michigan; Dermatology Specialists of Shelby, Shelby, Michigan.
Department of Dermatology, Northwestern Memorial Hospital, Chicago, Illinois.
Department of Dermatology, University Hospitals Case Medical Center, Cleveland, Ohio.
Department of Dermatology-Pediatrics, Johns Hopkins Children's Center, Baltimore, Maryland.
Laser and Skin Surgery Center of Indiana PC, Carmel, Indiana.
Department of Dermatology, Brown University, East Greenwich, Rhode Island.

Department of Dermatology, UCSF School of Medicine, San Francisco, California.
Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, Pennsylvania.
Department of Dermatology and Center for Ethnic Skin, Boston University School of Medicine, Boston, Massachusetts.
Skin Surgery Medical Group, Inc, San Diego, California.
Department of Nursing, Mayo Clinic College of Medicine, Rochester, Minnesota.
Department of Science, Quality and Practice, American Academy of Dermatology, Schaumburg, Illinois.
Department of Science, Quality and Practice, American Academy of Dermatology, Schaumburg, Illinois. Electronic address: guidelines@aad.org.

There are an increasing number and variety of dermatologic surgical procedures performed safely in the office setting. This evidence-based guideline addresses important clinical questions that arise regarding the use and safety of local anesthesia for dermatologic office-based procedures. In addition to recommendations for dermatologists, this guideline also takes into account patient preferences while optimizing their safety and quality of care. The clinical recommendations presented here are based on the best evidence available as well as expert opinion.

Dermatology
Mahmoud BH, **Ozog D**, **Burnett C**, and Cohen JL. Prospective randomized split-face comparative study between topical botulinum toxin a surface application and local injection for crow's feet *Dermatol Surg* 2016;PMID: 26990256. Full Text

Department of Dermatology, Henry Ford Hospital, Detroit, Michigan Department of Dermatology, Ain Shams University, Cairo, Egypt Department of Dermatology, Henry Ford Hospital, Detroit, Michigan Department of Dermatology, Henry Ford Hospital, Detroit, Michigan Dermatology Associates of Wisconsin, Glendale, Wisconsin AboutSkin Dermatology and DermSurgery, Englewood, Colorado.

Dermatology
Silpa-archa N, **Griffith JL**, **Williams MS**, **Lim HW**, and **Hamzavi IH**. Prospective comparison of recipient-site preparation with fractional carbon dioxide laser vs. dermabrasion and recipient-site dressing composition in melanocyte-keratinocyte transplantation procedure in vitiligo: A preliminary study *Br J Dermatol* 2016;PMID: Not assigned. Full Text

I.H. Hamzavi, Multicultural Dermatology Center Department of Dermatology Henry Ford Hospital 3031 W. Grand Blvd, Suite 800 Detroit 48202MI U.S.A

Dermatology
Stein Gold L, Weiss J, Rueda MJ, Liu H, and Tanghetti E. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3 %/benzoyl peroxide 2.5 % gel: A randomized, double-blind, parallel-group, controlled study *Am J Clin Dermatol* 2016;PMID: 26945741. Article Request Form

Department of Dermatology, Henry Ford Medical Center, Detroit, MI, USA. lstein1@hfhs.org.
Henry Ford Medical Group, 6530 Farmington Rd, West Bloomfield, MI, 48322, USA. lstein1@hfhs.org.
Gwinnett Clinical Research Center Inc., Snellville, GA, USA.
Galderma Laboratories LP, Fort Worth, TX, USA.
Galderma Research and Development Inc., Princeton, NJ, USA.
Center for Dermatology and Laser Surgery, Sacramento, CA, USA.

BACKGROUND: A need exists for topical treatments in managing more severe inflammatory acne. OBJECTIVES: The objectives of this study were to evaluate the efficacy and safety of adapalene 0.3 %/benzoyl peroxide 2.5 % (0.3 % A/BPO) topical gel in subjects with moderate and severe inflammatory acne. METHODS: This was a multicenter, randomized, double-blind, parallel-group study. Randomization was stratified by acne severity (50 % moderate and 50 % severe). Subjects received 0.3 % A/BPO, 0.1 % A/BPO (benchmark), or vehicle (comparator) once daily for 12 weeks. Co-primary efficacy endpoints were success rate at week 12 (the percentage of subjects rated 'clear' or 'almost clear' with at least a 2-grade improvement on Investigator's Global Assessment [IGA]) and change in inflammatory (IN) and noninflammatory (NIN) lesion counts from baseline to week 12. Secondary efficacy endpoints were percent changes in IN and NIN lesion counts. Safety endpoints were incidence of adverse events (AEs) and local tolerability signs/symptoms. RESULTS: A total of 503 subjects were randomized: 217, 217, and 69 subjects in the 0.3 % A/BPO, 0.1 % A/BPO, and vehicle groups, respectively. For success rate (subjects rated 'clear' or 'almost

clear' with >/=2-grade improvement in IGA), 0.3 % A/BPO was superior to vehicle, with a treatment difference of 22.7 % (33.7 vs. 11.0 %; 95 % confidence interval [CI] 12.8-32.6, p < 0.001). At week 12, 0.3 % A/BPO was superior to vehicle for mean reduction from baseline in IN (27.0 vs. 14.4) and NIN lesion counts (40.2 vs. 18.5), as well as for percentage reduction from baseline in IN (68.7 vs. 39.2 %) and NIN lesion counts (68.3 vs. 37.4 %) (all p < 0.001). Among subjects with severe inflammatory acne (IGA = 4), 0.1 % A/BPO did not reach statistical significance for success rate compared with vehicle (p = 0.443), whereas 0.3 % A/BPO demonstrated significantly greater efficacy (p = 0.029, requiring >/=3-point IGA improvement). Additionally, 0.3 % A/BPO was safe and well-tolerated. CONCLUSIONS: Results of this clinical trial demonstrate the significantly greater efficacy of adapalene 0.3 % A/BPO topical gel compared with vehicle as well as a good safety profile in the treatment of moderate to severe inflammatory non-nodulocystic acne, which increases patients' treatment options. CLINICALTRIALS. GOV IDENTIFIER: NCT01880320.

Dermatology

Wei Q, Liu Y, Liu P, Hao J, Liang M, **Mi QS**, Chen JK, and Dong Z. MicroRNA-489 induction by hypoxia-inducible factor-1 protects against ischemic kidney injury *J Am Soc Nephrol* 2016;PMID: 26975439. Full Text

Department of Cellular Biology and Anatomy, Medical College of Georgia at Augusta University and Charlie Norwood Veterans Affairs Medical Center, Augusta, Georgia; zdong@gru.edu 30912.qwei@gru.edu.
Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin;
Department of Cellular Biology and Anatomy, Medical College of Georgia at Augusta University and Charlie Norwood Veterans Affairs Medical Center, Augusta, Georgia; Kidney Institute, Changzheng Hospital of Second Military Medical University, Shanghai, China;
Kidney Institute, Changzheng Hospital of Second Military Medical University, Shanghai, China; Departments of Dermatology and Internal Medicine, Henry Ford Health System, Detroit, Michigan; and.
Department of Cellular Biology and Anatomy, Medical College of Georgia at Augusta University and Charlie Norwood Veterans Affairs Medical Center, Augusta, Georgia;
Department of Cellular Biology and Anatomy, Medical College of Georgia at Augusta University and Charlie Norwood Veterans Affairs Medical Center, Augusta, Georgia; The Second Xiangya Hospital, Central South University, Changsha, China zdong@gru.edu 30912.qwei@gru.edu.

MicroRNAs have been implicated in ischemic AKI. However, the specific microRNA species that regulates ischemic kidney injury remains unidentified. Our previous microarray analysis revealed microRNA-489 induction in kidneys of mice subjected to renal ischemia-reperfusion. In this study, we verified the induction of microRNA-489 during ischemic AKI in mice and further examined the underlying mechanisms. Hypoxia-inducible factor-1alpha deficiency associated with diminished microRNA-489 induction in cultured rat proximal tubular cells subjected to hypoxia and kidney tissues of mice after renal ischemia-reperfusion injury. Moreover, genomic analysis revealed that microRNA-489 is intronic in the calcitonin receptor gene, and chromatin immunoprecipitation assays showed increased binding of hypoxia-inducible factor-1 to a specific site in the calcitonin receptor gene promoter after hypoxia. Inhibition of microRNA-489 increased apoptosis in renal tubular cells after ATP depletion injury in vitro, whereas microRNA-489 mimics mediated protection. In mice, inhibition of microRNA-489 enhanced tubular cell death and ischemic AKI without significantly affecting tubular cell proliferation. Deep sequencing identified 417 mRNAs that were recruited to the RNA-induced silencing complex by microRNA-489. Of the identified mRNAs, 127 contain microRNA-489 targeting sites, and of those, 18 are involved in the cellular stress response, including the poly(ADP-ribose) polymerase 1 gene implicated in ischemic kidney injury. Sequence analysis and in vitro studies validated poly(ADP-ribose) polymerase 1 as a microRNA-489 target. Together, these results suggest that microRNA-489 is induced via hypoxia-inducible factor-1 during ischemic AKI to protect kidneys by targeting relevant genes.

Dermatology

Zabetian S, **Friedman BJ**, and **McHargue C**. A case of idiopathic granulomatous mastitis associated with erythema nodosum, arthritis, and reactive cough *JAAD Case Rep* 2016; 2(2):125-127. PMID: Not assigned.
Article Request Form

S. Zabetian, Detroit, United States

Dermatology

Zhang X, Gu J, Yu FS, **Zhou L**, and **Mi QS**. TGF-beta1-induced transcription factor networks in Langerhans cell development and maintenance *Allergy* 2016;PMID: 26948524. Full Text

Henry Ford Immunology Program, Henry Ford Health System, Detroit, MI, 48202, USA.

Department of Dermatology, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Dermatology, Second Military Medical University Changhai Hospital, 168 Changhai Rd, Shanghai, 200433, China.
Department of Ophthalmology, Wayne State University School of Medicine, Detroit, USA.
Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, USA.
Department of Internal Medicine, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, USA.

Langerhans cells (LC) represent a specialized subset of evolutionarily conserved dendritic cells (DC) that populate stratified epithelial tissues, which are essential for the induction of skin and mucosal immunity and tolerance, including allergy. TGF-beta1 has been confirmed to be a predominant factor involved in LC development. Despite great advances in the understanding of LC ontogeny and diverse replenishment patterns, the underlying molecular mechanisms remain elusive. This review focuses on the recent discoveries in TGF-beta1-mediated LC development and maintenance, with special attention to the involved transcription factors and related regulators.

Emergency Medicine

Miller J, Thompson R, Akhtar S, Jackson P, **Goldberg J**, **Bitrus R**, and **Lewandowski C**. Pumping against gravity - cardiac function affects fluctuations in cerebral blood flow caused by head position change in acute ischemic stroke *Stroke* 2016; 47PMID: Not assigned. Abstract

J. Miller, Emergency Medicine, Henry Ford Hosp, Detroit, United States

Introduction: Acute ischemic stroke (AIS) patients often have the head-of-bed (HOB) elevated to 300 while in the Emergency Department (ED). Flat HOB positioning has been shown to impact cerebral flow. Whether this holds true in undifferentiated, ED stroke patients is unknown. Hypothesis: We tested the hypothesis that 00 HOB positioning improves middle cerebral artery (MCA) mean flow velocity (MFV) in AIS compared to 300. We secondarily tested the hypothesis that lower cardiac output (CO) is associated with greater fluctuation of MFV. Methods: This was a quasi-experimental study with repeat measurements of MCA MFV at 300 and 00 HOB position. Patients > 18 years presenting to the ED within 12 hours of symptom onset and a NIHSS ≥ 4 were eligible. After applying non-invasive monitoring of mean arterial pressure (MAP) and CO, an investigator used transcranial Doppler to obtain bilateral MCA MFV at 300 and 00 HOB position. If a signal was unobtainable on the ischemic side, the contralateral MFV was used for analysis. The primary analysis comprised all subjects with confirmed stroke on subsequent imaging and included student t-test for continuous measures. Secondary analysis used multiple linear regression to test if baseline NIHSS, age, MAP and CO were associated with changes in MFV. Results: There were 38 subjects enrolled, of whom 32 had confirmed AIS and were included in analysis. The mean age was 66 (±15) years and NIHSS 7 (±6). Stroke location was mixed (50% lacunar, 25% posterior and 25% anterior circulation). Averaged across all subjects, the MFV did not significantly increase when changing the HOB position from a 300 to 00 (+0.7 cm/s, 95% CI -1.6 to 3.1). Nevertheless, 16% (95% CI 5-33%) of subjects had a ≥ 20% increase and 47% (95% CI 29-65%) had any increase in MFV at 00 compared to 300 HOB. Adjusting for age, NIHSS and MAP, lower CO was associated with greater change in MFV (+2 cm/s [95% CI 0.2-3.7 cm/s] for every 1 L/min lower cardiac output, p=0.03). Conclusions: In conclusion, in a mixed sample of ED AIS patients, lower HOB position does not significantly impact cerebral flow on average, yet a considerable proportion of individuals may benefit from lower HOB position. Low cardiac output may identify those that benefit most.

Emergency Medicine

Morris D, **Chopp M**, **Cheung WL**, **Cui Y**, **Zhang T**, **Lu M**, **Zhang L**, and **Zhang ZG**. Thymosin β4 for the treatment of sub-acute stroke in aged rats *Stroke* 2016; 47PMID: Not assigned. Abstract

D. Morris, Emergency Medicine, Henry Ford Hosp, Detroit, United States

Introduction: Thymosin β4 (Tβ4) is a 5K peptide which influences cellular migration by inhibiting organization of the actin-cytoskeleton. Tβ4 has neurorestorative properties and is a potential candidate for the treatment of sub-acute stroke. Previous research demonstrated that Tβ4 improved neurological outcome in a young (3 months) rat model of embolic stroke. Hypothesis: We hypothesized that Tβ4 would improve neurological outcome in an aged rat model of embolic stroke when administered 24 hours after embolic stroke. Methods: Aged Male Wistar rats (Charles River, France 18-21 months) were subjected to embolic middle cerebral artery occlusion (MCAo). Rats were randomized to receive Tβ4 (12 mg/kg, Regenerx Biopharmaceuticals, Inc.) or control 24 hrs after MCAo and then every 3 days for 4 additional doses. The dose of 12 mg/kg was the maximal dose of Tβ4 that showed functional improvement in a young rat model of embolic stroke. Functional tests were performed weekly. The rats were sacrificed 56 days after MCAo and lesion volumes measured. Generalized Estimating Equations were used to compare the treatment effect on

functional recovery and t-test for lesion volumes. Results and Conclusions: Twenty-three rats were included in the study: control group (n=12) and Tβ4 group (n=11). After randomization, there were three deaths in both the control and Tβ4 groups. The Tβ4 treatment reduced infarct volume by more than 50% (12.8% ± 9.3%, mean ± SE, $p<0.05$) compared to the control group (26.0% ± 4.3%). However, Tβ4 did not show improvement in functional outcome compared to control. Lesion volumes in the treated group showed a correlation to functional testing of ($R=0.85$, $p<0.05$), whereas no correlation was observed in the control group ($R=0.19$). Conclusions: The Tβ4 treatment of stroke aged animals significantly reduces infarct volume compared to vehicle treated stroke. Dissociation between infarct volume and functional outcome in the control group suggests, a ceiling effect of these functional tests in aged animals may obscure proper evaluation of functional outcome between the Tβ4 and control groups. Additional studies and more sensitive behavioral tests are needed to examine the dissociation between infarct volume and functional outcomes in aged ischemic rats.

Emergency Medicine
Nagarwala J, **Dev S**, and **Markin A**. The vomiting patient. Small bowel obstruction, cyclic vomiting, and gastroparesis *Emerg Med Clin North Am* 2016;PMID: Not assigned. Abstract

J. Nagarwala, Department of Emergency Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, Clara Ford Pavillion-#263, Detroit, MI 48202

Vomiting and abdominal pain are common in patients in the emergency department. This article focuses on small bowel obstruction (SBO), cyclic vomiting, and gastroparesis. Through early diagnosis and appropriate management, the morbidity and mortality associated with SBOs can be significantly reduced. Management of SBOs involves correction of physiologic and electrolyte disturbances, bowel rest and removing the source of the obstruction. Treatment of acute cyclic vomiting is primarily directed at symptom control, volume and electrolyte repletion, and appropriate specialist follow-up. The mainstay of therapy for gastroparesis is metoclopramide.

Emergency Medicine
Wilson SP, and **Nowak RM**. Excluding acute aortic dissection: The need for a reliable biomarker *Heart Lung* 2016;PMID: 26948698. Full Text

Department of Emergency Medicine, Henry Ford Hospital System, 2799 W. Grand Blvd, Detroit, MI 48202, USA. Electronic address: wilsonseanpatrick@gmail.com.

Gastroenterology
Meighani A, **Jafri SM**, **Raoufi M**, and **Salgia R**. Splenic artery embolization for treatment of refractory ascites after liver transplantation *ACG Case Rep J* 2016; 3(2):136-138. PMID: 26958571. Full Text

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI.
Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI.
Department of Pathology, Henry Ford Hospital, Detroit, MI.

Post-transplantation refractory ascites is uncommon; however, it can be a serious problem, increasing both morbidity and mortality in patients. Despite scant literature available, splenic artery embolization (SAE) has been shown to be an effective treatment for refractory ascites after cadaveric orthotopic liver transplantation (OLT). We report a successful use of therapeutic SAE for refractory ascites post-OLT.

Gastroenterology
Roberts SK, Mangia A, Pianko S, Thompson AJ, Cooper C, Conway B, Bourlière M, Asselah T, Berg T, Zeuzem S, Rosenberg WM, Agarwal K, Gane EJ, Stedman CA, Mazzotta F, Tran TT, **Gordon SC**, Brainard DM, Afdhal NH, and Foster GR. Sofosbuvir/velpatasvir for 12 wks vs sofosbuvir + ribavirin for 24 wks in GT3 HCV: The ASTRAL-3 study *Hepatol Int* 2016; 10(1):S11-S12. PMID: Not assigned. Abstract

S.K. Roberts, Alfred Health and Monash University, Melbourne, Australia

Introduction: Velpatasvir (VEL) is a pangenotypic HCV NS5A inhibitor. In Phase 2 studies, the combination of sofosbuvir (SOF) and VEL for 12 weeks demonstrated high efficacy in patients with genotype 3 HCV. This international, multi-center, Phase 3 study compared treatment with a fixed dose combination (FDC) of SOF/ VEL for 12 weeks to SOF + RBV for 24 weeks, in patients with genotype 3 HCV. Methods: Patients at 75 sites were

randomized 1:1 to receive SOF/ VEL (400 mg/100 mg daily) FDC for 12 weeks or SOF (400 mg daily) with RBV (1000-1200 mg daily) for 24 weeks. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12). Results: Of the 552 patients treated, 62 % were male, 89 % were white, 26 % had prior treatment failure, and 30 % had cirrhosis. Nine patients, all from the SOF + RBV treatment group, discontinued treatment due to adverse events. Hemoglobin decline and total bilirubin increases were more commonly observed in the group treated with SOF + RBV consistent with RBV-induced hemolysis. No other significant lab abnormalities were observed. The SVR12 rate receiving SOF/VEL for 12 weeks was 95 % (264/277) and was statistically superior to the 80 % (221/275) SVR12 rate in patients treated with SOF + RBV for 24 weeks ($p<0.001$). Conclusions: The once daily, all-oral, single tablet regimen of SOF/ VEL was well tolerated in treatment-naïve and treatment-experienced genotype 3 HCV-infected patients with and without cirrhosis. There were no discontinuations due to adverse events and a lower incidence of fatigue, insomnia and irritability in patients treated with SOF/VEL for 12 weeks compared to patients treated with SOF + RBV for 24 weeks.

Gastroenterology

Younossi ZM, Park H, Dietrich D, Saab S, Ahmed A, and **Gordon SC**. The value of cure for chronic Hepatitis C (CH-C) to the society *Hepatol Int* 2016; 10(1):S167. PMID: Not assigned. Abstract

Z.M. Younossi, Center for Outcomes Research in Liver Disease, Washington DC, United States

Background: All oral regimens for CHC have >95 % cure rates. HCV cure leads to improvement quality of life and long-term outcomes including cirrhosis, liver cancer and liver mortality and their associated costs to the society. This study aimed to assess the value of cure with different GT 1 treatment regimens. Methods: We took the US societal perspective. Treatment eligible GT1 TN patients entered a Markov model which projected quality- adjusted life-years (QALYs) gained over their lifetime. We compared no treatment to approved treatments [2nd generation (sofosbuvir + PR and simeprevir + PR], and all-oral regimens i.e. ledipasvir/sofosbuvir and ombitasvir + paritaprevir/ritonavir + dasabuvir). Data inputs were based on literature, public sources and consensus by hepatologists; SVR rates were from Phase III trials. Results: Treating all eligible TN CHC patients in the US with 2nd generation triple, or all-oral regimens were projected to incur drug costs of •109billion and •128billion. Using a •50,000 threshold for the value of a QALY, these regimens were associated with •129billion and •198billion savings from HCV cure. Subtracting the cost associated with these regimens from the economic gains of HCV cure yields the value of cure: -•20billion (2nd generation) and -•69billion (all-oral). These savings were even greater if the total lifetime costs of CHC complications were added, resulting in value of cure: -•149billion (2nd generation) and -•257billion (all-oral).

Global Health Initiative

Kaljee L, Zhang L, Langhaug L, Munjile K, Tembo S, Menon A, Stanton B, Li X, and Malungo J. A randomized-control trial for the teachers' diploma programme on psychosocial care, support and protection in Zambian government primary schools *Psychol Health Med* 2016:1-12. PMID: 26965476. Article Request Form

Henry Ford Health System, Global Health Initiative, Clara Ford Pavilion , Detroit , MI , USA.
Wayne State University, Pediatric Prevention Research Center , Detroit , MI , USA.
REPSSI , Harare , Zimbabwe.
RuralNet , Lusaka , Zambia.
RuralNet , Lusaka , Zambia.
Department of Psychology , University of Zambia , Lusaka , Zambia.
Office of Research, School of Medicine , Wayne State University , Detroit MI , USA.
Arnold School of Public Health, SmartState Center for Healthcare Quality , University of South Carolina , Colombia , SC , USA.
Department of Population Studies , University of Zambia , Lusaka , Zambia.

Orphaned and vulnerable children (OVC) experience poverty, stigma, and abuse resulting in poor physical, emotional, and psychological outcomes. The Teachers' Diploma Programme on Psychosocial Care, Support, and Protection is a child-centered 15-month long-distance learning program focused on providing teachers with the knowledge and skills to enhance their school environments, foster psychosocial support, and facilitate school-community relationships. A randomized controlled trial was implemented in 2013-2014. Both teachers (n=325) and students (n=1378) were assessed at baseline and 15-months post-intervention from randomly assigned primary schools in Lusaka and Eastern Provinces, Zambia. Multilevel linear mixed models (MLM) indicate positive significant changes for intervention teachers on outcomes related to self-care, teaching resources, safety, social support, and gender equity. Positive outcomes for intervention students related to future orientation, respect, support, safety, sexual abuse, and bullying. Outcomes support the hypothesis that teachers and students benefit from a program designed to enhance teachers' psychosocial skills and knowledge.

Hematology, Oncology and the Josephine Ford Cancer Institute

Farhan S, **Pelland D**, **Wautelet S**, **Neme K**, **Mikulandric N**, **Trapp MA**, **Szymanski S**, **Ruemenapp K**, **Peres E**, and **Janakiraman N**. Impact of cytomegalovirus on early chimerism in patients with myeloid disorders undergoing stem cell transplantation using reduced toxicity ablative conditioning regimen *Biol Blood Marrow Transplant* 2016; 22(3):S318-S318. PMID: Not assigned. Abstract

[Farhan, Shatha; Peres, Edward; Janakiraman, Nalini] Henry Ford Hosp, Hematol Oncol & Bone Marrow Transplantat, Detroit, MI 48202 USA. [Pelland, Danielle; Wautelet, Susan; Trapp, Mary Ann; Szymanski, Sarah; Ruemenapp, Kenneth] Henry Ford Hosp, Detroit, MI 48202 USA. [Neme, Klodiana; Mikulandric, Nancy] Henry Ford Hosp, Pharm, Detroit, MI 48202 USA.

Background ABO mismatched (mm) hematopoietic cell transplantation (HCT) can be associated with delayed hemolysis, delayed red cell engraftment, autoimmune hemolytic anemia (AIHA), pure red cell aplasia (PRCA) and delayed platelet engraftment. The reported incidence of red cell complications is about 10 – 15% of each mismatched category, they are less likely to occur if methotrexate is included as part of the graft versus host disease prophylaxis. These complications are mediated by anti-ABO antibodies derived from transplanted donor lymphocytes (minor mm) or recipient lymphocytes (major mm), we hypothesized that post transplantation cyclophosphamide (PTCy) would lead to a lower incidence due to its potency as an anti-B cell agent.Method - We performed a retrospective analysis of data collected on patients undergoing a non-myeloablative haploidentical peripheral blood stem cell (PBSC) transplant at three centers - (FHCRC, KCH and LCI) from March 2009 to July 2015. Patients were included if they received PTCy and did not suffer graft failure. Patients were grouped according to ABO compatibility status (compatible, minor and major mm) and comparisons of red cell transfusions, occurrence of hemolysis and platelet engraftment data were made amongst the three groups.Results- Sixty-three patients are included in this analysis, ABO compatible - 37 (59%), major ABO mm - 16 (25%) and minor ABO mm - 10 (16%). No patient was diagnosed with delayed hemolysis due to passenger lymphocytes, PRCA or AIHA. There were no statistically significant differences in the number of red blood cell units transfused, day of last transfusion, peak bilirubin (data from 2 centers only) and platelet engraftment amongst the groups (Table 1).Conclusion- The patterns of red cell transfusions, occurrence of hemolysis and platelet engraftment kinetics are similar between ABO matched and ABO mismatched non-myeloablative haploidentical PBSC transplantation with PTCy. It is possible that this may be due to the potent anti B-cell effect of PTCy. Analysis of a larger cohort is warranted to confirm these findings and to evaluate whether PTCy is able to abrogate the reported higher mortality associated with ABO mismatched HCT.

Hematology, Oncology and the Josephine Ford Cancer Institute

Hijaz M, Das S, **Mert I**, Gupta A, **Al-Wahab Z**, **Tebbe C**, **Dar S**, **Chhina J**, **Giri S**, **Munkarah A**, Seal S, and **Rattan R**. Folic acid tagged nanoceria as a novel therapeutic agent in ovarian cancer *BMC Cancer* 2016; 16(1):220. PMID: 26979107. Full Text

Division of Gynecology Oncology, Department of Women's Health, Henry Ford Hospital, Detroit, MI, USA.
Advanced Materials Processing and Analysis Center, Nanoscience and Technology Center, Materials Science and Engineering, University of Central Florida, Orlando, FL, USA.
Wayne State University, Detroit, MI, USA.
Department of Neurology, Henry Ford Hospital, Detroit, MI, USA.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA.
College of Medicine, University of Central Florida, Orlando, FL, USA.
Division of Gynecology Oncology, Department of Women's Health, Henry Ford Hospital, Detroit, MI, USA. rrattan1@hfhs.org.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. rrattan1@hfhs.org.

BACKGROUND: Nanomedicine is a very promising field and nanomedical drugs have recently been used as therapeutic agents against cancer. In a previous study, we showed that Nanoceria (NCe), nanoparticles of cerium oxide, significantly inhibited production of reactive oxygen species, cell migration and invasion of ovarian cancer cells in vitro, without affecting cell proliferation and significantly reduced tumor growth in an ovarian cancer xenograft nude model. Increased expression of folate receptor-alpha, an isoform of membrane-bound folate receptors, has been described in ovarian cancer. To enable NCe to specifically target ovarian cancer cells, we conjugated nanoceria to folic acid (NCe-FA). Our aim was to investigate the pre-clinical efficacy of NCe-FA alone and in combination with Cisplatin. METHODS: Ovarian cancer cell lines were treated with NCe or NCe-FA. Cell viability was assessed by MTT and colony forming units. In vivo studies were carried in A2780 generated mouse xenografts treated with 0.1 mg/Kg NCe, 0.1 mg/Kg; NCe-FA and cisplatinum, 4 mg/Kg by intra-peritoneal injections. Tumor weights and burden scores were determined. Immunohistochemistry and toxicity assays were used to evaluate treatment effects. RESULTS: We show that folic acid conjugation of NCe increased the cellular NCe internalization and inhibited cell proliferation. Mice treated with NCe-FA had a lower tumor burden compared to NCe, without any vital organ toxicity.

Combination of NCe-FA with cisplatinum decreased the tumor burden more significantly. Moreover, NCe-FA was also effective in reducing proliferation and angiogenesis in the xenograft mouse model. CONCLUSION: Thus, specific targeting of ovarian cancer cells by NCe-FA holds great potential as an effective therapeutic alone or in combination with standard chemotherapy.

Hematology, Oncology and the Josephine Ford Cancer Institute
Ibrahim RB, Skewes MD, and **Kuriakose P**. 'Sailing in troubled waters': a review of the use of anticoagulation in adult cancer patients with thrombocytopenia *Blood Coagul Fibrinolysis* 2016;PMID: 26945262. Full Text

aDepartment of Pharmacology and Toxicology, College of Osteopathic Medicine, Michigan State University bSchool of Medicine, Wayne State University cCollege of Osteopathic Medicine, Michigan State University dDivision of Hematology/Oncology, Department of Internal Medicine, Henry Ford Hospital/Josephine Ford Cancer Center eSchool of Medicine, Wayne State University Medical School, Detroit, Michigan, USA.

Simply providing anticoagulation therapy is not as straightforward of a solution in cancer patients who have concurrent thrombocytopenia owing to the increased risk of bleeding complications. Currently, few guidelines are in place to assist clinicians in safely managing thrombocytopenic cancer patients on anticoagulation. The purpose of this review is to critically examine the available body of biomedical literature surrounding anticoagulant use against the backdrop of cancer-related thrombocytopenia in adult patients. Available evidence for the use of parenteral anticoagulants (low molecular weight heparins, unfractionated heparin, pentasaccharides, and direct thrombin inhibitors) and oral anticoagulants (vitamin K antagonists and novel oral anticoagulants) in thrombocytopenic cancer patients is described. The review revealed many inconsistencies between reports on this topic, which made it difficult to draw firm conclusions as to, for example, the ideal well tolerated anticoagulant dose in thrombocytopenic cancer patients? Intriguingly, critical clinical information including (but not limited) patient platelet nadirs, platelet counts during bleeding episodes, and platelet transfusion support was absent from a not-so-insignificant number of publications. Despite these shortcomings, the review sets out to formulate recommendations on the management of anticoagulation, at prophylactic or treatment doses, in adult cancer patients who also have concurrent thrombocytopenia. It also enlists a call for the medical community, by mapping select clinical guideposts, for further research in this setting. With the inclusion of these criteria in future studies, only then formal recommendations on the ideal safe dosage of anticoagulants in cancer patients, based on solid evidence, are conceived.

Hematology, Oncology and the Josephine Ford Cancer Institute
Kumar N, **Nakagawa P**, **Janic B**, **Romero CA**, **Worou ME**, **Monu SR**, **Peterson EL**, **Shaw J**, **Valeriote F**, Ongeri EM, Niyitegeka JV, **Rhaleb NE**, and **Carretero OA**. The anti-inflammatory peptide Ac-SDKP is released from thymosin beta4 by renal meprin alpha and prolyl oligopeptidase *Am J Physiol Renal Physiol* 2016:ajprenal.00562.02015. PMID: 26962108. Full Text

Henry Ford Health System.
Henry Ford Hospital.
North Carolina A & T State University.
North Carolina A&T State University.
Henry Ford Hospital Ocarret1@hfhs.org.

N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a natural tetra-peptide with anti-inflammatory and anti-fibrotic properties. We have previously shown that prolyl-oligopeptidase (POP) is involved in the Ac-SDKP release from thymosin beta4 (Tbeta4). However, POP can only hydrolyze peptides shorter than 30 amino acids and Tbeta4 is 43 amino acids long. This indicates that before POP hydrolysis takes place, Tbeta4 is hydrolyzed by another peptidase that releases N-terminal intermediate peptide(s) less than 30 amino acids. Our peptidase database search pointed out meprin alpha metalloprotease as a potential candidate. Therefore, we hypothesized that prior to POP hydrolysis, Tbeta4 is hydrolyzed by meprin alpha. In vitro, we found that the incubation of Tbeta4 with both, meprin alpha and POP released Ac-SDKP, whereas no Ac-SDKP was released when Tbeta4 was incubated with either meprin alpha or POP alone. Incubation of Tbeta4 with rat kidney homogenates significantly released Ac-SDKP, which was blocked by meprin alpha inhibitor, actinonin. In addition, kidneys from meprin alpha knockout (KO) mice showed significantly lower basal Ac-SDKP amount, compared to wild-type mice. Kidney homogenates from meprin alpha KO mice failed to release Ac-SDKP from Tbeta4. In vivo, we observed that, rats treated with ACE inhibitor, captopril, increased plasma concentrations of Ac-SDKP, which was inhibited by the co-administration of actinonin (vehicle 3.1+/-0.2 nmol/L; captopril 15.1+/-0.7 nmol/L; captopril + actinonin 6.1+/-0.3 nmol/L; P<0.005). Similar results were obtained with urinary Ac-SDKP after actinonin treatment. We conclude that, release of Ac-SDKP from Tbeta4 is mediated by successive hydrolysis involving meprin alpha and POP.

Hematology, Oncology and the Josephine Ford Cancer Institute

Munkarah A, Mert I, **Chhina J**, **Hamid S**, **Poisson L**, **Hensley-Alford S**, **Giri S**, and **Rattan R**. Targeting of free fatty acid receptor 1 in EOC: A novel strategy to restrict the adipocyte-EOC dependence *Gynecol Oncol* 2016; 141(1):72-79. PMID: 27016232. Full Text

Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: amunkar1@hfhs.org.
Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: imert@med.wayne.edu.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA. Electronic address: jchhina1@hfhs.org.
Department of Neurology, Henry Ford Hospital, USA. Electronic address: hsuhail1@hfhs.org.
Center for Bioinformatics, Henry Ford Hospital, USA; Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: lpoisso1@hfhs.org.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: salford1@hfhs.org.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA; Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: sgiri1@hfhs.org.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: rrattan1@hfhs.org.

OBJECTIVES: Adipocyte derived free fatty acids (FFA) promote epithelial ovarian cancer (EOC) by acting as a fuel source to support the energy requirement of the cancer cells. FFA may also exert biological effects through signaling pathways. Recently, a family of FFA activated G-protein coupled receptors (FFAR/GPCRs) was identified. Our objective was to investigate the role of FFAR/GPCRs in EOC and assess their potential as therapeutic targets. METHODS: The mRNA (RT-PCR) expression of FFAR/GPCR family members (FFAR1/GPR40; FFAR2/GPR43, FFAR3/GPR41, FFAR4/GPR120 and GPR84) was examined in: (1) a syngeneic mouse model of EOC fed high energy diet (60% fat) or regular diet (30% fat), (2) EOC cell lines exposed to free fatty acids and (3) specimens from 13 histologically normal ovaries and 28 high grade ovarian serous carcinomas. The GPR 40 antagonist, GW1100, was used to inhibit FFAR1/GPR40 and cell survival was assayed by MTT in various cell lines. RESULTS: High Grade Serous carcinoma specimens expressed significantly increased GPR40 compared to normal ovaries (p=0.0020). Higher expression was noted in advanced stage disease. ID8 ovarian tumors from mice fed with high fat diet also showed higher GPR40 expression. Exposing EOC cells to FFAs, increased GPR40 expression. Treatment of EOC cell lines with GW100 resulted in growth inhibition and was associated with an alteration in their energy metabolism. CONCLUSION: FFA-induced cancer cell growth may be partly mediated through FFAR1/GPR40. Targeting of FFAR1/GPR40 may be an attractive treatment strategy in EOC, and possibly offers a targeted treatment for a subset of EOC patients.

Hematology, Oncology and the Josephine Ford Cancer Institute

Nabi S, **Kahlon P**, Bozorgnia F, Arshad A, Saleem A, and **Kuriakose P**. Analyzing relationship between monoclonal gammopathy of undetermined significance (MGUS) with different types of neuropathy: an observational study *Indian J Hematol Blood Transfus* 2016; 32(2):186-192. PMID: Not assigned. Full Text

S. Nabi, Department of Internal Medicine, Henry Ford Health System, Detroit, United States

To analyze multiple variables, including immunoglobulin subtypes in patients with monoclonal gammopathy of undetermined significance (MGUS) and different types of neuropathy. This was a retrospective, single center study done in a tertiary care hospital in the United States. The data was collected for years 2001–2011. Inclusion criteria were the presence of MGUS and neuropathy. Exclusion criteria were the presence of other factors such as diabetes, vitamin B12 deficiency, alcoholism etc. which can cause neuropathy. Patients with IgM MGUS were compared with patients having Non-IgM MGUS. A total of 281 patients were analyzed in this study. The average age at the time of diagnosis of MGUS and neuropathy was 68 years. The most common type of neuropathy was sensorimotor peripheral neuropathy (46 %). The most common location of neuropathy was the lower extremities (68 %). Among our patients, 52 % had their neuropathy symptoms for 1–5 years before presenting to the clinic. When IgM MGUS was compared with Non-IgM MGUS, a statistically significant difference was found in terms of race (White vs. Others, OR 4.43, 95 % CI 2.13, 9.19, $p < 0.001$) and survival status (OR 1.98, 95 % CI 1.01, 3.90, $p = 0.046$). Patients with MGUS are prone to develop different types of neuropathies. Caucasians are more likely to have IgM MGUS as compared to other races. IgM MGUS is generally related to worse outcomes as compared to Non-IgM MGUS. Medical therapies, including gabapentin and pregabalin are effective treatments and the response rate can be as high as 80–90 % with these medications.

Hematology, Oncology and the Josephine Ford Cancer Institute

Saste AB, **Jiang F**, **Arias-Stella J**, **Gamalski S**, **Peres E**, **Janakiraman N**, and **Farhan S**. Emberger syndrome with concomitant GATA2, NPM1 and FLT3-ITD mutations in remission after allogeneic stem cell transplant *Biol Blood Marrow Transplant* 2016; 22(3):S208-S209. PMID: Not assigned. Abstract - Full Text

[Saste, Abhijit Balkrishna] Henry Ford Hlth Syst, Hematol Oncol Bone Marrow Transplant, Detroit, MI USA. [Jiang, Feng; Gamalski, Steven] Henry Ford Hlth Syst, Hematol Oncol, Detroit, MI USA. [Arias-Stella, Javier, III] Henry Ford Hlth Syst, Dept Pathol & Lab Med, Detroit, MI USA. [Peres, Edward; Janakiraman, Nalini; Farhan, Shatha] Henry Ford Hosp, Hematol Oncol & Bone Marrow Transplantat, Detroit, MI 48202 USA.

Hematology, Oncology and the Josephine Ford Cancer Institute

Zhou Q, Abraham AD, Li L, Babalmorad A, Bagby S, Arcaroli JJ, Hansen RJ, **Valeriote FA**, Gustafson DL, **Schaack J**, Messersmith WA, and LaBarbera DV. Topoisomerase IIalpha mediates TCF-dependent epithelial-mesenchymal transition in colon cancer *Oncogene* 2016;PMID: 26947016. Full Text

Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA.
Department of Immunology and Microbiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA.
Division of Medical Oncology, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA.
University of Colorado Cancer Center, University of Colorado Anschutz Medical Campus, Aurora, CO, USA.
Colorado State University, Flint Animal Cancer Center, Fort Collins, CO, USA.
Josephine Ford Cancer Center, Henry Ford Health Systems, Detroit, MI, USA.

Aberrant T-cell factor (TCF) transcription is implicated in the majority of colorectal cancers (CRCs). TCF transcription induces epithelial-mesenchymal transition (EMT), promoting a tumor-initiating cell (TIC) phenotype characterized by increased proliferation, multidrug resistance (MDR), invasion and metastasis. The data presented herein characterize topoisomerase IIalpha (TopoIIalpha) as a required component of TCF transcription promoting EMT. Using chromatin immunoprecipitation (ChIP) and protein co-immunoprecipitation (co-IP) studies, we show that TopoIIalpha forms protein-protein interactions with beta-catentin and TCF4 and interacts with Wnt response elements (WREs) and promoters of direct target genes of TCF transcription, including: MYC, vimentin, AXIN2 and LEF1. Moreover, both TopoIIalpha and TCF4 ChIP with the N-cadherin promoter, which is a new discovery indicating that TCF transcription may directly regulate N-cadherin expression. TopoIIalpha N-terminal ATP-competitive inhibitors, exemplified by the marine alkaloid neoamphimedine (neo), block TCF activity in vitro and in vivo. Neo effectively inhibits TopoIIalpha and TCF4 from binding WREs/promoter sites, whereas protein-protein interactions remain intact. Neo inhibition of TopoIIalpha-dependent TCF transcription also correlates with significant antitumor effects in vitro and in vivo, including the reversion of EMT, the loss of TIC-mediated clonogenic colony formation, and the loss of cell motility and invasion. Interestingly, non-ATP-competitive inhibitors of TopoIIalpha, etoposide and merbarone, were ineffective at preventing TopoIIalpha-dependent TCF transcription. Thus, we propose that TopoIIalpha participation in TCF transcription may convey a mechanism of MDR to conventional TopoIIalpha inhibitors. However, our results indicate that TopoIIalpha N-terminal ATP-binding sites remain conserved and available for drug targeting. This article defines a new strategy for targeted inhibition of TCF transcription that may lead to effective therapies for the treatment of CRC and potentially other Wnt-dependent cancers.

Hypertension and Vascular Research

Kumar N, **Nakagawa P**, **Janic B**, **Romero CA**, **Worou ME**, **Monu SR**, **Peterson EL**, **Shaw J**, **Valeriote F**, Ongeri EM, Niyitegeka JV, **Rhaleb NE**, and **Carretero OA**. The anti-inflammatory peptide Ac-SDKP is released from thymosin beta4 by renal meprin alpha and prolyl oligopeptidase *Am J Physiol Renal Physiol* 2016:ajprenal.00562.02015. PMID: 26962108. Full Text

Henry Ford Health System.
Henry Ford Hospital.
North Carolina A & T State University.
North Carolina A&T State University.
Henry Ford Hospital Ocarret1@hfhs.org.

N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a natural tetra-peptide with anti-inflammatory and anti-fibrotic properties. We have previously shown that prolyl-oligopeptidase (POP) is involved in the Ac-SDKP release from thymosin beta4 (Tbeta4). However, POP can only hydrolyze peptides shorter than 30 amino acids and Tbeta4 is 43 amino acids long. This indicates that before POP hydrolysis takes place, Tbeta4 is hydrolyzed by another peptidase

that releases N-terminal intermediate peptide(s) less than 30 amino acids. Our peptidase database search pointed out meprin alpha metalloprotease as a potential candidate. Therefore, we hypothesized that prior to POP hydrolysis, Tbeta4 is hydrolyzed by meprin alpha. In vitro, we found that the incubation of Tbeta4 with both, meprin alpha and POP released Ac-SDKP, whereas no Ac-SDKP was released when Tbeta4 was incubated with either meprin alpha or POP alone. Incubation of Tbeta4 with rat kidney homogenates significantly released Ac-SDKP, which was blocked by meprin alpha inhibitor, actinonin. In addition, kidneys from meprin alpha knockout (KO) mice showed significantly lower basal Ac-SDKP amount, compared to wild-type mice. Kidney homogenates from meprin alpha KO mice failed to release Ac-SDKP from Tbeta4. In vivo, we observed that, rats treated with ACE inhibitor, captopril, increased plasma concentrations of Ac-SDKP, which was inhibited by the co-administration of actinonin (vehicle 3.1+/-0.2 nmol/L; captopril 15.1+/-0.7 nmol/L; captopril + actinonin 6.1+/-0.3 nmol/L; P<0.005). Similar results were obtained with urinary Ac-SDKP after actinonin treatment. We conclude that, release of Ac-SDKP from Tbeta4 is mediated by successive hydrolysis involving meprin alpha and POP.

Hypertension and Vascular Research
Munukutla S, **Pan G**, **Deshpande M**, Thandavarayan RA, Krishnamurthy P, and **Palaniyandi SS**. Alcohol toxicity in diabetes and its complications: A double trouble? *Alcohol Clin Exp Res* 2016;PMID: 27013182. Full Text

Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.
Department of Cardiovascular Sciences, Center for Cardiovascular Regeneration, Houston Methodist Research Institute, Houston, Texas.
Department of Physiology, Wayne State University, Detroit, Michigan.

BACKGROUND: Eight percent of the U.S. population has been diagnosed with diabetes mellitus (DM), while another large percentage has gone undiagnosed. As the epidemiology of this disease constitutes a larger percentage of the American population, another factor presents a dangerous dilemma that can exacerbate the hazardous effects imposed by DM. Excessive alcohol consumption concerns the health of more than 50% of all adults. When this heavy-alcohol-drinking population overlaps with DM and its complications, the effects can be dangerous. In this review, we term it as "double trouble." METHODS: We provide evidence of alcohol-induced exacerbation of organ damage in diabetic conditions. In certain cases, we have explained how diabetes and alcohol induce similar pathological effects. RESULTS: Known exacerbated complications include those related to heart diseases, liver damage, kidney dysfunction, as well as retinal and neurological impairment. Often, pathophysiological damage concludes with end-stage disorders and even mortality. The metabolic, cell signaling, and pathophysiological changes associated with "double trouble" would lead to the identification of novel therapeutic targets. CONCLUSIONS: This review summarizes the epidemiology, diagnosis, pathophysiology, metabolic, and cell signaling alterations and finally brushes upon issues and strategies to manage the "double trouble."

Hypertension and Vascular Research
Zhu L, **Yang XP**, **Janic B**, **Rhaleb NE**, **Harding P**, **Nakagawa P**, **Peterson EL**, and **Carretero OA**. Ac-SDKP suppresses TNFalpha-induced ICAM-1 expression in endothelial cells via inhibition of IkappaB kinase and NF-kappaB activation *Am J Physiol Heart Circ Physiol* 2016:ajpheart.00252.02015. PMID: 26945075. Full Text

Henry Ford Hospital.
Henry Ford Health System.
Henry Ford Hospital Ocarret1@hfhs.org.

N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a naturally occurring tetrapeptide that prevents inflammation and fibrosis in hypertension and other cardiovascular diseases. We previously showed that in angiotensin II-induced hypertension, Ac-SDKP decreased the activation of nuclear transcription factor NF-kappaB, while in experimental autoimmune myocarditis and hypertension animal models it also reduced the expression of endothelial leukocyte adhesion molecule ICAM-1. However, the mechanisms by which Ac-SDKP down-regulated ICAM-1 expression are still unclear. TNFalpha is a pro-inflammatory cytokine that induces ICAM-1 expression in various cell types via TNF receptor 1 and activation of the classical NF-kappaB pathway. We hypothesized that in endothelial cells Ac-SDKP suppresses TNFalpha-induced ICAM-1 expression by decreasing IkappaB kinase (IKK) phosphorylation that as a consequence leads to a decrease of IkappaB phosphorylation, and NF-kappaB activation. To test this hypothesis, human coronary artery endothelial cells were treated with Ac-SDKP and then stimulated with TNFalpha. We found that TNFalpha-induced ICAM-1 expression was significantly decreased by Ac-SDKP in a dose-dependent manner. Ac-SDKP also decreased TNF-alpha-induced NF-kappaB translocation from cytosol to nucleus, as assessed by electrophoretic mobility shift assay, which correlated with a decrease in IkappaB phosphorylation. In addition, we found that Ac-SDKP decreased TNFalpha-induced IKK phosphorylation and IKKbeta expression. However, Ac-SDKP

had no effect on TNFalpha-induced phosphorylation of p38 MAP kinase or ERK. Thus, we conclude that Ac-SDKP inhibition of TNFalpha activation of canonical, i.e. IKKbeta dependent, NF-kappaB pathway and subsequent increase in ICAM-1 expression is achieved via inhibition of IKKbeta.

Infectious Diseases
Cassone M, McNamara SE, **Perri MB**, **Zervos M**, and Mody L. Impact of intervention measures on MRSA clonal type and carriage site prevalence *MBio* 2016; 7(2)PMID: 26956588. Full Text

Division of Geriatric and Palliative Care Medicine, University of Michigan, Ann Arbor, Michigan, USA mcas@med.umich.edu.
Division of Geriatric and Palliative Care Medicine, University of Michigan, Ann Arbor, Michigan, USA.
Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan, USA.
Division of Geriatric and Palliative Care Medicine, University of Michigan, Ann Arbor, Michigan, USA Geriatrics Research Education and Clinical Center, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA.

Infectious Diseases
Davey R.T., **Markowitz N.**, Beigel J., Wentworth D., Babiker A., Rehman T., Dewar R., Metcalf J., Uyeki T.M., Finley E.B., Standridge B., Riska P., Lane H.C., Gordin F., Neaton J.D., Denning E., Duchene A., Engen N., Harrison M., Quan K., Thompson G., Sanchez A., Hoover M., Natarajan V., Holley H.P., Tierney J., Voell J., Baxter J., Bigley D., Coburn P., Faber L., Gardner E., Harlow L., Jain M., Makohon L., Mcconnell R., Moghe J., Nahra R., Omotosho B., Petersen T., Polenakovik H., Rizza S., Scott J., Shoen A., Solorzano C., Temesgen Z., and J. W. INSIGHT FLU005: An Anti-Influenza Virus Hyperimmune Intravenous Immunoglobulin Pilot Study *J Infect Dis* 2016; 213(4):574-578. PMID: 26374911. Full Text

Hemagglutination inhibition (HAI) antibody responses to anti-influenza virus hyperimmune intravenous immunoglobulin (hIVIG) were characterized. Thirty-one patients with influenza during the 2013-2014 season were randomly assigned to receive 0.25 g/kg of hIVIG (n = 16) or placebo (n = 15). For hIVIG recipients, the ratio of geometric mean titers (1 hour after infusion/before infusion) was 4.00 (95% confidence interval [CI], 2.61-6.13) for 2009 pandemic influenza A(H1N1) and 1.76 (95% CI, 1.33-2.32) for influenza A(H3N2) and influenza B. Among patients with 2009 pandemic influenza A(H1N1), ratios for hIVIG (n = 9) versus placebo (n = 8) were higher 1 hour after infusion (3.9 [95% CI, 2.3-6.7]) and sustained through day 3 (2.0 [95% CI, 1.0-4.0]). hIVIG administration significantly increases HAI titer levels among patients with influenza, supporting the need to perform a clinical outcomes study. CLINICAL TRIALS REGISTRATION: NCT02008578.

Infectious Diseases
Gammon HM, **Shelton CB**, **Siegert C**, **Dawson C**, **Sexton E**, **Burmeister C**, **Gnam G**, and **Siddiqui A**. Self-turning for pressure injury prevention *Wound Medicine* 2016; 12:15-18. PMID: Not assigned Article Request Form

A. Siddiqui, Division of Plastic Surgery, K-16, Henry Ford Hospital, Detroit, United States

The study objective was to determine if hospitalized patients who are designated as self-turn would reposition themselves appropriately in the acute care setting. This was a prospective case series in a general practice unit of an 800-bed urban tertiary care hospital. Patients were instructed on the importance of mobility for pressure ulcer prevention and subsequently monitored on a continuous bedside pressure mapping device. Primary outcomes included intervals of inactivity and pressure ulcer incidence. During the 3-month study interval, only 2 patients had a documented 4-h interval without measurable repositioning. None of the 101 consecutive patients enrolled in the study developed pressure ulcers. General practice unit patients that are given proper instruction and designated as self-turn can reliably be considered low-risk for hospital acquired pressure ulcers. Based on our prospective study, patients designated as self-turn do reposition themselves.

Infectious Diseases
Kenney RM, Cole KA, **Perri MB**, Dumkow LE, **Samuel LP**, **Zervos MJ**, and **Davis SL**. Reply to "urinary tract infections: Resistance is futile" *Antimicrob Agents Chemother* 2016; 60(4):2598. PMID: 27016558. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA rkenney1@hfhs.org.
Department of Pharmacy Services, University of Toledo Medical Center, Toledo, Ohio, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Pharmacy Services, Mercy Health Saint Mary's, Grand Rapids, Michigan, USA.

Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, Michigan, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan, USA Wayne State University School of Medicine, Detroit, Michigan, USA.
Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA.

Infectious Diseases
Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, 3rd, **Alangaden GJ**, Brown JM, Fredricks DN, Heinz WJ, Herbrecht R, Klimko N, Klyasova G, Maertens JA, Melinkeri SR, Oren I, Pappas PG, Racil Z, Rahav G, Santos R, Schwartz S, Vehreschild JJ, Young JH, Chetchotisakd P, Jaruratanasirikul S, Kanj SS, Engelhardt M, Kaufhold A, Ito M, Lee M, Sasse C, Maher RM, Zeiher B, and Vehreschild MJ. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis *Lancet Infect Dis* 2016;PMID: 26969258. Full Text

Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA, USA.
University of Texas Medical School at Houston and Memorial Hermann Texas Medical Center, University of Texas, Houston, TX, USA.
Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Koln, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany. Electronic address: oliver.cornely@uk-koeln.de.
Department of Medicine, University of Chicago, IL, USA; Division of Infectious Diseases, University of Chicago, IL, USA.
Department of Medicine, Duke University, Durham, NC, USA; Division of Infectious Diseases, Duke University, Durham, NC, USA.
Departments of Medicine, University of California, Davis, CA, USA; Division of Infectious Diseases and Medical Microbiology and Immunology, University of California, Davis, CA, USA.
Division of Infectious Diseases, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.
Division of Blood and Marrow Transplantation, Stanford University Medical Center, Stanford, CA, USA.
Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.
University of Wurzburg Medical Centre, Wurzburg, Germany.
Department of Oncology and Hematology, Hautepierre Hospital, University of Strasbourg, Strasbourg, France.
North Western State Medical University, St Petersburg, Russia.
National Research Center for Hematology, Moscow, Russia.
Department of Hematology, University Hospital Gasthuisberg, Leuven, Belgium.
Deenanath Mangeshkar Hospital and Research Centre, Erandawane, Pune, India.
Unit of Infectious Diseases, Rambam Health Care Campus, Haifa, Israel.
Division of Infectious Diseases, University of Alabama at Birmingham, AL, USA.
University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic.
Infectious Disease Unit, Sheba Medical Center, Tel Hashomer, Israel.
Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.
Medizinische Klinik III, Charite, Campus Benjamin Franklin, Berlin, Germany.
Department I of Internal Medicine, University Hospital of Cologne, and German Centre for Infection Research, partner site Bonn-Cologne, Cologne, Germany.
Department of Medicine, University of Minnesota, Minneapolis, MN, USA; Division of Infectious Diseases, University of Minnesota, Minneapolis, MN, USA.
Division of Infectious Disease and Tropical Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand.
Department of Medicine, Songklanagarind Hospital, Prince of Songkla University, Hat Yai, Thailand.
Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.
Basilea Pharmaceutica International, Basel, Switzerland.
Astellas Pharma Global Development, Northbrook, IL, USA.

BACKGROUND: Mucormycosis is an uncommon invasive fungal disease with high mortality and few treatment options. Isavuconazole is a triazole active in vitro and in animal models against moulds of the order Mucorales. We assessed the efficacy and safety of isavuconazole for treatment of mucormycosis and compared its efficacy with amphotericin B in a matched case-control analysis. METHODS: In a single-arm open-label trial (VITAL study), adult patients (>/=18 years) with invasive fungal disease caused by rare fungi, including mucormycosis, were recruited from 34 centres worldwide. Patients were given isavuconazole 200 mg (as its intravenous or oral water-soluble prodrug, isavuconazonium sulfate) three times daily for six doses, followed by 200 mg/day until invasive fungal disease resolution, failure, or for 180 days or more. The primary endpoint was independent data review committee-determined overall response-ie, complete or partial response (treatment success) or stable or progressive disease

(treatment failure)-according to prespecified criteria. Mucormycosis cases treated with isavuconazole as primary treatment were matched with controls from the FungiScope Registry, recruited from 17 centres worldwide, who received primary amphotericin B-based treatment, and were analysed for day-42 all-cause mortality. VITAL is registered with ClinicalTrials.gov, number NCT00634049. FungiScope is registered with ClinicalTrials.gov, number NCT01731353. FINDINGS: Within the VITAL study, from April 22, 2008, to June 21, 2013, 37 patients with mucormycosis received isavuconazole for a median of 84 days (IQR 19-179, range 2-882). By day 42, four patients (11%) had a partial response, 16 (43%) had stable invasive fungal disease, one (3%) had invasive fungal disease progression, three (8%) had missing assessments, and 13 (35%) had died. 35 patients (95%) had adverse events (28 [76%] serious). Day-42 crude all-cause mortality in seven (33%) of 21 primary-treatment isavuconazole cases was similar to 13 (39%) of 33 amphotericin B-treated matched controls (weighted all-cause mortality: 33% vs 41%; p=0.595). INTERPRETATION: Isavuconazole showed activity against mucormycosis with efficacy similar to amphotericin B. Isavuconazole can be used for treatment of mucormycosis and is well tolerated. FUNDING: Astellas Pharma Global Development, Basilea Pharmaceutica International.

Infectious Diseases

Meighani A, **Hart BR**, Mittal C, **Miller N**, **John A**, and **Ramesh M**. Predictors of fecal transplant failure *Eur J Gastroenterol Hepatol* 2016;PMID: 26934528. Full Text

aDepartment of Internal Medicine and Infectious Disease, Henry Ford Hospital, Detroit, Michigan bDepartment of Gastroenterology and Hepatology, University of Colorado, Denver, Denver, Colorado, USA.

BACKGROUND: Clostridium difficile infection (CDI) is a significant healthcare burden, with increased morbidity and mortality. Traditional treatment regimens using antibiotics for recurrent CDI are significantly less successful compared with 80-90% with fecal microbiota transplantation (FMT). There is a paucity of data on failure rates and mortality after FMT in CDI. This study aims to identify the rates of failure, relapse, and mortality associated with FMT as well as the risk factors for FMT failure. METHODS: A large retrospective cohort study was carried out including all patients who underwent FMT from December 2012 through May 2014. Patient factors (demographics, comorbidities, immune-suppression, transplant history, antibiotics used, hospitalization, and surgeries), disease factors (number of episodes of CDI, treatments, and severity), and transplant factors (route and number of FMT) were examined. Failure of treatment was defined as no resolution of diarrhea in patients who had been treated with one or more fecal microbiota transplantation within 90 days of FMT. RESULTS: A total of 201 patients (age 66.6+/-18.3 years, 62.2% women) were included. The overall failure rate was 12.4%. Patients with failed fecal transplant had increased number of FMTs compared with those who responded (mean 1.92+/-0.997 vs. 1.29+/-0.615; P=0.004). No colectomies or death related to CDI were found in our patient population. Significant predictors of failure were female sex (P=0.016), previous hospitalization (P=0.006), and surgery before FMT (P=0.005). The overall mortality rate was 9.0% and failure of FMT was associated with an increased risk of death (odds ratio=5.833, confidence interval 2.01-16.925; P<0.05). CONCLUSION: FMT is a suitable alterative to antibiotic use for recurrent CDIs, with a high success rate. The results indicate that hospital-acquired CDI may be a predictor of failure of FMT.

Internal Medicine

Ananthasubramaniam K, **Garikapati K**, and **Williams CT**. Progressive left ventricular hypertrophy after heart transplantation: Insights and mechanisms suggested by multimodal images *Tex Heart Inst J* 2016; 43(1):65-68. PMID: Not assigned. Full Text

K. Ananthasubramaniam, Heart and Vascular Institute, Henry Ford Hospital, Detroit, United States

Immunosuppression is the typical measure to prevent rejection after heart transplantation. Although rejection is the usual cause of cardiac hypertrophy, numerous other factors warrant consideration. Calcineurin inhibitors rarely cause hypertrophic cardiomyopathy; the few relevant reports have described children after orthotopic kidney or liver transplantation. We present the case of a 73-year-old woman, an asymptomatic orthotopic heart transplantation patient, in whom chronic immunosuppression with prednisone and cyclosporine apparently caused a phenotype of hypertrophic cardiomyopathy. The natural course of her midapical hypertrophy was revealed by single-photon-emission computed tomography, positron-emission tomography, and 2-dimensional echocardiography. Clinicians and radiographers should be alert to progressive left ventricular hypertrophy and various perfusion patterns in heart transplantation patients even in the absence of underlying coronary artery disease. Toward this end, we recommend that advanced imaging methods be used to their fullest extent.

Internal Medicine

Beaird OE, Freifeld A, Ison MG, Lawrence SJ, Theodoropoulos N, Clark NM, Razonable RR, **Alangaden G**, Miller R, Smith J, Young JA, Hawkinson D, Pursell K, and Kaul DR. Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative *Transpl Infect Dis* 2016;PMID: 26923867. Full Text

Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA.
Department of Internal Medicine, University of Nebraska, Omaha, Nebraska, USA.
Department of Internal Medicine, Northwestern University, Chicago, Illinois, USA.
Department of Internal Medicine, Washington University, St. Louis, Missouri, USA.
Department of Internal Medicine, The Ohio State University, Columbus, Ohio, USA.
Department of Internal Medicine, Loyola University Medical Center, Maywood, Illinois, USA.
Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA.
Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan, USA.
Department of Internal Medicine, University of Iowa, Iowa City, Iowa, USA.
Department of Internal Medicine, University of Wisconsin, Madison, Wisconsin, USA.
Department of Internal Medicine, University of Minnesota, Minneapolis, Minnesota, USA.
Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA.
Department of Internal Medicine, University of Chicago, Chicago, Illinois, USA.

BACKGROUND: The optimal treatment for respiratory syncytial virus (RSV) infection in adult immunocompromised patients is unknown. We assessed management of RSV and other non-influenza respiratory viruses in Midwestern transplant centers. METHODS: A survey assessing strategies for RSV and other non-influenza respiratory viral infections was sent to 13 centers. RESULTS: Multiplex polymerase chain reaction assay was used for diagnosis in 11/12 centers. Eight of 12 centers used inhaled ribavirin (RBV) in some patient populations. Barriers included cost, safety, lack of evidence, and inconvenience. Six of 12 used intravenous immunoglobulin (IVIG), mostly in combination with RBV. Inhaled RBV was used more than oral, and in the post-stem cell transplant population, patients with lower respiratory tract infection (LRTI), graft-versus-host disease, and more recent transplantation were treated at higher rates. Ten centers had experience with lung transplant patients; all used either oral or inhaled RBV for LRTI, 6/10 treated upper respiratory tract infection (URTI). No center treated non-lung solid organ transplant (SOT) recipients with URTI; 7/11 would use oral or inhaled RBV in the same group with LRTI. Patients with hematologic malignancy without hematopoietic stem cell transplantation were treated with RBV at a similar frequency to non-lung SOT recipients. Three of 12 centers, in severe cases, treated parainfluenza and metapneumovirus, and 1/12 treated coronavirus. CONCLUSIONS: Treatment of RSV in immunocompromised patients varied greatly. While most centers treat LRTI, treatment of URTI was variable. No consensus was found regarding the use of oral versus inhaled RBV, or the use of IVIG. The presence of such heterogeneity demonstrates the need for further studies defining optimal treatment of RSV in immunocompromised hosts.

Internal Medicine

Kenney RM, Cole KA, **Perri MB**, Dumkow LE, **Samuel LP**, **Zervos MJ**, and **Davis SL**. Reply to "urinary tract infections: Resistance is futile" *Antimicrob Agents Chemother* 2016; 60(4):2598. PMID: 27016558. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA rkenney1@hfhs.org.
Department of Pharmacy Services, University of Toledo Medical Center, Toledo, Ohio, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Pharmacy Services, Mercy Health Saint Mary's, Grand Rapids, Michigan, USA.
Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, Michigan, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan, USA Wayne State University School of Medicine, Detroit, Michigan, USA.
Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA.

Internal Medicine

Meighani A, **Hart BR**, Mittal C, **Miller N**, **John A**, and **Ramesh M**. Predictors of fecal transplant failure *Eur J Gastroenterol Hepatol* 2016;PMID: 26934528. Full Text

aDepartment of Internal Medicine and Infectious Disease, Henry Ford Hospital, Detroit, Michigan bDepartment of Gastroenterology and Hepatology, University of Colorado, Denver, Denver, Colorado, USA.

BACKGROUND: Clostridium difficile infection (CDI) is a significant healthcare burden, with increased morbidity and mortality. Traditional treatment regimens using antibiotics for recurrent CDI are significantly less successful compared with 80-90% with fecal microbiota transplantation (FMT). There is a paucity of data on failure rates and mortality after FMT in CDI. This study aims to identify the rates of failure, relapse, and mortality associated with FMT as well as the risk factors for FMT failure. METHODS: A large retrospective cohort study was carried out including all patients who underwent FMT from December 2012 through May 2014. Patient factors (demographics, comorbidities, immune-suppression, transplant history, antibiotics used, hospitalization, and surgeries), disease factors (number of episodes of CDI, treatments, and severity), and transplant factors (route and number of FMT) were examined. Failure of treatment was defined as no resolution of diarrhea in patients who had been treated with one or more fecal microbiota transplantation within 90 days of FMT. RESULTS: A total of 201 patients (age 66.6+/-18.3 years, 62.2% women) were included. The overall failure rate was 12.4%. Patients with failed fecal transplant had increased number of FMTs compared with those who responded (mean 1.92+/-0.997 vs. 1.29+/-0.615; P=0.004). No colectomies or death related to CDI were found in our patient population. Significant predictors of failure were female sex (P=0.016), previous hospitalization (P=0.006), and surgery before FMT (P=0.005). The overall mortality rate was 9.0% and failure of FMT was associated with an increased risk of death (odds ratio=5.833, confidence interval 2.01-16.925; P<0.05). CONCLUSION: FMT is a suitable alterative to antibiotic use for recurrent CDIs, with a high success rate. The results indicate that hospital-acquired CDI may be a predictor of failure of FMT.

Internal Medicine

Meighani A, **Jafri SM**, **Raoufi M**, and **Salgia R**. Splenic artery embolization for treatment of refractory ascites after liver transplantation *ACG Case Rep J* 2016; 3(2):136-138. PMID: 26958571. Full Text

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI.
Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI.
Department of Pathology, Henry Ford Hospital, Detroit, MI.

Post-transplantation refractory ascites is uncommon; however, it can be a serious problem, increasing both morbidity and mortality in patients. Despite scant literature available, splenic artery embolization (SAE) has been shown to be an effective treatment for refractory ascites after cadaveric orthotopic liver transplantation (OLT). We report a successful use of therapeutic SAE for refractory ascites post-OLT.

Internal Medicine

Miller-Matero LR, **Dykuis KE**, **Albujoq K**, **Martens K**, **Fuller BS**, **Robinson V**, and **Willens DE**. Benefits of integrated behavioral health services: The physician perspective *Fam Syst Health* 2016; 34(1):51-55. PMID: 26963777. Full Text

Department of Behavioral Health, Henry Ford Health System.
Department of Internal Medicine, Henry Ford Health System.

INTRODUCTION: There are benefits of integrating a behavioral health specialist in primary care; however, little is known about the physicians' perspectives. The purpose of this study was to explore primary care physicians' beliefs regarding the benefits of integrated care for both patients and themselves. METHOD: Fifteen senior staff physicians and 78 residents completed surveys regarding their opinions of referring to a psychologist in a patient-centered medical home. RESULTS: The top reasons that physicians believed their patients followed through with a visit with an integrated psychologist included that they recommended it (79.5%) and that patients can be seen in the same primary care clinic (76.9%). The overwhelming majority of physicians were satisfied with having access to an integrated psychologist (97.4%). Physicians believed that integrated care directly improves patient care (93.8%), is a needed service (90.3%), and helps provide better care to patients (80.9%). In addition, physicians reported that having an integrated psychologist reduces their personal stress level (90.1%). CONCLUSION: Primary care physicians may be motivated to integrate behavioral health services into their clinics knowing that other physicians believe that it directly and indirectly improves patient care and physician stress. (PsycINFO Database Record

Internal Medicine

Munukutla S, **Pan G**, **Deshpande M**, Thandavarayan RA, Krishnamurthy P, and **Palaniyandi SS**. Alcohol toxicity in diabetes and its complications: A double trouble? *Alcohol Clin Exp Res* 2016;PMID: 27013182. Full Text

Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.

Department of Cardiovascular Sciences, Center for Cardiovascular Regeneration, Houston Methodist Research Institute, Houston, Texas.
Department of Physiology, Wayne State University, Detroit, Michigan.

BACKGROUND: Eight percent of the U.S. population has been diagnosed with diabetes mellitus (DM), while another large percentage has gone undiagnosed. As the epidemiology of this disease constitutes a larger percentage of the American population, another factor presents a dangerous dilemma that can exacerbate the hazardous effects imposed by DM. Excessive alcohol consumption concerns the health of more than 50% of all adults. When this heavy-alcohol-drinking population overlaps with DM and its complications, the effects can be dangerous. In this review, we term it as "double trouble." METHODS: We provide evidence of alcohol-induced exacerbation of organ damage in diabetic conditions. In certain cases, we have explained how diabetes and alcohol induce similar pathological effects. RESULTS: Known exacerbated complications include those related to heart diseases, liver damage, kidney dysfunction, as well as retinal and neurological impairment. Often, pathophysiological damage concludes with end-stage disorders and even mortality. The metabolic, cell signaling, and pathophysiological changes associated with "double trouble" would lead to the identification of novel therapeutic targets. CONCLUSIONS: This review summarizes the epidemiology, diagnosis, pathophysiology, metabolic, and cell signaling alterations and finally brushes upon issues and strategies to manage the "double trouble."

Internal Medicine
Nabi S, **Kahlon P**, Bozorgnia F, Arshad A, Saleem A, and **Kuriakose P**. Analyzing relationship between monoclonal gammopathy of undetermined significance (MGUS) with different types of neuropathy: an observational study *Indian J Hematol Blood Transfus* 2016; 32(2):186-192. PMID: Not assigned. Full Text

S. Nabi, Department of Internal Medicine, Henry Ford Health System, Detroit, United States

To analyze multiple variables, including immunoglobulin subtypes in patients with monoclonal gammopathy of undetermined significance (MGUS) and different types of neuropathy. This was a retrospective, single center study done in a tertiary care hospital in the United States. The data was collected for years 2001–2011. Inclusion criteria were the presence of MGUS and neuropathy. Exclusion criteria were the presence of other factors such as diabetes, vitamin B12 deficiency, alcoholism etc. which can cause neuropathy. Patients with IgM MGUS were compared with patients having Non-IgM MGUS. A total of 281 patients were analyzed in this study. The average age at the time of diagnosis of MGUS and neuropathy was 68 years. The most common type of neuropathy was sensorimotor peripheral neuropathy (46 %). The most common location of neuropathy was the lower extremities (68 %). Among our patients, 52 % had their neuropathy symptoms for 1–5 years before presenting to the clinic. When IgM MGUS was compared with Non-IgM MGUS, a statistically significant difference was found in terms of race (White vs. Others, OR 4.43, 95 % CI 2.13, 9.19, $p < 0.001$) and survival status (OR 1.98, 95 % CI 1.01, 3.90, $p = 0.046$). Patients with MGUS are prone to develop different types of neuropathies. Caucasians are more likely to have IgM MGUS as compared to other races. IgM MGUS is generally related to worse outcomes as compared to Non-IgM MGUS. Medical therapies, including gabapentin and pregabalin are effective treatments and the response rate can be as high as 80–90 % with these medications.

Internal Medicine
Nagarwala J, **Dev S**, and **Markin A**. The vomiting patient. Small bowel obstruction, cyclic vomiting, and gastroparesis *Emerg Med Clin North Am* 2016;PMID: Not assigned. Abstract

J. Nagarwala, Department of Emergency Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, Clara Ford Pavillion-#263, Detroit, MI 48202

Vomiting and abdominal pain are common in patients in the emergency department. This article focuses on small bowel obstruction (SBO), cyclic vomiting, and gastroparesis. Through early diagnosis and appropriate management, the morbidity and mortality associated with SBOs can be significantly reduced. Management of SBOs involves correction of physiologic and electrolyte disturbances, bowel rest and removing the source of the obstruction. Treatment of acute cyclic vomiting is primarily directed at symptom control, volume and electrolyte repletion, and appropriate specialist follow-up. The mainstay of therapy for gastroparesis is metoclopramide.

Internal Medicine
Wells KE, **Cajigal S**, **Peterson EL**, **Ahmedani BK**, Kumar R, **Lanfear DE**, Burchard EG, and **Williams LK**. Assessing differences in inhaled corticosteroid response by self-reported race-ethnicity and genetic ancestry among asthmatic subjects *J Allergy Clin Immunol* 2016;PMID: 27016472. Full Text

Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich. Electronic address: kewells1@aol.com.
Department of Internal Medicine, Henry Ford Health System, Detroit, Mich.
Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich.
Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Mich.
Department of Pediatrics, The Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Ill.
Department of Bioengineering & Therapeutic Sciences, University of California San Francisco, San Francisco, Calif; Department of Medicine, University of California San Francisco, San Francisco, Calif.
Department of Internal Medicine, Henry Ford Health System, Detroit, Mich; Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Mich.

BACKGROUND: Inhaled corticosteroids (ICSs) are the preferred treatment for achieving asthma control. However, little is known regarding the factors contributing to treatment response and whether treatment response differs by population group. OBJECTIVE: We sought to assess behavioral, sociodemographic, and genetic factors related to ICS response among African American and European American subjects with asthma. METHODS: Study participants were part of the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE). The analytic sample included asthmatic subjects aged 12 to 56 years with greater than 12% bronchodilator reversibility and percent predicted FEV1 of between 40% and 90%. Participants received 6 weeks of inhaled beclomethasone dipropionate. The primary measure of ICS response was a change in Asthma Control Test (ACT) score; the secondary measure was a change in prebronchodilator FEV1. Adherence was measured with electronic monitors. Genetic ancestry was estimated for African American participants by using genome-wide genotype data. RESULTS: There were 339 study participants; 242 self-identified as African American and 97 as European American. Baseline ACT score, percent predicted FEV1, degree of bronchodilator response, and ICS adherence were significantly associated with ICS response. A baseline ACT score of 19 or less was useful in identifying those who would respond, as evidenced by the significant dose-response relationship with ICS adherence. Neither self-reported race-ethnicity among all participants nor proportion of African ancestry among African American participants was associated with ICS responsiveness. CONCLUSIONS: Our findings suggest that baseline lung function measures and self-reported asthma control predict ICS response, whereas self-reported race-ethnicity and genetic ancestry do not.

Internal Medicine

Zhang X, Gu J, Yu FS, **Zhou L**, and **Mi QS**. TGF-beta1-induced transcription factor networks in Langerhans cell development and maintenance *Allergy* 2016;PMID: 26948524. Full Text

Henry Ford Immunology Program, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Dermatology, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Dermatology, Second Military Medical University Changhai Hospital, 168 Changhai Rd, Shanghai, 200433, China.
Department of Ophthalmology, Wayne State University School of Medicine, Detroit, USA.
Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, USA.
Department of Internal Medicine, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, USA.

Langerhans cells (LC) represent a specialized subset of evolutionarily conserved dendritic cells (DC) that populate stratified epithelial tissues, which are essential for the induction of skin and mucosal immunity and tolerance, including allergy. TGF-beta1 has been confirmed to be a predominant factor involved in LC development. Despite great advances in the understanding of LC ontogeny and diverse replenishment patterns, the underlying molecular mechanisms remain elusive. This review focuses on the recent discoveries in TGF-beta1-mediated LC development and maintenance, with special attention to the involved transcription factors and related regulators. This article is protected by copyright. All rights reserved.

Nephrology

Weir MR, Pearson TC, **Patel A**, Peddi VR, Kalil R, Scandling J, Chan L, Baliga P, Melton L, Mulgaonkar S, Waid T, Schaefer H, Youssef N, Anandagoda L, McCollum D, Lawson S, and Gordon R. Long-term follow-up of kidney transplant recipients in the spare-the-nephron-trial *Transplantation* 2016;PMID: 26950714. Full Text

1 School of Medicine, University of Maryland, Baltimore, MD. 2 Emory University, Atlanta, GA. 3 Henry Ford Hospital, Detroit, MI. 4 California Pacific Medical Center, San Francisco, CA. 5 University of Iowa, Iowa City, IA. 6 Stanford University, Palo Alto, CA. 7 University of Colorado, Denver, CO. 8 Medical University of South Carolina, Charleston,

SC. 9 Baylor University Medical Center, Dallas, TX. 10 St. Barnabas Medical Center, Newark, NJ. 11 University of Kentucky, Lexington, KY. 12 Vanderbilt University Medical Center, Nashville, TN. 13 Our Lady of Lourdes Medical Center, Camden, NJ. 14 CTI Clinical Trial and Consulting Services, Cincinatti, OH.

In the Spare-the-Nephron (STN) Study, kidney transplant recipients randomized about 115 days posttransplant to convert from CNI (calcineurin inhibitor)/MMF to sirolimus (SRL)/MMF had a significantly greater improvement in measured GFR (mGFR) at 12 months compared with those kept on CNI/MMF. The difference at 24 months was not statistically significant. From 14 top enrolling centers, 128 of 175 patients identified with a functioning graft at 2 years consented to enroll in an observational, noninterventional extension study to collect retrospectively and prospectively annual follow-up data for the interval since baseline (completion of the parent STN study at 24 months posttransplant). Overall, 11 patients died, including 5 (7.6%) in the SRL/MMF group and 6 (9.7%) in the CNI/MMF group. Twenty-two grafts have been lost including 10 (15.2%) in the SRL/MMF arm and 12 (19.4%) in the CNI/MMF arm. Death and chronic rejection were the most common causes of graft loss in both arms. There were modestly more cardiovascular events in the MMF/SRL group. Estimated creatinine clearance (Cockcroft-Gault) from baseline out to 6 additional years (8 years posttransplant, ITT analysis, SRL/MMF, n = 34; CNI/MMF, n = 26) was 63.2 +/- 28.5 mL/min/1.73 m in the SRL/MMF group and 59.2 +/- 27.2 mL/min/1.73 m in the CNI/MMF group and was not statistically significant, but there is a clinically meaningful trend for improved long-term renal function in the SRL/MMF group compared with the CNI/MMF group. The long-term decision for immunosuppression needs to be carefully individualized.

Nephrology
Yee J. PGX: Pharmacogenomics during generation X *Adv Chronic Kidney Dis* 2016; 23(2):57-60. PMID: 26979142. Full Text

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI.

Neurology
Alentorn A, Hoang-Xuan K, and **Mikkelsen T**. Presenting signs and symptoms in brain tumors *Handb Clin Neurol* 2016; 134:19-26. PMID: 26948346. Article Request Form

Department of Neurology 2, Groupe Hospitalier Pitie-Salpetriere, Paris, France; Inserm Experimental Neuro-Oncology Laboratory, Institut du Cerveau et de la Moelle, Universite Pierre et Marie Curie, Paris, France. Department of Neurology 2, Groupe Hospitalier Pitie-Salpetriere, Paris, France; Inserm Experimental Neuro-Oncology Laboratory, Institut du Cerveau et de la Moelle, Universite Pierre et Marie Curie, Paris, France. Electronic address: khe.hoang-xuan@psl.aphp.fr.
Hermelin Brain Tumor Center and Departments of Neurology and Neurosurgery, Henry Ford Hospital, Detroit, MI, USA; Wayne State University, Detroit, MI, USA.

Focal symptoms and signs occurring during brain tumor clinical presentation are dependent on a number of factors. Location and rate of growth are the most critical, followed by overall lesion size and nature, whether infiltrating or causing the displacement of neural structures, but also the presence or extent of associated pathology, including edema, hemorrhage, vascular compromise, and cerebrospinal fluid obstruction. Mechanisms of presenting symptomatology can be divided into tumor and peritumoral factors. Tumor factors include histology, for example, in that seizures are common in patients with certain low-grade gliomas. Peritumoral factors, including regional hypoxia and ionic changes in the peritumoral zone, may influence neuronal activity and extracellular glutamate may be associated with neuronal hyperexcitability. Blood-brain barrier breakdown may predispose to seizure and localized neuronal dysfunction. Finally, signs and symptoms in brain tumors can be generalized, associated with increased intracranial brain pressure, but can also be localized, based on the involvement of the major structures of the central nervous system.

Neurology
Buller B, **Moore T**, **Zhang Y**, **Pikula E**, **Martin C**, **Mortazavi F**, **Rosene D**, **Chopp M**, and **Zhang Z**. Exosomes from rhesus monkey MSCs promote neuronal growth and myelination *Stroke* 2016; 47PMID: Not assigned. Abstract

B. Buller, Neurology, Henry Ford Health System, Detroit, United States

Introduction: Treatment of rodents with bone marrow mesenchymal stromal cells (MSCs) enhances functional recovery after stroke. We have shown in a series of studies that much or all of this effect is mediated through release of exosomes-small, membrane bound vesicles that contain many biomolecules-by the MSCs, and that functional

benefit is dependent on white matter remodeling. Hypothesis: We hypothesize that exosomes derived from monkey MSCs enhance axonal growth and myelination. Methods: We isolated MSCs from the bone marrow of a young adult rhesus monkey, and harvested their exosomes from MSC culture medium. Results: We first investigated the effect of exosomes on cultured organotypic brain slices from the cerebrum of rat pups. Treatment of brain slices with exosomes markedly increased myelination in cortex and corpus callosum compared to control. Image analysis of 3D reconstructions showed that exosomes increased connections of oligodendrocyte processes with axons by 48%, suggesting enhancement of initiation of myelination. To examine the effect of exosomes directly on neurons and oligodendrocyte progenitor cells (OPCs), exosomes were applied to either cortical neurons cultured in a microfluidic chamber or OPCs. We found that exosomes significantly ($p<0.05$) increased axonal length (526±22μm vs. 320±15μm for control, n=75/group) and increased the number of NG2+ OPCs by twofold compared to control ($P < 0.01$). However, exosomes had no significant effect on mature, MBP expressing oligodendrocytes. Conclusion: Our data suggest that exosomes enhance myelination by a two-pronged effect. First, they promote axonal growth, and second, they increase the number of available OPCs. Increased axonal growth may trigger OPCs to myelinate axons. This work is the first to demonstrate the therapeutic potential of monkey exosomes for axonal growth and myelination.

Neurology

Cui C, **Chopp M**, Ye X, **Zacharek A**, **Ning R**, Yan T, **Cui X**, **Yu P**, **Roberts C**, and **Chen J**. Mir-145 mediates bone-marrow-stromal cell derived from type-one diabetes (t1dm) rats induced neurorestorative effects in T1DM rats *Stroke* 2016; 47PMID: Not assigned. Abstract

C. Cui, Henry Ford Hosp, Detroit, United States

Objective: Treatment of stroke with bone-marrow-stromal cells (BMSCs) derived from type-one diabetes (T1DM) rats (DM-BMSCs) improves functional recovery compared to BMSCs derived from normal rats (Nor-BMSCs) and non treatment T1DM rats. In the study, we tested the mechanisms underlying the benefit of the treatment of T1DM stroke with DM-BMSCs. Methods: T1DM rats induced by streptozocin in male Wistar rats were subjected to 2h middle cerebral artery occlusion (MCAo) and were treated at 24h after MCAo via tail vein with: 1) vehicle control; 2) DM-BMSCs; 3) DM-BMSCs with miR-145 overexpression (miR-145+/+DM-BMSCs)(5×106) (n=8/group). A battery of functional tests, vascular,white matter (WM) measurements, and cell culture experiments were performed. Results: In vitro, DM-BMSCs exhibited reduced level of miR-145, and increased survival rate compared to Nor-BMSCs. miR-145+/+DM-BMSCs significantly decreased DM-BMSCs survival. DM-BMSCs media increased capillary tube formation and axonal outgrowth in cultured primary cortical neurons (PCNs) compared to Nor-BMSCs media. While miR-145+/+DM-BMSCs exhibited reverse effects compared to DM-BMSCs media. In vivo, DM-BMSCs improved functional outcome, vascular and WM remodeling in the ischemic border zone (IBZ) compared to T1DM-MCAo rats. However, miR-145+/+DM-BMSCs significantly attenuated DM-BMSCs induced beneficial effects. To further test the underlying mechanism of miR-145 mediated DM-BMSCs induced therapeutic effects in T1DM stroke rats, miR-145 target genes adenosine triphosphate-binding cassette transporter 1 (ABCA1) and insulin-like growth factor 1 receptor (IGFR-1) were measured in IBZ. ABCA1 and IGFR1 have neurorestorative effects. Reduction of IGF1 contributes ABCA1 deficiency induced damage in ischemic brain. We found that DM-BMSCs significantly decreased miR-145, increased ABCA1 and IGFR-1 expression in IBZ compared to Nor-BMSCs. While miR-145+/+DM-BMSCs significantly decreased ABCA1 and IGFR-1 expression in IBZ. Conclusion: DM-BMSCs exhibit decreased miR-145 expression and increase miR-145 target gene ABCA1 and IGFR-1 expression in ischemic brain. The miR-145/ABCA1/IGFR-1 pathway may contribute to DM-BMSCs induced neurorestorative effects in T1DM stroke.

Neurology

Cui X, **Chen J**, **Zacharek A**, **Cui Y**, **Roberts C**, and **Chopp M**. ABCA1/HDL pathway mediates GW3965 induced neurorestoration and white matter remodeling after stroke *Stroke* 2016; 47PMID: Not assigned. Abstract

X. Cui, Neurology Rsch, Henry Ford Hosp, Detroit, United States

ATP-binding cassette transporter A1 (ABCA1), a major cholesterol transporter in the central nervous system, plays an important role in the formation of brain HDL-cholesterol. ABCA1 is up-regulated by the transcription factors, liver X receptors (LXRs). Our previous study using brain-specific ABCA1 deficient (floxed, nestin-Cre positive, ABCA1-B/-B) and ABCA1 floxed-control (ABCA1fl/fl) mice showed that ABCA1 has anti-inflammatory effects and reduces white matter (WM) damage in ischemic stroke models. Here, we further test whether GW3965, a synthetic LXR agonist treatment of stroke increases ABCA1 and HDL, and thereby improves WM-remodeling and functional outcome. Adult male ABCA1fl/fl and ABCA1-B/-B mice were subjected to permanent extraluminal distal middle cerebral artery occlusion (dMCAo) by transcranial ligation method. Animals were gavaged with saline or GW3965 (10 mg/kg) starting 24h after dMCAo and daily till sacrificed 14 days after dMCAo. There were no differences in the lesion volume and blood levels of total cholesterol and triglyceride before and after dMCAo between ABCA1-B/-B and ABCA1fl/fl mice.

However, GW3965 treatment significantly increased blood HDL levels in ABCA1fl/fl mice, but not in ABCA1-B/-B mice 14 days after dMCAo. GW3965 treatment of ABCA1fl/fl stroke mice, but not in ABCA1-B/-B stroke mice, also increased: 1) WM-density identified by Luxol Fast Blue (myelin marker), Bielshowsky silver (axon marker), and SMI31 (phosphorylated neurofilament marker) staining; 2) the number of platelet-derived growth factor receptor alpha positive oligodendrocyte progenitor cells; 3) ABCA1, synaptophysin and myelin basic protein expression in the ischemic brain; 4) functional outcome 7 and 14 days after dMCAo, compared with non-treatment ABCA1fl/fl stroke mice ($p<0.05$, n=9/group). GW3965 and HDL treatment significantly increase axonal/neurite outgrowth in cultured primary cortical neurons derived from ABCA1fl/fl embryos, but not in neurons derived from ABCA1-B/-B embryos. Treatment of stroke with GW3965 significantly increased blood level of HDL, increased ABCA1 expression and WM-remodeling in the ischemic brain. Increasing ABCA1 may contribute to GW3965 induced neurorestoration and WM remodeling after stroke.

Neurology

Hijaz M, Das S, **Mert I**, Gupta A, **Al-Wahab Z**, **Tebbe C**, **Dar S**, **Chhina J**, **Giri S**, **Munkarah A**, Seal S, and **Rattan R**. Folic acid tagged nanoceria as a novel therapeutic agent in ovarian cancer *BMC Cancer* 2016; 16(1):220. PMID: 26979107. Full Text

Division of Gynecology Oncology, Department of Women's Health, Henry Ford Hospital, Detroit, MI, USA.
Advanced Materials Processing and Analysis Center, Nanoscience and Technology Center, Materials Science and Engineering, University of Central Florida, Orlando, FL, USA.
Wayne State University, Detroit, MI, USA.
Department of Neurology, Henry Ford Hospital, Detroit, MI, USA.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA.
College of Medicine, University of Central Florida, Orlando, FL, USA.
Division of Gynecology Oncology, Department of Women's Health, Henry Ford Hospital, Detroit, MI, USA. rrattan1@hfhs.org.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. rrattan1@hfhs.org.

BACKGROUND: Nanomedicine is a very promising field and nanomedical drugs have recently been used as therapeutic agents against cancer. In a previous study, we showed that Nanoceria (NCe), nanoparticles of cerium oxide, significantly inhibited production of reactive oxygen species, cell migration and invasion of ovarian cancer cells in vitro, without affecting cell proliferation and significantly reduced tumor growth in an ovarian cancer xenograft nude model. Increased expression of folate receptor-alpha, an isoform of membrane-bound folate receptors, has been described in ovarian cancer. To enable NCe to specifically target ovarian cancer cells, we conjugated nanoceria to folic acid (NCe-FA). Our aim was to investigate the pre-clinical efficacy of NCe-FA alone and in combination with Cisplatin. METHODS: Ovarian cancer cell lines were treated with NCe or NCe-FA. Cell viability was assessed by MTT and colony forming units. In vivo studies were carried in A2780 generated mouse xenografts treated with 0.1 mg/Kg NCe, 0.1 mg/Kg; NCe-FA and cisplatinum, 4 mg/Kg by intra-peritoneal injections. Tumor weights and burden scores were determined. Immunohistochemistry and toxicity assays were used to evaluate treatment effects. RESULTS: We show that folic acid conjugation of NCe increased the cellular NCe internalization and inhibited cell proliferation. Mice treated with NCe-FA had a lower tumor burden compared to NCe, without any vital organ toxicity. Combination of NCe-FA with cisplatinum decreased the tumor burden more significantly. Moreover, NCe-FA was also effective in reducing proliferation and angiogenesis in the xenograft mouse model. CONCLUSION: Thus, specific targeting of ovarian cancer cells by NCe-FA holds great potential as an effective therapeutic alone or in combination with standard chemotherapy.

Neurology

Jiang Q. Magnetic resonance imaging and cell-based neurorestorative therapy after brain injury *Neural Regen Res* 2016; 11(1):7-14. PMID: 26981068. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, MI, USA.

Restorative cell-based therapies for experimental brain injury, such as stroke and traumatic brain injury, substantially improve functional outcome. We discuss and review state of the art magnetic resonance imaging methodologies and their applications related to cell-based treatment after brain injury. We focus on the potential of magnetic resonance imaging technique and its associated challenges to obtain useful new information related to cell migration, distribution, and quantitation, as well as vascular and neuronal remodeling in response to cell-based therapy after brain injury. The noninvasive nature of imaging might more readily help with translation of cell-based therapy from the laboratory to the clinic.

Neurology
Katakowski M, and **Chopp M**. Exosomes as tools to suppress primary brain tumor *Cell Mol Neurobiol* 2016;PMID: 26983831. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, MI, USA. chopp@neuro.hfh.edu.
Department of Physics, Oakland University, Rochester, MI, USA. chopp@neuro.hfh.edu.

Exosomes are small microvesicles released by cells that efficiently transfer their molecular cargo to other cells, including tumor. Exosomes may pass the blood-brain barrier and have been demonstrated to deliver RNAs contained within to brain. As they are non-viable, the risk profile of exosomes is thought to be less than that of cellular therapies. Exosomes can be manufactured at scale in culture, and exosomes can be engineered to incorporate therapeutic miRNAs, siRNAs, or chemotherapeutic molecules. As natural biological delivery vehicles, interest in the use of exosomes as therapeutic delivery agents is growing. We previously demonstrated a novel treatment whereby mesenchymal stromal cells were employed to package tumor-suppressing miR-146b into exosomes, which were then used to reduce malignant glioma growth in rat. The use of exosomes to raise the immune system against tumor is also drawing interest. Exosomes from dendritic cells which are antigen-presenting, and have been used for treatment of brain tumor may be divided into three categories: (1) exosomes for immunomodulation-based therapy, (2) exosomes as delivery vehicles for anti-tumor nucleotides, and (3) exosomes as drug delivery vehicles. Here, we will provide an overview of these three applications of exosomes to treat brain tumor, and examine their prospects on the long road to clinical use.

Neurology
Li C, **Zhang Y**, **Levin AM**, **Chopp M**, and **Zhang ZG**. Characterization of micrornas and their target proteins in distal axons of cortical neurons *Stroke* 2016; 47PMID: Not assigned. Abstract

C. Li, Dept of Neurology, Henry Ford Hosp, Detroit, United States

Introduction: Axonal growth is essential for the establishment of a functional neuronal network. Molecular information of axon is limited. MicroRNAs (miRNAs) regulate post-transcriptional gene expression. We hypothesized that axonal miRNAs are locally relevant to their target genes. Methods: Proteins and RNAs were extracted from distal axons of cortical neurons cultured in a microfluidic device. A mass spectrometer and miRNA arrays were used to measure proteins and miRNAs, respectively. Ingenuity Pathway Analysis (IPA) and Database for Annotation, Visualization and Integrated Discovery (DAVID) bioinformatic tools were used to make in silico predictions of functionally relevant miRNA target genes. Results: Proteomic showed that distal axons contained 883 proteins. Bioinformatic analysis showed the presence of 94 proteins that regulate axonal growth. To identify relevant miRNAs to these 94 proteins, miRNAs with 8mer sites that exactly match target genes were considered, based on the fact that 8mer sites efficaciously affect miRNA-target interactions. Of the 94 genes, we found that there were 56 candidate genes that can be targeted by 62 miRNAs enriched in axons. Among them, we validated 13 proteins and 11 miRNAs, respectively, by means of Western blot and RT-PCR. To examine target genes, we treated axons with chondroitin sulfate proteoglycans (CSPGs) that inhibit axonal growth and examined alterations of these proteins and miRNAs in the distal axons. We found that elevation of miR-203a, -133b, -29abc and -92ab were associated with reduced AKT, MTOR, PI3Kp85, DPYSL2, MAP1B, PPP2CA and DCX proteins, whereas decreased miR-15b, -26b, -34b, -376b, -128, -381 and -195 were accompanied by increased proteins of EZR, KIF5A, RTN4, GSK3B, and ROCK2. Bioinformatic analysis revealed that these miRNAs and proteins are highly related to the axonal growth network. These data suggest that miRNAs altered by CSPGs functionally target these genes for mediating the inhibitory effect of CSPGs on axonal growth. Conclusions: Our bioinformatic analyses of miRNAs and proteins in the distal axon identifies an interconnected group of miRNAs and their target genes that regulate axonal growth, which provides new insight into the molecular mechanisms underlying axonal growth.

Neurology
Li L, **Chopp M**, **Ding G**, **Qu C**, **Nejad-Davarani SP**, **Davoodi-Bojd E**, **Li Q**, **Mahmood A**, and **Jiang Q**. Diffusion-derived mri measures of longitudinal microstructural remodeling induced by marrow stromal cell therapy after TBI *J Neurotrauma* 2016;PMID: 26993214. Full Text

Henry Ford Hospital, Neurology , 2799 West Grand Boulevard , Detroit, Michigan, United States , 48202 ; lli2@hfhs.org.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States.
Oakland University, Physics, Rochester, Michigan, United States ; MCHOPP1@hfhs.org.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; gding1@hfhs.org.
Henry Ford Hospital, Neurosurgery, Detroit, Michigan, United States ; cqu1@hfhs.org.

Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; siamak@umich.edu.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; esdavoodi@gmail.com.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; QLI1@hfhs.org.
Henry Ford Hospital, Neurosurgery, Detroit, Michigan, United States ; amahmoo2@hfhs.org.
Oakland University, Physics, Rochester, Michigan, United States ; QJIANG1@hfhs.org.

Using magnetic resonance imaging (MRI) and an animal model of traumatic brain injury (TBI), we investigated the capacity and sensitivity of diffusion-derived measures, fractional anisotropy (FA) and diffusion entropy, to longitudinally identify structural plasticity in the injured brain in response to the transplantation of human bone marrow stromal cells (hMSCs). Male Wistar rats (300-350g, n=30) were subjected to controlled cortical impact TBI. At 6 hours or 1 week post-injury, these rats were intravenously injected with 1 ml of saline (at 6 hours or 1 week, n=5/group) or with hMSCs in suspension (3x106 hMSCs, at 6 hours or 1 week, n=10/group). In vivo MRI measurements and sensorimotor function estimates were performed on all animals pre-injury, 1 day, and weekly for 3 weeks post-injury. Bielshowsky's silver and Luxol fast blue staining were used to reveal the axon and myelin status, respectively, with and without cell treatment after TBI. Based on image data and histological observation, regions of interest encompassing the structural alterations were made and the values of FA and entropy were monitored in these specific brain regions. Our data demonstrate that administration of hMSCs after TBI leads to enhanced white matter reorganization particularly along the boundary of contusional lesion which can be identified by both FA and entropy. Compared to the therapy carried out at 1 week post-TBI, cell intervention executed at 6 hours expedites the brain remodeling process and results in an earlier functional recovery. While FA and entropy present a similar capacity to dynamically detect the microstructural changes in the tissue regions with predominant orientation of fiber tracts, entropy exhibits a sensitivity superior to FA, in probing the structural alterations in the tissue areas with complex fiber patterns.

Neurology

Miller DJ, **Shah K**, **Modi S**, **Mahajan A**, **Zahoor S**, and **Affan M**. The evolution and application of cardiac monitoring for occult atrial fibrillation in cryptogenic stroke and TIA *Curr Treat Options Neurol* 2016; 18(4):17. PMID: 26923607. Full Text

Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. dmille12@hfhs.org.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. kshah8@hfhs.org.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. smodi3@hfhs.org.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. amahaja1@hfhs.org.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. szahoor2@hfhs.org.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. maffan1@hfhs.org.

OPINION STATEMENT: The evaluation of the stroke and transient ischemic attack (TIA) patient has been historically predominated by the initial evaluation in the hospital setting. As the etiology of stroke has eluded us in approximately one third of all acute events, the medical community has been eager to seek the answer to this mystery. In recent years, we have seen an explosion of innovations and trends allowing for a more detailed post stroke assessment strategy aimed at the identification of occult atrial fibrillation as the etiologic cause for the cryptogenic event. This has been achieved through the evolution and aggressive application and study of prolonged and advanced cardiac monitoring. This review is aimed to clarify and elucidate the standard and novel cardiac monitoring methods that have become available for use by the medical community and expected in the higher level care of cryptogenic stroke and TIA patients. These cardiac monitoring methods and devices are as heterogeneous as our patient population and have their own advantages and disadvantages. Many factors may be taken into consideration in choosing the appropriate cardiac monitoring method and are highlighted for consideration in this review. With a judicious approach to investigating the cryptogenic stroke population, and applying a wealth of novel treatment options, we may move forward into a new era of stroke prevention.

Neurology

Morris D, **Chopp M**, **Cheung WL**, **Cui Y**, **Zhang T**, **Lu M**, **Zhang L**, and **Zhang ZG**. Thymosin β4 for the treatment of sub-acute stroke in aged rats *Stroke* 2016; 47PMID: Not assigned. Abstract

D. Morris, Emergency Medicine, Henry Ford Hosp, Detroit, United States

Introduction: Thymosin β4 (Tβ4) is a 5K peptide which influences cellular migration by inhibiting organization of the actin-cytoskeleton. Tβ4 has neurorestorative properties and is a potential candidate for the treatment of sub-acute stroke. Previous research demonstrated that Tβ4 improved neurological outcome in a young (3 months) rat model of

embolic stroke. Hypothesis: We hypothesized that Tβ4 would improve neurological outcome in an aged rat model of embolic stroke when administered 24 hours after embolic stroke. Methods: Aged Male Wistar rats (Charles River, France 18-21 months) were subjected to embolic middle cerebral artery occlusion (MCAo). Rats were randomized to receive Tβ4 (12 mg/kg, Regenerx Biopharmaceuticals, Inc.) or control 24 hrs after MCAo and then every 3 days for 4 additional doses. The dose of 12 mg/kg was the maximal dose of Tβ4 that showed functional improvement in a young rat model of embolic stroke. Functional tests were performed weekly. The rats were sacrificed 56 days after MCAo and lesion volumes measured. Generalized Estimating Equations were used to compare the treatment effect on functional recovery and t-test for lesion volumes. Results and Conclusions: Twenty-three rats were included in the study: control group (n=12) and Tβ4 group (n=11). After randomization, there were three deaths in both the control and Tβ4 groups. The Tβ4 treatment reduced infarct volume by more than 50% (12.8% ± 9.3%, mean ± SE, $p<0.05$) compared to the control group (26.0% ± 4.3%). However, Tβ4 did not show improvement in functional outcome compared to control. Lesion volumes in the treated group showed a correlation to functional testing of ($R=0.85$, $p<0.05$), whereas no correlation was observed in the control group ($R=0.19$). Conclusions: The Tβ4 treatment of stroke aged animals significantly reduces infarct volume compared to vehicle treated stroke. Dissociation between infarct volume and functional outcome in the control group suggests, a ceiling effect of these functional tests in aged animals may obscure proper evaluation of functional outcome between the Tβ4 and control groups. Additional studies and more sensitive behavioral tests are needed to examine the dissociation between infarct volume and functional outcomes in aged ischemic rats.

Neurology

Munkarah A, Mert I, **Chhina J**, **Hamid S**, **Poisson L**, **Hensley-Alford S**, **Giri S**, and **Rattan R**. Targeting of free fatty acid receptor 1 in EOC: A novel strategy to restrict the adipocyte-EOC dependence *Gynecol Oncol* 2016; 141(1):72-79. PMID: 27016232. Full Text

Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: amunkar1@hfhs.org.
Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: imert@med.wayne.edu.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA. Electronic address: jchhina1@hfhs.org.
Department of Neurology, Henry Ford Hospital, USA. Electronic address: hsuhail1@hfhs.org.
Center for Bioinformatics, Henry Ford Hospital, USA; Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: lpoisso1@hfhs.org.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: salford1@hfhs.org.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA; Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: sgiri1@hfhs.org.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: rrattan1@hfhs.org.

OBJECTIVES: Adipocyte derived free fatty acids (FFA) promote epithelial ovarian cancer (EOC) by acting as a fuel source to support the energy requirement of the cancer cells. FFA may also exert biological effects through signaling pathways. Recently, a family of FFA activated G-protein coupled receptors (FFAR/GPCRs) was identified. Our objective was to investigate the role of FFAR/GPCRs in EOC and assess their potential as therapeutic targets. METHODS: The mRNA (RT-PCR) expression of FFAR/GPCR family members (FFAR1/GPR40; FFAR2/GPR43, FFAR3/GPR41, FFAR4/GPR120 and GPR84) was examined in: (1) a syngeneic mouse model of EOC fed high energy diet (60% fat) or regular diet (30% fat), (2) EOC cell lines exposed to free fatty acids and (3) specimens from 13 histologically normal ovaries and 28 high grade ovarian serous carcinomas. The GPR 40 antagonist, GW1100, was used to inhibit FFAR1/GPR40 and cell survival was assayed by MTT in various cell lines. RESULTS: High Grade Serous carcinoma specimens expressed significantly increased GPR40 compared to normal ovaries ($p=0.0020$). Higher expression was noted in advanced stage disease. ID8 ovarian tumors from mice fed with high fat diet also showed higher GPR40 expression. Exposing EOC cells to FFAs, increased GPR40 expression. Treatment of EOC cell lines with GW100 resulted in growth inhibition and was associated with an alteration in their energy metabolism. CONCLUSION: FFA-induced cancer cell growth may be partly mediated through FFAR1/GPR40. Targeting of FFAR1/GPR40 may be an attractive treatment strategy in EOC, and possibly offers a targeted treatment for a subset of EOC patients.

Neurology

Nagaraja TN, **Keenan KA**, **Ewing JR**, and **Knight RA**. Surrogate MRI signatures for contrast enhanced imaging that predict acute blood-brain barrier damage in ischemia-reperfusion *Stroke* 2016; 47PMID: Not assigned. Abstract

T.N. Nagaraja, Neurosurgery, Henry Ford Hosp, Detroit, United States

Background and Purpose: Contrast-enhanced magnetic resonance imaging (CE-MRI) is used to measure blood-brain barrier (BBB) damage after stroke, but is contra-indicated in patients with compromised kidney function. Thus, there is a need for non-contrast MRI techniques that portend BBB damage. We examined the relationships between CE-MRI and non-contrast MRI measures to test whether the latter serve as surrogate biomarkers of BBB damage in acute stroke. Methods: Male Wistar rats (~300 g; N=22) were subjected to focal cerebral ischemia-reperfusion using a middle cerebral artery suture occlusion model. They were imaged in a 7 Tesla Bruker MRI system. The parameters measured were: cerebral blood flow (CBF), T2, T1 and T1-under-off resonance-saturation (T1sat). All data except CBF were expressed as ipsilateral-to-contralateral ratios (I-C). Post-reperfusion BBB damage was measured by CE-MRI via blood-to-brain forward volumetric transfer constant (Ktrans) maps. CBF, T2, T1 and T1sat were compared to Ktrans from the same region of interest (ROI). Scatterplots with Pearson correlation coefficients (r) were used to compare the data and significances inferred at $p<0.05$. Results: Preoptic area (PoA) and striatum (Str) were found ischemic in nearly all rats, with neocortical areas lesser affected. During occlusion, CBF in PoA and Str were 26±15 and 42±18 ml/100g/min (20-25% of contralateral side), respectively. After reperfusion, CBF was 78±27 and 99±50 ml/100g/min in PoA and Str, respectively. Contrast enhancement or BBB damage was observed in the PoA in all 22 rats and in 17 in Str. The I-C values of T2, T1 and T1sat elevated between occlusion and reperfusion periods and were associated with increased Ktrans values ($p=0.05$). The extent of CBF reduction during occlusion was significant and correlated inversely with increased Ktrans ($r=-0.5$; $p=0.03$), but this relationship was lost after reperfusion ($r=0.3$; $p=0.3$). Conclusions: The data suggest that reduction in CBF during occlusion and post-reperfusion elevation of T2, T1, and T1sat (i.e. vasogenic edema) are reliable predictors of impending BBB damage in acute stroke. With further confirmation, non-contrast based MRI evaluation of the BBB in acute stroke may be utilized in cases where CE-MRI is not possible.

Neurology

Shankar A, Borin TF, Iskander A, Varma NR, Achyut BR, Jain M, **Mikkelsen T**, Guo AM, Chwang WB, Ewing JR, **Bagher-Ebadian H**, and Arbab AS. Combination of vatalanib and a 20-HETE synthesis inhibitor results in decreased tumor growth in an animal model of human glioma *Onco Targets Ther* 2016; 9:1205-1219. PMID: 27022280. Full Text

Tumor Angiogenesis Laboratory, Cancer Center, Georgia Regents University, Augusta, GA, USA.
Laboratory of Molecular Investigation of Cancer (LIMC), Faculty of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Brazil.
Department of Radiology, Cellular and Molecular Imaging Laboratory, Detroit, MI, USA.
Department of Neurosurgery, Henry Ford Health System, Detroit, MI, USA.
Department of Pharmacology, New York Medical College, Valhalla, NY, USA.
Department of Neurology and Radiology, Henry Ford Health System, Detroit, MI, USA.

BACKGROUND: Due to the hypervascular nature of glioblastoma (GBM), antiangiogenic treatments, such as vatalanib, have been added as an adjuvant to control angiogenesis and tumor growth. However, evidence of progressive tumor growth and resistance to antiangiogenic treatment has been observed. To counter the unwanted effect of vatalanib on GBM growth, we have added a new agent known as N-hydroxy-N'-(4-butyl-2 methylphenyl)formamidine (HET0016), which is a selective inhibitor of 20-hydroxyeicosatetraenoic acid (20-HETE) synthesis. The aims of the studies were to determine 1) whether the addition of HET0016 can attenuate the unwanted effect of vatalanib on tumor growth and 2) whether the treatment schedule would have a crucial impact on controlling GBM. METHODS: U251 human glioma cells (4x10(5)) were implanted orthotopically. Two different treatment schedules were investigated. Treatment starting on day 8 (8-21 days treatment) of the tumor implantation was to mimic treatment following detection of tumor, where tumor would have hypoxic microenvironment and well-developed neovascularization. Drug treatment starting on the same day of tumor implantation (0-21 days treatment) was to mimic cases following radiation therapy or surgery. There were four different treatment groups: vehicle, vatalanib (oral treatment 50 mg/kg/d), HET0016 (intraperitoneal treatment 10 mg/kg/d), and combined (vatalanib and HET0016). Following scheduled treatments, all animals underwent magnetic resonance imaging on day 22, followed by euthanasia. Brain specimens were equally divided for immunohistochemistry and protein array analysis. RESULTS: Our results demonstrated a trend that HET0016, alone or in combination with vatalanib, is capable of controlling the tumor growth compared with that of vatalanib alone, indicating attenuation of the unwanted effect of vatalanib. When both vatalanib and HET0016 were administered together on the day of the tumor implantation (0-21 days treatment), tumor volume, tumor blood volume, permeability, extravascular and extracellular space volume, tumor cell proliferation, and cell migration were decreased compared with that of the vehicle-treated group. CONCLUSION: HET0016 is capable of controlling tumor growth and migration, but these effects are dependent on the timing of drug administration. The addition of HET0016 to vatalanib may attenuate the unwanted effect of vatalanib.

Neurology

Shehadah A, Kassis H, **Li C**, **Zhang Y**, **Cui Y**, **Roberts C**, **Sadry N**, **Liu X**, **Chopp M**, and Zhang ZG. Class IIa histone deacetylases are essential for neuronal remodeling and functional recovery after stroke *Stroke* 2016; 47PMID: Not assigned. Abstract

A. Shehadah, Vascular Nerurology, NIH/NINDS, Bethesda, United States

Background: Histone deacetylases (HDACs) have recently emerged as a potential therapeutic target for stroke. We have previously demonstrated that stroke induces nuclear shuttling of class IIa HDAC isoform 4 (but not 5) in neurons. In this study, using a rat model for middle cerebral artery occlusion (MCAO), we tested whether class IIa HDACs are essential to endogenous neuronal remodeling and functional recovery after stroke. Methods: Adult male Wistar rats (n=13/group) were subjected to MCAO. At 1 day after MCAO, rats were gavaged with: SAHA (non-selective HDAC inhibitor, 25 mg/kg/d), MC1568 (selective inhibitor of class IIa HDAC, 25 mg/kg/2d) or vehicle for 7 days. A battery of behavioral tests was performed. Lesion volume was measured at 28 days after MCAO and immunohistochemistry was performed using antibodies against microtubule associated protein 2 (MAP2, dendrites), phosphorylated neurofilament heavy chain (pNFH, axons) and myelin basic protein (MBP, myelination). Nuclear HDAC activity was measured using a colorimetric assay. Results: Stroke significantly increased total HDAC activity in the ipsilateral hemisphere compared to the contralateral hemisphere (2 fold; $p<0.05$). Stroke-increased HDAC activity was significantly decreased by the administration of SAHA, as well as by MC1568. However, SAHA, but not MC1568, significantly improved functional outcome compared to vehicle-control. Selective class IIa inhibition with MC1568 increased mortality and lesion volume (43% vs. 35% in vehicle-control, $p<0.05$). In addition, MC1568 significantly decreased MAP2, pNFH and MBP immunoreactivity in the peri-infarct cortex compared to vehicle-control. Quantitative RT-PCR analysis of neurons isolated by laser capture microdissection revealed that MC1568, but not SAHA, downregulated CREB and c-FOS expression ($p<0.05$). Additionally, MC1568 decreased the expression of phosphorylated CREB (active) in neurons compared to vehicle-control. Conclusions: Selective inhibition of class IIa HDACs impairs neuronal remodeling and neurological outcome. Inactivation of CREB and c-FOS by MC1568 likely contributes to this detrimental effect. Thus, class IIa HDACs play a crucial role in regulating brain remodeling and functional recovery after stroke.

Neurology

Wang D, Li T, Wei H, Wang Y, Yang G, Tian Y, Zhao Z, Wang L, Yu S, Zhang Y, **Chen J**, Jiang R, and Zhang JN. Atorvastatin enhances angiogenesis to reduce subdural hematoma in a rat model *J Neurol Sci* 2016; 362:91-99. PMID: 26944125. Full Text

Department of Neurosurgery, Tianjin Medical University, General Hospital, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: 54454241@qq.com.
Department of Neurosurgery, Tianjin Medical University, General Hospital, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: lt19880619@sina.com.
Department of Neurosurgery, Tianjin Medical University, General Hospital, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: huijiewei@126.com.
Department of Neurosurgery, Tianjin Medical University, General Hospital, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: sinuosiwo@sina.com.
Department of Neurosurgery, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: yangguili1985@163.com.
Department of Neurosurgery, Tianjin Medical University, General Hospital, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: yetian1986@gmail.com.
Department of Neurosurgery, Tianjin Medical University, General Hospital, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: ZilongZ@BloodWorksNW.org.
Department of Neurosurgery, Tianjin 5th Center Hospital, Tianjin, China. Electronic address: 757171007@qq.com.
Department of Neurosurgery, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: yshpvip@sina.com.
Department of Neurosurgery, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: friskyzyq@163.com.
Department of Neurology, Henry Ford Hospital, Detroit, USA. Electronic address: jieli@neuro.hfh.edu.

Department of Neurosurgery, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: jiang116216@163.com.
Department of Neurosurgery, Tianjin Medical University, General Hospital, Tianjin Key Laboratory of Injuries, Variations and Regeneration of Nervous System, Tianjin Neurological Institute, Tianjin, China. Electronic address: jianningzhang@hotmail.com.

BACKGROUND AND PURPOSE: Statins are active in reducing plasma lipids, suppressing inflammation and promoting angiogenesis. Because angiogenesis is critical for the absorbance of subdural hematoma (SDH), we hypothesize that atorvastatin promotes angiogenesis to enhance hematoma absorption. METHODS: SDH was induced in adult Wistar rats and treated with 3mg/kg, 8mg/kg of atorvastatin, or vehicle saline daily for 7days. The treated rats were examined for the level of CD34+/CD133+ endothelial progenitor cells (EPCs) in the circulation by flow cytometry, hematoma volumes by magnetic resonance imaging (MRI), and changes in cognitive functions. We also examined angiogenesis in the hematoma wall by transmission electronic microscopy and immunohistochemistry for the expression of vascular endothelial growth factor (VEGF), matrix metalloprotease 9 (MMP 9) and angiopoietin. RESULTS: SDH volume was significantly reduced and neurological deficits improved in rats receiving the low dose atorvastatin compared to those receiving either the high dose of atorvastatin or saline. Consistent with these outcome measures, the low dose atorvastatin increased the expression of angiopoient-1 and VEGF and reduced MMP9 expression in the connective tissue of the SDH wall, resulting in an increased vascular density and enhanced vascular maturation. CONCLUSIONS: The low-dose atorvastatin is effective in reducing SDH and improving neurological deficits in a rat model, primarily by promoting angiogenesis and vascular maturation.

Neurology
Yu X, Xu X, Jackson A, Sun J, Huang P, Mao Y, Chen Z, Lou M, **Jiang Q**, and Zhang M. Blood brain barrier disruption in diabetic stroke related to unfavorable outcome *Cerebrovasc Dis* 2016; 42(1-2):49-56. PMID: 26986824.
Article Request Form

Department of Radiology, The 2nd Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, China.

BACKGROUND: Diabetes mellitus (DM) is associated with a wide range of microvascular abnormalities in the brain. These include the dysfunction of the blood brain barrier (BBB). In this study, we test the hypotheses that disruption of the BBB in patients presenting with acute stroke is common in patients with DM and is related to outcome. METHODS: Sixty-two consecutive patients with ischemic stroke in the middle cerebral artery territory were enrolled within 3-7 days after onset. In ischemic lesion, BBB disruption was detected by parenchymal enhancement (PE) on 5 min delayed post-contrast T1 weighted imaging. National Institute of Health Stroke Score (NIHSS) assessed neurologic impairment on admission. Clinical outcome at 3 months was classified as unfavorable if the modified Rankin scale was >1. The independent factors associated with clinical outcome were analyzed using multivariate logistic regression analysis and OR with its 95% CIs were estimated. RESULTS: An unfavorable stroke outcome was found in 19 diabetic patients and 21 non-diabetic patients. Diabetic patients had a significantly higher frequency of PE than non-diabetic patients (58.6 vs. 27.3%, p = 0.013) and DM was independently associated with PE (OR 4.40; 95% CI 1.22-15.83; p = 0.023). PE was significantly more common in diabetic patients with unfavorable stroke outcome (73.7%) than in other 3 subgroups: diabetic patients with favorable stroke outcome (30.0%), non-diabetic patients with favorable stroke outcome (38.1%) and unfavorable stroke outcome (8.3%; p = 0.002). PE was independently associated with unfavorable outcome (UO) in diabetic stroke (DS; OR 7.04; 95% CI 1.20-41.52; p = 0.031). Admission NIHSS score was associated with UO in non-DS (NDS) (OR 1.71; 95% CI 1.10-2.66; p = 0.017). CONCLUSIONS: Compared with NDS, DS had increased BBB disruption defined by the presence of PE. A different form of the relationship between admission NIHSS and UO in NDS, BBB disruption was related with UO in diabetic patients after stroke.

Neurology
Zhang RL, **Chopp M**, Pan W, Zhang X, **Liu X**, **Wei M**, **Roberts C**, **Wang X**, and **Zhang ZG**. Inducible conditional deletion of dicer in neural progenitor cells induces cognitive impairment *Stroke* 2016; 47PMID: Not assigned. Abstract

R.L. Zhang, Henry Ford Hosp, Detroit, United States

Background: MicroRNAs regulate adult neurogenesis. Conditional deletion of Dicer in neural stem cells (NSCs) causes postnatal death. The functional role of Dicer in adult neurogenesis remains unknown. Using mice with inducible conditional knock-down of Dicer in adult NSCs, we investigated the effect of ablation of Dicer on neurogenesis and cognitive function. Methods and Results: Young adult Ascl1-CreER:Dicerflox/flox mice (Dicer Cko, n= 32) were administered (i.p) with tamoxifen daily for 5 consecutive days and age matched wild-type litters (n= 30) were used as control. The mice were sacrificed at 2, 14 or 30 days after injection. Immunstaining was performed to

detect phenotypes of subventricular zone (SVZ) cells. An array of cognitive tests including Morris Water Maze, odor-based novelty recognition, and sociability test were performed. Primary NPCs were isolated from the SVZ for vitro studies. Compared to control, Dicer CKo had 54% reduction of Dicer protein in NPCs. Cognitive tests showed that CKo spent 35% less time in the correct quadrant ($p<0.05$) of Morris Water Maze, significantly reduced time exploring new odor objects, 44 ±10% ($p<0.05$) in Cko animals compared with 77 ±10% in control, and significantly less time with other mice when they encountered a strange mouse during the sociability test (70 ± 9 vs 118 ±7 seconds, $p<0.05$). CKo significantly ($p<0.05$) reduced BrdU+ (16±2% vs 24±3%), and Ki67+ NPCs (25±3% vs 33±3%), doublecortin (DCX)+ neuroblasts (2± 0.6% vs 6± 1%), and Ng2+ oligodendrocyte progenitor cells (OPCs, 8±1% vs 12± 2%) in the SVZ. However, Dicer CKo animals exhibited a significant increase ($p<0.05$) of apoptotic NPCs (14±0.5% vs 10 ±0.3%). These in vivo findings were consistent with data from cultured NPCs. Dicer CKo also showed significant ($p<0.05$) reduction DCX+ neuroblasts in the rostral migratory stream and APC+ mature oligodendrocytes in the corpus callosum. Conclusion: Our data demonstrated that inducible conditional ablation of Dicer in Ascl1 lineage NPCs impairs neurogenesis and oligodendrogenesis in adult SVZ niche and white matter, and induces cognitive impairment, indicating that Dicer in adult NPCs is essential for maintaining neurogenesis and oligodendrogenesis and is important for cognitive function.

Neurology

Zhang Y, **Chopp M**, **Liu XS**, **Katakowski M**, **Wang X**, Tian X, Wu D, and **Zhang ZG**. Exosomes derived from mesenchymal stromal cells promote axonal growth of cortical neurons *Mol Neurobiol* 2016;PMID: 26993303. Full Text

Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI, 48202, USA.
Department of Physics, Oakland University, Rochester, MI, 48309, USA.
Troy High School, Troy, MI, 48098, USA.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI, 48202, USA.
zhazh@neuro.hfh.edu.

Treatment of brain injury with exosomes derived from mesenchymal stromal cells (MSCs) enhances neurite growth. However, the direct effect of exosomes on axonal growth and molecular mechanisms underlying exosome-enhanced neurite growth are not known. Using primary cortical neurons cultured in a microfluidic device, we found that MSC-exosomes promoted axonal growth, whereas attenuation of argonaut 2 protein, one of the primary microRNA (miRNA) machinery proteins, in MSC-exosomes abolished their effect on axonal growth. Both neuronal cell bodies and axons internalized MSC-exosomes, which was blocked by botulinum neurotoxins (BoNTs) that cleave proteins of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex. Moreover, tailored MSC-exosomes carrying elevated miR-17-92 cluster further enhanced axonal growth compared to native MSC-exosomes. Quantitative RT-PCR and Western blot analysis showed that the tailored MSC-exosomes increased levels of individual members of this cluster and activated the PTEN/mTOR signaling pathway in recipient neurons, respectively. Together, our data demonstrate that native MSC-exosomes promote axonal growth while the tailored MSC-exosomes can further boost this effect and that tailored exosomes can deliver their selective cargo miRNAs into and activate their target signals in recipient neurons. Neuronal internalization of MSC-exosomes is mediated by the SNARE complex. This study reveals molecular mechanisms that contribute to MSC-exosome-promoted axonal growth, which provides a potential therapeutic strategy to enhance axonal growth.

Neurosurgery

Alentorn A, Hoang-Xuan K, and **Mikkelsen T**. Presenting signs and symptoms in brain tumors *Handb Clin Neurol* 2016; 134:19-26. PMID: 26948346. Article Request Form

Department of Neurology 2, Groupe Hospitalier Pitie-Salpetriere, Paris, France; Inserm Experimental Neuro-Oncology Laboratory, Institut du Cerveau et de la Moelle, Universite Pierre et Marie Curie, Paris, France.
Department of Neurology 2, Groupe Hospitalier Pitie-Salpetriere, Paris, France; Inserm Experimental Neuro-Oncology Laboratory, Institut du Cerveau et de la Moelle, Universite Pierre et Marie Curie, Paris, France. Electronic address: khe.hoang-xuan@psl.aphp.fr.
Hermelin Brain Tumor Center and Departments of Neurology and Neurosurgery, Henry Ford Hospital, Detroit, MI, USA; Wayne State University, Detroit, MI, USA.

Focal symptoms and signs occurring during brain tumor clinical presentation are dependent on a number of factors. Location and rate of growth are the most critical, followed by overall lesion size and nature, whether infiltrating or causing the displacement of neural structures, but also the presence or extent of associated pathology, including edema, hemorrhage, vascular compromise, and cerebrospinal fluid obstruction. Mechanisms of presenting symptomatology can be divided into tumor and peritumoral factors. Tumor factors include histology, for example, in

that seizures are common in patients with certain low-grade gliomas. Peritumoral factors, including regional hypoxia and ionic changes in the peritumoral zone, may influence neuronal activity and extracellular glutamate may be associated with neuronal hyperexcitability. Blood-brain barrier breakdown may predispose to seizure and localized neuronal dysfunction. Finally, signs and symptoms in brain tumors can be generalized, associated with increased intracranial brain pressure, but can also be localized, based on the involvement of the major structures of the central nervous system.

Neurosurgery

Li L, **Chopp M**, **Ding G**, **Qu C**, **Nejad-Davarani SP**, **Davoodi-Bojd E**, **Li Q**, **Mahmood A**, and **Jiang Q**. Diffusion-derived mri measures of longitudinal microstructural remodeling induced by marrow stromal cell therapy after TBI *J Neurotrauma* 2016;PMID: 26993214. Full Text

Henry Ford Hospital, Neurology , 2799 West Grand Boulevard , Detroit, Michigan, United States , 48202 ; lli2@hfhs.org.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States.
Oakland University, Physics, Rochester, Michigan, United States ; MCHOPP1@hfhs.org.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; gding1@hfhs.org.
Henry Ford Hospital, Neurosurgery, Detroit, Michigan, United States ; cqu1@hfhs.org.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; siamak@umich.edu.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; esdavoodi@gmail.com.
Henry Ford Hospital, Neurology, Detroit, Michigan, United States ; QLI1@hfhs.org.
Henry Ford Hospital, Neurosurgery, Detroit, Michigan, United States ; amahmoo2@hfhs.org.
Oakland University, Physics, Rochester, Michigan, United States ; QJIANG1@hfhs.org.

Using magnetic resonance imaging (MRI) and an animal model of traumatic brain injury (TBI), we investigated the capacity and sensitivity of diffusion-derived measures, fractional anisotropy (FA) and diffusion entropy, to longitudinally identify structural plasticity in the injured brain in response to the transplantation of human bone marrow stromal cells (hMSCs). Male Wistar rats (300-350g, n=30) were subjected to controlled cortical impact TBI. At 6 hours or 1 week post-injury, these rats were intravenously injected with 1 ml of saline (at 6 hours or 1 week, n=5/group) or with hMSCs in suspension (3x106 hMSCs, at 6 hours or 1 week, n=10/group). In vivo MRI measurements and sensorimotor function estimates were performed on all animals pre-injury, 1 day, and weekly for 3 weeks post-injury. Bielshowsky's silver and Luxol fast blue staining were used to reveal the axon and myelin status, respectively, with and without cell treatment after TBI. Based on image data and histological observation, regions of interest encompassing the structural alterations were made and the values of FA and entropy were monitored in these specific brain regions. Our data demonstrate that administration of hMSCs after TBI leads to enhanced white matter reorganization particularly along the boundary of contusional lesion which can be identified by both FA and entropy. Compared to the therapy carried out at 1 week post-TBI, cell intervention executed at 6 hours expedites the brain remodeling process and results in an earlier functional recovery. While FA and entropy present a similar capacity to dynamically detect the microstructural changes in the tissue regions with predominant orientation of fiber tracts, entropy exhibits a sensitivity superior to FA, in probing the structural alterations in the tissue areas with complex fiber patterns.

Neurosurgery

Li M, Jia Q, Chen T, Zhao Z, **Chen J**, and Zhang J. The role of vascular endothelial growth factor and vascular endothelial growth inhibitor in clinical outcome of traumatic brain injury *Clin Neurol Neurosurg* 2016; 144:7-13. PMID: 26945876. Full Text

Department of Neurosurgery, Tianjin Neurological Institute, Tianjin Medical University General Hospital, Tianjin 300052, PR China.
Department of Neurosurgery, Tianjin Huanhu Hospital, Tianjin 300060, PR China.
Department of Neurosurgery, Second Hospital of Tianjin Medical University, Tianjin 300211, PR China.
Department of Neurology, Henry Ford Hospital, Detroit MI 48202, USA.
Department of Neurosurgery, Tianjin Neurological Institute, Tianjin Medical University General Hospital, Tianjin 300052, PR China. Electronic address: 812879698@qq.com.

OBJECTIVES: Tumor necrosis factor superfamily-15 (TNFSF15) also known as vascular endothelial growth inhibitor (VEGI) is a cytokine that modulates anti-angiogenesis and inflammation. Vascular endothelial growth factor (VEGF) promotes angiogenesis and vascular permeability following traumatic brain injury (TBI). The balance of VEGF and VEGI may play a key role in the maintenance of vascular and immune system homeostasis in the brain. However, the dynamic changes of circulating VEGF and VEGI after traumatic brain injury (TBI) and the correlation between plasma

VEGF and plasma VEGI remains obscure. In this study, we were to investigate whether circulating VEGF and VEGI can be used as prognostic markers for patients with TBI. PATIENTS AND METHODS: A prospective clinical study was conducted in two neurosurgical intensive care units of Tianjin Medical University General Hospital and Tianjin Huanhu Hospital (Tianjin, China). 40 patients and 30 healthy controls were recruited. The recruited subjects were aged over 18 with randomized gender and GCS. 1mL of blood was withdrawn on 1, 4, 7, 14, and 21days after TBI. Blood samples were centrifuged at 3000rpm and the supernatants were used to measure VEGF and VEGI by ELISA kit. RESULTS: 1) Circulating VEGF in TBI patients was decreased on the 1st day after TBI, then climbed up on the 4th day, reaching a maximum level on the14th day after TBI, as compared to normal controls. VEGF level returned to normal level on 21th day after TBI. 2) Circulating VEGI in TBI patients was decreased on the 1st and 4th day after TBI, then climbed up on the 7th day after TBI, reaching a maximum level on 14th day after TBI, as compared to normal controls. VEGI levels declined to normal level on 21th day after TBI. 3) There was a significant positive correlation between circulating VEGF and VEGI. 4) However, TBI patients whose conditions had improved exhibited lower VEGF levels 7days after TBI when compared to TBI patients whose condition had deteriorated. Survivors exhibited higher VEGI levels 7days after TBI when compared to non-survivors. 5)TBI patients whose condition had improved exhibited higher VEGI levels when compared to TBI patients whose condition had deteriorated 21days after TBI. Patients with mild TBI exhibited higher VEGI levels than those with moderate and severe TBI 21days after TBI. 6) A lower rate of recovery and higher hospital mortality were found in patients with VEGF/VEGI ratio>/=2.366 as compared to those with VEGF/VEGI ratio<2.366 7days after TBI. CONCLUSIONS: 1) VEGF level positively correlates with VEGI after TBI. 2) The elevation of VEGF exhibits an adverse effect from 4 to 14days after TBI while it has an advantageous effect from 14 to 21days after TBI. Increasing VEGI levels are beneficial in recovery after TBI. Controlling the ratio of VEGF/VEGI may benefit the clinical outcome following TBI.

Neurosurgery

Nagaraja TN, **Keenan KA**, **Ewing JR**, and **Knight RA**. Surrogate MRI signatures for contrast enhanced imaging that predict acute blood-brain barrier damage in ischemia-reperfusion *Stroke* 2016; 47PMID: Not assigned. Abstract

T.N. Nagaraja, Neurosurgery, Henry Ford Hosp, Detroit, United States

Background and Purpose: Contrast-enhanced magnetic resonance imaging (CE-MRI) is used to measure blood-brain barrier (BBB) damage after stroke, but is contra-indicated in patients with compromised kidney function. Thus, there is a need for non-contrast MRI techniques that portend BBB damage. We examined the relationships between CE-MRI and non-contrast MRI measures to test whether the latter serve as surrogate biomarkers of BBB damage in acute stroke. Methods: Male Wistar rats (~300 g; N=22) were subjected to focal cerebral ischemia-reperfusion using a middle cerebral artery suture occlusion model. They were imaged in a 7 Tesla Bruker MRI system. The parameters measured were: cerebral blood flow (CBF), T2, T1 and T1-under-off resonance-saturation (T1sat). All data except CBF were expressed as ipsilateral-to-contralateral ratios (I-C). Post-reperfusion BBB damage was measured by CE-MRI via blood-to-brain forward volumetric transfer constant (Ktrans) maps. CBF, T2, T1 and T1sat were compared to Ktrans from the same region of interest (ROI). Scatterplots with Pearson correlation coefficients (r) were used to compare the data and significances inferred at $p<0.05$. Results: Preoptic area (PoA) and striatum (Str) were found ischemic in nearly all rats, with neocortical areas lesser affected. During occlusion, CBF in PoA and Str were 26±15 and 42±18 ml/100g/min (20-25% of contralateral side), respectively. After reperfusion, CBF was 78±27 and 99±50 ml/100g/min in PoA and Str, respectively. Contrast enhancement or BBB damage was observed in the PoA in all 22 rats and in 17 in Str. The I-C values of T2, T1 and T1sat elevated between occlusion and reperfusion periods and were associated with increased Ktrans values ($p=0.05$). The extent of CBF reduction during occlusion was significant and correlated inversely with increased Ktrans ($r=-0.5$; $p=0.03$), but this relationship was lost after reperfusion ($r=0.3$; $p=0.3$). Conclusions: The data suggest that reduction in CBF during occlusion and post-reperfusion elevation of T2, T1, and T1sat (i.e. vasogenic edema) are reliable predictors of impending BBB damage in acute stroke. With further confirmation, non-contrast based MRI evaluation of the BBB in acute stroke may be utilized in cases where CE-MRI is not possible.

Neurosurgery

Reinard K, **Nerenz DR**, **Basheer A**, **Tahir R**, Jelsema T, **Schultz L**, **Malik G**, **Air EL**, and **Schwalb JM**. Racial disparities in the diagnosis and management of trigeminal neuralgia *J Neurosurg* 2016:1-7. PMID: 26967783. Full Text

Department of Neurosurgery, Henry Ford Medical Group, and.
Wayne State University School of Medicine, Detroit, Michigan.

OBJECTIVE A number of studies have documented inequalities in care and outcomes for a variety of clinical conditions. The authors sought to identify racial and socioeconomic disparities in the diagnosis and treatment of

trigeminal neuralgia (TN), as well as the potential underlying reasons for those disparities, which could serve as areas of focus for future quality improvement initiatives. METHODS The medical records of patients with an ICD-9 code of 350.1, signifying a diagnosis of TN, at the Henry Ford Medical Group (HFMG) in the period from 2006 to 2012 were searched, and clinical and socioeconomic data were retrospectively reviewed. Analyses were conducted to assess potential racial differences in subspecialty referral patterns and the specific type of treatment modality undertaken for patients with TN. RESULTS The authors identified 652 patients eligible for analysis. Compared with white patients, black patients were less likely to undergo percutaneous ablative procedures, stereotactic radiosurgery, or microvascular decompression ($p < 0.001$). However, there was no difference in the likelihood of blacks and whites undergoing a procedure once they had seen a neurosurgeon (67% vs 70%, respectively; $p = 0.712$). Blacks and whites were equally likely to be seen by a neurologist or neurosurgeon if they were initially seen in either the emergency room (38% vs 37%, $p = 0.879$) or internal medicine (48% vs 50%, $p = 0.806$). Among patients diagnosed (268 patients) after the 2008 publication of the European Federation of Neurological Societies and the American Academy of Neurology guidelines for medical therapy for TN, fewer than 50% were on medications sanctioned by the guidelines, and there were no statistically significant racial disparities between white and black patients ($p = 0.060$). CONCLUSIONS According to data from a large database from one of the nation's largest comprehensive health care systems, there were significant racial disparities in the likelihood of a patient undergoing a procedure for TN. This appeared to stem from outside HFMG from a difference in referral patterns to the neurologists and neurosurgeons.

Neurosurgery

Reinard KA, **Cook DM**, **Zakaria HM**, **Basheer AM**, **Chang VW**, and **Abdulhak MM**. A cohort study of the morbidity of combined anterior-posterior cervical spinal fusions: incidence and predictors of postoperative dysphagia *Eur Spine J* 2016;PMID: 26972082. Full Text

Department of Neurosurgery, K-11, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, 48202, USA. kreinar1@hfhs.org.
Division of Speech and Language Pathology, Henry Ford Hospital, Detroit, MI, USA.
Department of Neurosurgery, K-11, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, 48202, USA.

PURPOSE: To identify risk factors that may lead to the development of dysphagia after combined anterior and posterior (360 degrees) cervical fusion surgery. METHODS: A single center, retrospective analysis of patients who had same-day, 360 degrees fusion at Henry Ford Hospital between 2008 and 2012 was performed. Variables analyzed included demographics, medical co-morbidities, levels fused, and degree of dysphagia. RESULTS: The overall dysphagia rate was 37.7 %. Patients with dysphagia had a longer mean length of stay ($p < 0.001$), longer mean operative time ($p < 0.001$), greater intraoperative blood loss ($p = 0.002$), and fusion above the fourth cervical vertebra, C4, ($p = 0.007$). There were no differences in the rates of dysphagia when comparing patients undergoing primary or revision surgery ($p = 0.554$). CONCLUSION: Prolonged surgery and fusion above C4 lead to higher rates of dysphagia after 360 degrees fusions. Prior anterior cervical fusion does not increase the risk of dysphagia development.

Neurosurgery

Shankar A, Borin TF, Iskander A, Varma NR, Achyut BR, Jain M, **Mikkelsen T**, Guo AM, Chwang WB, Ewing JR, **Bagher-Ebadian H**, and Arbab AS. Combination of vatalanib and a 20-HETE synthesis inhibitor results in decreased tumor growth in an animal model of human glioma *Onco Targets Ther* 2016; 9:1205-1219. PMID: 27022280. Full Text

Tumor Angiogenesis Laboratory, Cancer Center, Georgia Regents University, Augusta, GA, USA.
Laboratory of Molecular Investigation of Cancer (LIMC), Faculty of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Brazil.
Department of Radiology, Cellular and Molecular Imaging Laboratory, Detroit, MI, USA.
Department of Neurosurgery, Henry Ford Health System, Detroit, MI, USA.
Department of Pharmacology, New York Medical College, Valhalla, NY, USA.
Department of Neurology and Radiology, Henry Ford Health System, Detroit, MI, USA.

BACKGROUND: Due to the hypervascular nature of glioblastoma (GBM), antiangiogenic treatments, such as vatalanib, have been added as an adjuvant to control angiogenesis and tumor growth. However, evidence of progressive tumor growth and resistance to antiangiogenic treatment has been observed. To counter the unwanted effect of vatalanib on GBM growth, we have added a new agent known as N-hydroxy-N'-(4-butyl-2 methylphenyl)formamidine (HET0016), which is a selective inhibitor of 20-hydroxyeicosatetraenoic acid (20-HETE) synthesis. The aims of the studies were to determine 1) whether the addition of HET0016 can attenuate the unwanted effect of vatalanib on tumor growth and 2) whether the treatment schedule would have a crucial impact on controlling GBM. METHODS: U251 human glioma cells (4x10(5)) were implanted orthotopically. Two different

treatment schedules were investigated. Treatment starting on day 8 (8-21 days treatment) of the tumor implantation was to mimic treatment following detection of tumor, where tumor would have hypoxic microenvironment and well-developed neovascularization. Drug treatment starting on the same day of tumor implantation (0-21 days treatment) was to mimic cases following radiation therapy or surgery. There were four different treatment groups: vehicle, vatalanib (oral treatment 50 mg/kg/d), HET0016 (intraperitoneal treatment 10 mg/kg/d), and combined (vatalanib and HET0016). Following scheduled treatments, all animals underwent magnetic resonance imaging on day 22, followed by euthanasia. Brain specimens were equally divided for immunohistochemistry and protein array analysis. RESULTS: Our results demonstrated a trend that HET0016, alone or in combination with vatalanib, is capable of controlling the tumor growth compared with that of vatalanib alone, indicating attenuation of the unwanted effect of vatalanib. When both vatalanib and HET0016 were administered together on the day of the tumor implantation (0-21 days treatment), tumor volume, tumor blood volume, permeability, extravascular and extracellular space volume, tumor cell proliferation, and cell migration were decreased compared with that of the vehicle-treated group. CONCLUSION: HET0016 is capable of controlling tumor growth and migration, but these effects are dependent on the timing of drug administration. The addition of HET0016 to vatalanib may attenuate the unwanted effect of vatalanib.

Nursing

Gammon HM, **Shelton CB**, **Siegert C**, **Dawson C**, **Sexton E**, **Burmeister C**, **Gnam G**, and **Siddiqui A**. Self-turning for pressure injury prevention *Wound Medicine* 2016; 12:15-18. PMID: Not assigned Article Request Form

A. Siddiqui, Division of Plastic Surgery, K-16, Henry Ford Hospital, Detroit, United States

The study objective was to determine if hospitalized patients who are designated as self-turn would reposition themselves appropriately in the acute care setting. This was a prospective case series in a general practice unit of an 800-bed urban tertiary care hospital. Patients were instructed on the importance of mobility for pressure ulcer prevention and subsequently monitored on a continuous bedside pressure mapping device. Primary outcomes included intervals of inactivity and pressure ulcer incidence. During the 3-month study interval, only 2 patients had a documented 4-h interval without measurable repositioning. None of the 101 consecutive patients enrolled in the study developed pressure ulcers. General practice unit patients that are given proper instruction and designated as self-turn can reliably be considered low-risk for hospital acquired pressure ulcers. Based on our prospective study, patients designated as self-turn do reposition themselves.

Obstetrics, Gynecology and Women's Health Services

Hijaz M, Das S, **Mert I**, Gupta A, **Al-Wahab Z**, **Tebbe C**, **Dar S**, **Chhina J**, **Giri S**, **Munkarah A**, Seal S, and **Rattan R**. Folic acid tagged nanoceria as a novel therapeutic agent in ovarian cancer *BMC Cancer* 2016; 16(1):220. PMID: 26979107. Full Text

Division of Gynecology Oncology, Department of Women's Health, Henry Ford Hospital, Detroit, MI, USA.
Advanced Materials Processing and Analysis Center, Nanoscience and Technology Center, Materials Science and Engineering, University of Central Florida, Orlando, FL, USA.
Wayne State University, Detroit, MI, USA.
Department of Neurology, Henry Ford Hospital, Detroit, MI, USA.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA.
College of Medicine, University of Central Florida, Orlando, FL, USA.
Division of Gynecology Oncology, Department of Women's Health, Henry Ford Hospital, Detroit, MI, USA. rrattan1@hfhs.org.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. rrattan1@hfhs.org.

BACKGROUND: Nanomedicine is a very promising field and nanomedical drugs have recently been used as therapeutic agents against cancer. In a previous study, we showed that Nanoceria (NCe), nanoparticles of cerium oxide, significantly inhibited production of reactive oxygen species, cell migration and invasion of ovarian cancer cells in vitro, without affecting cell proliferation and significantly reduced tumor growth in an ovarian cancer xenograft nude model. Increased expression of folate receptor-alpha, an isoform of membrane-bound folate receptors, has been described in ovarian cancer. To enable NCe to specifically target ovarian cancer cells, we conjugated nanoceria to folic acid (NCe-FA). Our aim was to investigate the pre-clinical efficacy of NCe-FA alone and in combination with Cisplatin. METHODS: Ovarian cancer cell lines were treated with NCe or NCe-FA. Cell viability was assessed by MTT and colony forming units. In vivo studies were carried in A2780 generated mouse xenografts treated with 0.1 mg/Kg NCe, 0.1 mg/Kg; NCe-FA and cisplatinum, 4 mg/Kg by intra-peritoneal injections. Tumor weights and burden scores were determined. Immunohistochemistry and toxicity assays were used to evaluate treatment effects. RESULTS: We show that folic acid conjugation of NCe increased the cellular NCe internalization and inhibited cell

proliferation. Mice treated with NCe-FA had a lower tumor burden compared to NCe, without any vital organ toxicity. Combination of NCe-FA with cisplatinum decreased the tumor burden more significantly. Moreover, NCe-FA was also effective in reducing proliferation and angiogenesis in the xenograft mouse model. CONCLUSION: Thus, specific targeting of ovarian cancer cells by NCe-FA holds great potential as an effective therapeutic alone or in combination with standard chemotherapy.

Obstetrics, Gynecology and Women's Health Services

Munkarah A, Mert I, **Chhina J**, **Hamid S**, **Poisson L**, **Hensley-Alford S**, **Giri S**, and **Rattan R**. Targeting of free fatty acid receptor 1 in EOC: A novel strategy to restrict the adipocyte-EOC dependence *Gynecol Oncol* 2016; 141(1):72-79. PMID: 27016232. Full Text

Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: amunkar1@hfhs.org.
Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: imert@med.wayne.edu.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA. Electronic address: jchhina1@hfhs.org.
Department of Neurology, Henry Ford Hospital, USA. Electronic address: hsuhail1@hfhs.org.
Center for Bioinformatics, Henry Ford Hospital, USA; Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: lpoisso1@hfhs.org.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: salford1@hfhs.org.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA; Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: sgiri1@hfhs.org.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: rrattan1@hfhs.org.

OBJECTIVES: Adipocyte derived free fatty acids (FFA) promote epithelial ovarian cancer (EOC) by acting as a fuel source to support the energy requirement of the cancer cells. FFA may also exert biological effects through signaling pathways. Recently, a family of FFA activated G-protein coupled receptors (FFAR/GPCRs) was identified. Our objective was to investigate the role of FFAR/GPCRs in EOC and assess their potential as therapeutic targets. METHODS: The mRNA (RT-PCR) expression of FFAR/GPCR family members (FFAR1/GPR40; FFAR2/GPR43, FFAR3/GPR41, FFAR4/GPR120 and GPR84) was examined in: (1) a syngeneic mouse model of EOC fed high energy diet (60% fat) or regular diet (30% fat), (2) EOC cell lines exposed to free fatty acids and (3) specimens from 13 histologically normal ovaries and 28 high grade ovarian serous carcinomas. The GPR 40 antagonist, GW1100, was used to inhibit FFAR1/GPR40 and cell survival was assayed by MTT in various cell lines. RESULTS: High Grade Serous carcinoma specimens expressed significantly increased GPR40 compared to normal ovaries (p=0.0020). Higher expression was noted in advanced stage disease. ID8 ovarian tumors from mice fed with high fat diet also showed higher GPR40 expression. Exposing EOC cells to FFAs, increased GPR40 expression. Treatment of EOC cell lines with GW100 resulted in growth inhibition and was associated with an alteration in their energy metabolism. CONCLUSION: FFA-induced cancer cell growth may be partly mediated through FFAR1/GPR40. Targeting of FFAR1/GPR40 may be an attractive treatment strategy in EOC, and possibly offers a targeted treatment for a subset of EOC patients.

Ophthalmology and Eye Care Services

Woodward MA, Bavinger JC, **Amin S**, Blachley TS, Musch DC, Lee PP, and Newman-Casey PA. Telemedicine for ophthalmic consultation services: use of a portable device and layering information for graders *J Telemed Telecare* 2016;PMID: 26936864. Full Text

Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, MI, USA
Institute for Healthcare Policy & Innovation, University of Michigan, Ann Arbor, MI, USA mariawoo@umich.edu.
Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, MI, USA.
Department of Ophthalmology, Henry Ford Health System, Detroit, MI, USA.
Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, MI, USA
Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA.
Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, MI, USA
Institute for Healthcare Policy & Innovation, University of Michigan, Ann Arbor, MI, USA.

INTRODUCTION: We compared remote, image-based patient consultations to in-person consultations at emergency department and inpatient hospital settings. METHODS: Patients evaluated by the ophthalmic consultation services (gold standard) were imaged over a two-week period. A trained study coordinator took anterior segment photographs

(AS) and posterior segment photographs (PS) with a portable camera (PictorPlus, Volk Optical, Cleveland, OH). Ophthalmologists (graders) determined photograph quality, presence of pathology, and their confidence in disease detection. At a separate session, graders reassessed photographs accompanied by a one-sentence summary of demographics and chief complaint (CHx). We computed accuracy and reliability statistics. RESULTS: We took AS photographs of 24 eyes of 15 patients and PS photographs of 39 eyes of 20 patients. The majority of images were rated as acceptable or excellent in quality (AS: 89-96%; PS: 70-75%). Graders detected AS pathology with 62-81% sensitivity based on photographs, increasing to 87-88% sensitivity with photographs plus CHx. Graders detected PS pathology with 79-86% sensitivity based on a photograph only, increasing to 100% sensitivity with photographs plus CHx. DISCUSSION: In this pilot study, there is evidence that portable ophthalmic imaging technologies could enable ophthalmologists to remotely evaluate anterior and posterior segment eye diseases with good sensitivity. The ophthalmologist could detect ocular pathology on photographs more accurately if they were provided brief clinical information.

Orthopaedics

Frisch NB, **Lynch JR**, **Banglmaier RF**, and **Silverton CD**. The effect of impact location on force transmission to the modular junctions of dual-taper modular hip implants *J Arthroplasty* 2016;PMID: 26970905. Full Text

Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan.

BACKGROUND: The purpose of this study was to investigate the effect that off-axis impaction has on stability of dual-taper modular implants as measured by forces delivered to and transmitted through the head-neck and neck-stem tapers, respectively. METHODS: One hundred forty-four impact tests were performed using 6 different directions: one on-axis and five 10 degrees off-axes. Four different simulations were performed measuring the head-neck only and 3 different neck angulations: 0 degrees , 8 degrees , and 15 degrees . A drop tower impactor delivered both on- and off-axis impaction from a constant height. Load cells positioned in the drop mass and at the head-neck (HN) or neck-stem (NS) junction measured the impact and joint forces, respectively. RESULTS: Impact force of the hammer on the head ranged from 3800-4500 N. Greatest impact force delivered to the head was typically with axial impact. However, greatest force transmission to the neck-stem junction was not necessarily with axial impacts. There was limited variability in the force measured at the NS junction for all impaction directions seen in the 8 degrees neck, whereas the 15 degrees neck had greater forces transmitted to the NS junction with off-axes impactions directed in the proximal and posterior-proximal directions. CONCLUSION: The location of the impact significantly influences the force transmitted to the head-neck and neck-stem junctions in dual-taper modular hip implants. Although axial impacts proved superior to off-axis impacts for the straight 0 degrees neck, greater force transmission with off-axis impacts for the angled necks suggests that off-axis impacts may potentially compromise the stability of dual-taper components.

Orthopaedics

Gardinier JD, Al-Omaishi S, Morris MD, and Kohn DH. PTH signaling mediates perilacunar remodeling during exercise *Matrix Biol* 2016;PMID: 26924474. Article Request Form

Bone and Joint Center, Henry Ford Hospital, Detroit, MI 48202, USA; Department of Biologic and Materials Sciences, University of Michigan, Ann Arbor, MI 48109, USA.
Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109, USA.
Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA.
Department of Biologic and Materials Sciences, University of Michigan, Ann Arbor, MI 48109, USA; Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109, USA. Electronic address: dhkohn@umich.edu.

Mechanical loading and release of endogenous parathyroid hormone (PTH) during exercise facilitate the adaptation of bone. However, it remains unclear how exercise and PTH influence the composition of bone and how exercise and PTH-mediated compositional changes influence the mechanical properties of bone. Thus, the primary purpose of this study was to establish compositional changes within osteocytes' perilacunar region of cortical bone following exercise, and evaluate the influence of endogenous PTH signaling on this perilacunar adaptation. Raman spectroscopy, scanning electron microscopy (SEM), and energy dispersive X-ray spectroscopy (EDS) were used to evaluate tissue composition surrounding individual lacuna within the tibia of 19week old male mice exposed to treadmill running for 3weeks. As a result of exercise, tissue within the perilacunar region (within 0-5mum of the lacuna wall) had a lower mineral-to-matrix ratio (MMR) compared to sedentary controls. In addition, exercise also increased the carbonate-to-phosphate ratio (CPR) across both perilacunar and non-perilacunar regions (5-10mum and 10-15mum from the lacuna walls). Tibial post-yield work had a significant negative correlation with perilacunar MMR. Inhibition of PTH activity with PTH(7-34) demonstrated that perilacunar remodeling during exercise was dependent on the cellular response to endogenous PTH. The osteocytes' response to endogenous PTH during exercise was

characterized by a significant reduction in SOST expression and significant increase in FGF-23 expression. The potential reduction in phosphate levels due to FGF-23 expression may explain the increase in carbonate substitution. Overall, this is the first study to demonstrate that adaptation in tissue composition is localized around individual osteocytes, may contribute to the changes in whole bone mechanics during exercise, and that PTH signaling during exercise contributes to these adaptations.

Orthopaedics

Keller RA, **Marshall NE**, **Bey MJ**, **Ahmed H**, **Scher CE**, **van Holsbeeck M**, and **Moutzouros V**. Pre- and postseason dynamic ultrasound evaluation of the pitching elbow *Arthroscopy* 2015; 31(9):1708-1715. PMID: 26354194. Full Text

Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan, U.S.A.. Electronic address: robkeller23@gmail.com.
Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan, U.S.A.
Bone and Joint Center, Henry Ford Health System, Detroit, Michigan, U.S.A.
Department of Radiology, Henry Ford Health System, Detroit, Michigan, U.S.A.

PURPOSE: To use ultrasound imaging to document changes over time (i.e., preseason v postseason) in the pitching elbow of high school baseball pitchers. METHODS: Twenty-two high school pitchers were prospectively followed. Pitchers were evaluated after a 2-month period of relative arm rest via preseason physical exams, dynamic ultrasound imaging of their throwing elbow, and the Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) assessment. Players were reevaluated within 1 week of their last game. Dynamic ultrasound images were then randomized, blinded to testing time point, and evaluated by 2 fellowship-trained musculoskeletal radiologists. RESULTS: Average pitcher age was 16.9 years. Average pitches thrown was 456.5, maximum velocity 77.7 mph, games pitched 7.3, and days off between starts 6.6. From preseason to postseason, there were significant increases in ulnar collateral ligament (UCL) thickness (P = .02), ulnar nerve cross-sectional area (P = .001), UCL substance heterogeneity (P = .001), and QuickDASH scores (P = .03). In addition, there was a nonsignificant increase in loaded ulnohumeral joint space (P = .10). No pitchers had loose bodies on preseason exam, while 3 demonstrated loose bodies postseason. The increase in UCL thickness was significantly associated with the number of bullpen sessions per week (P = .01). The increase in ulnar nerve cross-sectional area was significantly associated with the number of pitches (P = .04), innings pitched (P = .01), and games pitched (P = .04). CONCLUSIONS: The stresses placed on the elbow during only one season of pitching create adaptive changes to multiple structures about the elbow including UCL heterogeneity and thickening, increased ulnohumeral joint space laxity, and enlarged ulnar nerve cross-sectional area. LEVEL OF EVIDENCE: Level II prospective observational study.

Orthopaedics

Keller RA, **Marshall NE**, **Guest JM**, **Okoroha KR**, **Jung EK**, and **Moutzouros V**. Major League Baseball pitch velocity and pitch type associated with risk of ulnar collateral ligament injury *J Shoulder Elbow Surg* 2016; 25(4):671-675. PMID: 26995458. Full Text

Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, MI, USA. Electronic address: robkeller23@gmail.com.

BACKGROUND: The number of Major League Baseball (MLB) pitchers requiring ulnar collateral ligament (UCL) reconstructions is increasing. Recent literature has attempted to correlate specific stresses placed on the throwing arm to risk for UCL injury, with limited results. METHODS: Eighty-three MLB pitchers who underwent primary UCL reconstruction were evaluated. Pitching velocity and percent of pitch type thrown (fastball, curve ball, slider, and change-up) were evaluated 2 years before and after surgery. Data were compared with control pitchers matched for age, position, size, innings pitched, and experience. RESULTS: The evaluation of pitch velocity compared with matched controls found no differences in pre-UCL reconstruction pitch velocities for fastballs (91.5 vs. 91.2 miles per hour [mph], P = .69), curveballs (78.2 vs. 77.9 mph, P = .92), sliders (83.3 vs. 83.5 mph, P = .88), or change-ups (83.9 vs. 83.8 mph, P = .96). When the percentage of pitches thrown was evaluated, UCL reconstructed pitchers pitch significantly more fastballs than controls (46.7% vs. 39.4%, P = .035). This correlated to a 2% increase in risk for UCL injury for every 1% increase in fastballs thrown. Pitching more than 48% fastballs was a significant predictor of UCL injury, because pitchers over this threshold required reconstruction (P = .006). CONCLUSION: MLB pitchers requiring UCL reconstruction do not pitch at higher velocities than matched controls, and pitch velocity does not appear to be a risk factor for UCL reconstruction. However, MLB pitchers who pitch a high percentage of fastballs may be at increased risk for UCL injury because pitching a higher percent of fastballs appears to be a risk factor for UCL reconstruction.

Orthopaedics

Pepper AM, **North TW**, **Sunderland AM**, and **Davis JJ**. Intraoperative adductor canal block for augmentation of periarticular injection in total knee arthroplasty: A cadaveric study *J Arthroplasty* 2016;PMID: 26996675. Full Text

Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Function is often sacrificed for pain control after total knee arthroplasty. Motor-sparing blocks, including adductor canal block (ACB) and periarticular injection (PAI), have gained interest to address this compromise. Our study evaluates the anatomic feasibility, accuracy, and safety of intraoperative ACB as an adjunct to PAI by analyzing 3 different injection orientations and needle configurations. METHODS: Eleven cadaveric knees underwent a standard medial parapatellar arthrotomy. Blunt dissection through the suprapatellar recess was performed. Using a 10-mL syringe, various colors of dyed liquid gelatin were injected toward the proximal and distal adductor canal (AC) using 3 needle configurations. Medial dissection of the knee for each specimen was performed. The position of each needle and location of injected dye was identified and described relative to the AC. RESULTS: Accuracy of each injection orientation and/or needle configuration was different: 86% for a blunt needle in the distal AC, 57% for blunt needle in the proximal AC, and 14% for a spinal needle in the proximal AC. Puncture of the femoral artery was observed with the spinal needle 43% of the time and had the closest average proximity to the femoral artery with a distance of 5.9 mm. There were no vascular punctures using blunt needles, and the average distance from the femoral artery with proximal and distal orientation was 10.2 mm and 15.4 mm, respectively. CONCLUSION: Intraoperative ACB augmentation of PAI appears to be anatomically feasible and safe. There was decreased accuracy and increased risk of vascular puncture using a 3.5-inch spinal needle. A blunt 1.5-inch needle directed toward the distal AC had the highest accuracy while minimizing vascular injury.

Orthopaedics

Setzer TJ, Sundellranby I, **Les C**, **Pechy C**, and Beste S. Detecting malaria parasites postmortem: Experiments, results, and implications *Am J Phys Anthropol* 2016; 159:288. PMID: Not assigned. Article Request Form

T.J. Setzer, Anthropology, Oakland University, United States

Identifying malaria in bioarchaeological contexts remains a challenge to researchers studying the coevolution of pathogen and host. In this study, we conducted a controlled experiment to determine if malaria parasites can be detected with microscopy in a postmortem context. Murine models (donated by the Johns Hopkins Malaria Research Institute) infected with Plasmodium sp. were dissected ten days after death. Parasites were observed. The methods used to prepare hepatic and osseous tissues, which were embedded in paraffin and examined, using 1000x light microscopy, are presented. The effectiveness of Wright-Giemsa and QBC Fast malaria stains, which are standard stains used in histology to identify malaria parasites, are also compared. Implications for biological anthropologists, in particular bioarchaeologists and forensic anthropologist, are presented, as well as caveats concerning preservation, data collection protocols in the field, and the interpretation of results.

Orthopaedics

Wessell N, **Khalil J**, Zavatsky J, **Ghacham W**, and **Bartol S**. Verification of nerve decompression using mechanomyography *Spine J* 2016;PMID: 26940191. Full Text

Henry Ford Health System, Detroit, MI. Electronic address: nwessel1@hfhs.org.
Henry Ford Health System, Detroit, MI.
Spine & Scoliosis Specialists, Tampa, FL.

BACKGROUND CONTEXT: Assessment of nerve root decompression in surgery is largely based on visualization and tactile feedback. Often times, visualization can be limited, such as in minimally invasive surgery, and tactile feedback is a subjective assessment that makes the evaluation of successful nerve decompression difficult. Electromyography (EMG) has been proposed as an assessment tool but EMG responses are often difficult to quantify. Alternatively, mechanomyography (MMG) provides a quantifiable response with minimal signal to noise ratio compared to EMG. MMG provides a sensitive tool to accurately quantify mechanical responses to motor action potentials generated by electrical stimulus, allowing more reliable assessment of nerve decompression. PURPOSE: To assess the ability of mechanomyography to quantitatively demonstrate successful nerve root decompression. STUDY DESIGN: Prospective cohort, Therapeutic Level III, Urban Level I Trauma Center PATIENT SAMPLE:: Forty-six patients (72 affected nerve roots) undergoing decompression procedures for lower extremity radiculopathy caused by nerve root compression were enrolled in the study. The study population included 15 patients with herniated nucleus pulposus (HNP) and 31 with lateral recess stenosis (LRS). OUTCOME MEASURE: Visual-analog scale (VAS) score. METHODS: Seventy-two (72) nerves roots in 46 patients undergoing lumbar decompression

procedures, for lower extremity radicular symptoms, were tested using MMG. Nerves were stimulated upstream from the compression site and the lowest threshold current needed to generate a muscle response was determined. Signal response sizes were recorded before and after decompression. Visual-analog scale (VAS) scores were collected pre and post-operatively. RESULTS: Ninety percent (90%) of patients (65/72) had elevated stimulation thresholds (>1mA) prior to decompression. After decompression, 98% of patients (64/65) with elevated current thresholds exhibited a drop in threshold of >/= 1mA (p<0.001). A post-decompression increase in response amplitude was recorded in all patients. VAS scores improved post-decompression (6.8 vs. 1.1, p<0.001) with a positive correlation between decreased stimulation thresholds and degree of improvement in VAS scores (p<0.001). CONCLUSION: MMG is an effective tool that can be used to differentiate normal and compressed nerves by quantifying the mechanomyographic response to a stimulating current. MMG allows one to measure the effect of decompression, judge its effectiveness in real-time, and eliminate the subjectivity seen in tactile feedback methods. When the adequacy of decompression is uncertain, MMG can guide the surgeon towards additional or alternative procedures to ensure complete nerve root decompression.

Otolaryngology – Head and Neck Surgery

Choi SH, Terrell JE, Fowler KE, McLean SA, **Ghanem T**, Wolf GT, Bradford CR, Taylor J, and Duffy SA. Socioeconomic and other demographic disparities predicting survival among head and neck cancer patients *PLoS One* 2016; 11(3):e0149886. PMID: 26930647. Full Text

College of Nursing, Michigan State University, East Lansing, MI, United States of America.
University of Michigan Health System, Ann Arbor, MI, United States of America.
Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, MI, United States of America.
Henry Ford Hospital, Detroit, MI, United States of America.
Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI, United States of America.
College of Nursing, Ohio State University, Columbus, OH, United States of America.

BACKGROUND: The Institute of Medicine (IOM) report, "Unequal Treatment," which defines disparities as racially based, indicates that disparities in cancer diagnosis and treatment are less clear. While a number of studies have acknowledged cancer disparities, they have limitations of retrospective nature, small sample sizes, inability to control for covariates, and measurement errors. OBJECTIVE: The purpose of this study was to examine disparities as predictors of survival among newly diagnosed head and neck cancer patients recruited from 3 hospitals in Michigan, USA, while controlling for a number of covariates (health behaviors, medical comorbidities, and treatment modality). METHODS: Longitudinal data were collected from newly diagnosed head and neck cancer patients (N = 634). The independent variables were median household income, education, race, age, sex, and marital status. The outcome variables were overall, cancer-specific, and disease-free survival censored at 5 years. Kaplan-Meier curves and univariate and multivariate Cox proportional hazards models were performed to examine demographic disparities in relation to survival. RESULTS: Five-year overall, cancer-specific, and disease-free survival were 65.4% (407/622), 76.4% (487/622), and 67.0% (427/622), respectively. Lower income (HR, 1.5; 95% CI, 1.1-2.0 for overall survival; HR, 1.4; 95% CI, 1.0-1.9 for cancer-specific survival), high school education or less (HR, 1.4; 95% CI, 1.1-1.9 for overall survival; HR, 1.4; 95% CI, 1.1-1.9 for cancer-specific survival), and older age in decades (HR, 1.4; 95% CI, 1.2-1.7 for overall survival; HR, 1.2; 95% CI, 1.1-1.4 for cancer-specific survival) decreased both overall and disease-free survival rates. A high school education or less (HR, 1.4; 95% CI, 1.0-2.1) and advanced age (HR, 1.3; 95% CI, 1.1-1.6) were significant independent predictors of poor cancer-specific survival. CONCLUSION: Low income, low education, and advanced age predicted poor survival while controlling for a number of covariates (health behaviors, medical comorbidities, and treatment modality). Recommendations from the Institute of Medicine's Report to reduce disparities need to be implemented in treating head and neck cancer patients.

Otolaryngology – Head and Neck Surgery

Garcia-Rodriguez L, Dharia R, and Massey B. Ectopic thyroid tissue with Hashimoto's thyroiditis *Wis Med J* 2016; 115(1):46-48. PMID: Not assigned Full Text

L. Garcia-Rodriguez, Department of Otolaryngology, Detroit, United States

Objective: Ectopic thyroid gland is a rare occurrence with a prevalence of 1 per 100,000 to 300,000 people. Hashimoto's thyroiditis involving ectopic thyroid tissue is particularly unusual. We describe the presentation, workup, surgical management, and brief review of the literature. Methods: Retroactive review of an 83-year-old white female patient record. As a case report, this project was exempt from institutional review board approval. Results: We present a case of ectopic thyroid tissue located in the strap muscles with concurrent Hashimoto's thyroiditis. This

tissue initially was believed to represent metastatic follicular thyroid carcinoma. Conclusion: Whenever ectopic thyroid tissue is encountered, the gravest concern is metastatic thyroid cancer. The possibility of benign thyroid tissue should not be excluded even if the thyroid histology initially appears to be malignant in nature.

Otolaryngology – Head and Neck Surgery
Garcia-Rodriguez L, **Jones L**, **Chen KM**, **Datta I**, **Divine G**, and **Worsham MJ**. Causal network analysis of head and neck keloid tissue identifies potential master regulators *Laryngoscope* 2016;PMID: 26990118. Full Text

Department of Otolaryngology-Head and Neck Surgery, Henry Ford Hospital, Detroit, Michigan, U.S.A.
Department of Public Health Sciences Center for Bioinformatics, Henry Ford Health System, Detroit, Michigan, U.S.A.

OBJECTIVES/HYPOTHESIS: To generate novel insights and hypotheses in keloid development from potential master regulators. STUDY DESIGN: Prospective cohort. METHODS: Six fresh keloid and six normal skin samples from 12 anonymous donors were used in a prospective cohort study. Genome-wide profiling was done previously on the cohort using the Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA). The 190 statistically significant CpG islands between keloid and normal tissue mapped to 152 genes (P < .05). The top 10 statistically significant genes (VAMP5, ACTR3C, GALNT3, KCNAB2, LRRC61, SCML4, SYNGR1, TNS1, PLEKHG5, PPP1R13-alpha, false discovery rate <.015) were uploaded into the Ingenuity Pathway Analysis software's Causal Network Analysis (QIAGEN, Redwood City, CA). To reflect expected gene expression direction in the context of methylation changes, the inverse of the methylation ratio from keloid versus normal tissue was used for the analysis. Causal Network Analysis identified disease-specific master regulator molecules based on downstream differentially expressed keloid-specific genes and expected directionality of expression (hypermethylated vs. hypomethylated). RESULTS: Causal Network Analysis software identified four hierarchical networks that included four master regulators (pyroxamide, tributyrin, PRKG2, and PENK) and 19 intermediate regulators. CONCLUSIONS: Causal Network Analysis of differentiated methylated gene data of keloid versus normal skin demonstrated four causal networks with four master regulators. These hierarchical networks suggest potential driver roles for their downstream keloid gene targets in the pathogenesis of the keloid phenotype, likely triggered due to perturbation/injury to normal tissue. LEVEL OF EVIDENCE: NA Laryngoscope, 2016.

Otolaryngology – Head and Neck Surgery
Gross ND, Holsinger FC, Magnuson JS, Duvvuri U, Genden EM, **Ghanem TA**, **Yaremchuk KL**, Goldenberg D, Miller MC, Moore EJ, Morris LG, Netterville J, Weinstein GS, and Richmon J. Robotics in otolaryngology and head and neck surgery: Recommendations for training and credentialing: A report of the 2015 AHNS education committee, AAO-HNS robotic task force and AAO-HNS sleep disorders committee *Head Neck* 2016;PMID: 26950771. Full Text

Department of Head and Neck Surgery, Division of Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas.
Division of Head and Neck Surgery, Department of Otolaryngology - Head and Neck Surgery, Stanford University, Palo Alto, California.
Department of Otolaryngology - Head and Neck Surgery, Division of Surgery, Florida Hospital Group, Celebration, Florida.
Department of Otolaryngology - Head and Neck Surgery, University of Pittsburgh Medical Center, Veterans Administration Pittsburgh Health System, Pittsburgh, Pennsylvania.
Department of Otolaryngology - Head and Neck Surgery, Mount Sinai Hospital, New York, New York.
Department of Otolaryngology - Head and Neck Surgery, Henry Ford Hospital, Detroit, Michigan.
Division of Otolaryngology - Head and Neck Surgery, Penn State University College of Medicine, Hershey, Pennsylvania.
Department of Otolaryngology - Head and Neck Surgery, University of Rochester Medical Center, Rochester, New York.
Department of Otorhinolaryngology, Mayo Clinic, Rochester, Minnesota.
Department of Head and Neck Surgery, Division of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York.
Department of Otolaryngology - Head and Neck Surgery, Vanderbilt University Ingram Cancer Center, Nashville, Tennessee.
Department of Otorhinolaryngology - Head and Neck Surgery, University of Pennsylvania, Philadelphia, Pennsylvania.
Department of Otolaryngology - Head and Neck Surgery, Division of Surgery, Johns Hopkins University, Baltimore, Maryland.

Training and credentialing for robotic surgery in otolaryngology - head and neck surgery is currently not standardized, but rather relies heavily on industry guidance. This manuscript represents a comprehensive review of this increasingly important topic and outlines clear recommendations to better standardize the practice. The recommendations provided can be used as a reference by individuals and institutions alike, and are expected to evolve over time.

Otolaryngology – Head and Neck Surgery
Miller AJ, Bobian M, **Peterson E**, and **Deeb R**. Bleeding risk associated with resection of the middle turbinate during functional endoscopic sinus surgery *Am J Rhinol Allergy* 2016; 30(2):140-142. PMID: 26980395.
Article Request Form

Department of Otolaryngology, Henry Ford Health System, Detroit, Michigan, USA.

BACKGROUND: The decision to resect the middle turbinate (MT) during functional endoscopic sinus surgery is controversial. Although there have been a variety of studies that examined the functional outcome related to this maneuver, very few studies evaluated the potential for complications, in particular, epistaxis. OBJECTIVE: We sought to determine if resection of the MT during functional endoscopic sinus surgery leads to an increased risk for postoperative bleeding. METHODS: Patients who underwent functional endoscopic sinus surgery for chronic sinusitis or nasal polyposis between 2004 and 2014 at a single institution were analyzed for bleeding and other complications after resection of the MT. RESULTS: Between 2004 and 2014, 1185 sinus surgeries were performed by 18 surgeons. A propensity matched set of 228 patients who underwent turbinate resection, and 228 controls were selected based on predicted probabilities from a logistic regression that predicted turbinate resection and that was adjusted for age, sex, and procedure. There were 89 patients with bilateral turbinates removed and 139 with unilateral turbinates removed. There was no significant difference in major bleeding or other complication rates between the two groups. Patients who underwent resection of at least one MT were 3.95 times more likely to have minor bleeding compared with those who did not; this risk increased with the number of turbinates resected (trend $p = 0.008$). Patients on anticoagulation medications were at a significant risk of bleeding if their MT was removed ($p = 0.007$), whereas patients on aspirin or antiplatelet therapy were not at a significant risk. CONCLUSION: There was no increased risk of major bleeding or other complication associated with resection of the MT. However, there was a significantly increased minor bleeding rate associated with MT resection, particularly if the patient was on anticoagulants.

Otolaryngology – Head and Neck Surgery
Siddiqui F, **Bentley GA**, **McLean SA**, and **Ryu S**. Inflammatory pseudotumor of the pharynx: A rare entity *Indian J Cancer* 2015; 52(4):668-669. PMID: 26960513. Full Text

Department of Radiation Oncology, Henry Ford Health Systems, Detroit, MI-48202, USA.
Department of Otolaryngology, Head and Neck Surgery, Henry Ford Health Systems, Detroit, MI-48202, USA.

Palliative Medicine
Chasteen K, **Awdish R**, **Mendez M**, **Buick D**, and **Kokas M**. Clear conversations: A comprehensive curriculum to facilitate translation of skills learned in simulated settings to improve communication in real clinical encounters *J Pain Symptom Manage* 2016; 51(2):384-385. PMID: Not assigned. Abstract

K. Chasteen, Henry Ford Hospital, Detroit, United States

Objectives • Apply a protocol for deliberate practice of communication skills in real encounters with the aid of a mobile app and online template. • Demonstrate at least two communication skills learned in simulation (eg, ask-tell-ask, empathic response, open-ended question to elicit patient values) in a real clinical encounter. Background. Communication skills training with simulated patients has gained traction in many academic centers as a way to improve communication skills. However, the optimal method to facilitate translation of skills learned in simulated settings to improve communication in real clinical encounters has not been described. Methods. We developed a comprehensive communication skills curriculum for physicians in the ICU that consists of (1) simulation-based communication skills workshops for ICU fellows, residents, and attending physicians; (2) standardized pre- and postfamily meeting team huddles following a template in a mobile app, which includes setting a communication goal and getting specific feedback; (3) online evaluation template to record family meeting feedback as a procedure; and (4) mandatory family meetings within 72 hours for all patients in the ICU with APACHE IV mortality >30%. We conducted a prospective cohort 2-week pilot study. We implemented the curriculum in one ICU unit and compared it to another geographically distinct ICU unit where the attending, fellow, and residents had not received simulation training or training on other aspects of the curriculum. Our main outcome measure was family satisfaction with

physician communication in the ICU using a 10-question modified HCAPS survey. A secondary outcome was trainee self-perceived preparedness for end-of-life communication tasks in the ICU pre and post intervention. Results. Patients in the intervention group (n=15) scored significantly higher on satisfaction with physician communication than the control group (n=16) (p=0.0178). Trainees in the intervention group showed significant improvement in self-perceived preparedness in communication skills between pre and post intervention in expressing empathy, responding to families who deny the seriousness of their loved one's illness, and discussing spiritual issues. There were no significant differences pre and post intervention in the control group. Discussion. This comprehensive communication curriculum combining simulation-based training, deliberate practice at the bedside with the aid of a mobile app and online evaluation template, and mandatory early family meetings for high risk patients was associated with improved patient satisfaction with physician communication in the ICU and increased trainee preparedness for difficult communication tasks. Conclusion. This communication curriculum could serve as a model for optimal inpatient communication skills training for residents and fellows across all disciplines.

Pathology

Kenney RM, Cole KA, **Perri MB**, Dumkow LE, **Samuel LP**, **Zervos MJ**, and **Davis SL**. Reply to "urinary tract infections: Resistance is futile" *Antimicrob Agents Chemother* 2016; 60(4):2598. PMID: 27016558. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA rkenney1@hfhs.org.
Department of Pharmacy Services, University of Toledo Medical Center, Toledo, Ohio, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Pharmacy Services, Mercy Health Saint Mary's, Grand Rapids, Michigan, USA.
Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, Michigan, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan, USA Wayne State University School of Medicine, Detroit, Michigan, USA.
Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA.

Pathology

Meighani A, **Jafri SM**, **Raoufi M**, and **Salgia R**. Splenic artery embolization for treatment of refractory ascites after liver transplantation *ACG Case Rep J* 2016; 3(2):136-138. PMID: 26958571. Full Text

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI.
Department of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI.
Department of Pathology, Henry Ford Hospital, Detroit, MI.

Post-transplantation refractory ascites is uncommon; however, it can be a serious problem, increasing both morbidity and mortality in patients. Despite scant literature available, splenic artery embolization (SAE) has been shown to be an effective treatment for refractory ascites after cadaveric orthotopic liver transplantation (OLT). We report a successful use of therapeutic SAE for refractory ascites post-OLT.

Pathology

Saste AB, **Jiang F**, **Arias-Stella J**, **Gamalski S**, **Peres E**, **Janakiraman N**, and **Farhan S**. Emberger syndrome with concomitant GATA2, NPM1 and FLT3-ITD mutations in remission after allogeneic stem cell transplant *Biol Blood Marrow Transplant* 2016; 22(3):S208-S209. PMID: Not assigned. Abstract

[Saste, Abhijit Balkrishna] Henry Ford Hlth Syst, Hematol Oncol Bone Marrow Transplant, Detroit, MI USA. [Jiang, Feng; Gamalski, Steven] Henry Ford Hlth Syst, Hematol Oncol, Detroit, MI USA. [Arias-Stella, Javier, III] Henry Ford Hlth Syst, Dept Pathol & Lab Med, Detroit, MI USA. [Peres, Edward; Janakiraman, Nalini; Farhan, Shatha] Henry Ford Hosp, Hematol Oncol & Bone Marrow Transplantat, Detroit, MI 48202 USA.

Pathology

Williamson SR, and Cheng L. Clear cell renal cell tumors: Not all that is "clear" is cancer *Urol Oncol* 2016;PMID: 26988177. Full Text

Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI; Josephine Ford Cancer Institute, Henry Ford Health System, Detroit, MI; Wayne State University School of Medicine, Detroit, MI.

Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN; Department of Urology, Indiana University School of Medicine, Indianapolis, IN. Electronic address: liang_cheng@yahoo.com.

Continued improvement of our understanding of the clinical, histologic, and genetic features of renal cell tumors has progressively evolved renal tumor classification, revealing an expanding array of distinct tumor types with different implications for prognosis, patient counseling, and treatment. Although clear cell renal cell carcinoma is unequivocally the most common adult renal tumor, there is growing evidence that some "clear cell" renal neoplasms, such as exemplified by multilocular cystic clear cell renal neoplasm of low malignant potential (formerly multilocular cystic renal cell carcinoma), do not have the same potential for insidious progression and metastasis, warranting reclassification as low malignant potential tumors or benign neoplasms. Still other novel tumor types such as clear cell papillary renal cell carcinoma have been more recently recognized, which similarly have shown a conspicuous absence of aggressive behavior to date, suggesting that these too may be recategorized as noncancerous or may be premalignant neoplasms. This importance for prognosis is increasingly significant in the modern era, in which renal masses are increasingly found incidentally by imaging techniques at a small tumor size, raising consideration for less aggressive management options guided by renal mass biopsy diagnosis, including imaging surveillance, tumor ablation, or partial nephrectomy.

Pharmacy

Chackunkal E, **Dhanapal Vogel V**, **Grycki M**, and **Kostoff D**. Improving adherence to the Epic Beacon ambulatory workflow *J Oncol Pharm Pract* 2016;PMID: 26988246. Full Text

Henry Ford Hospital, Detroit, MI, USA Dkostof1@hfhs.org.

Computerized physician order entry has been shown to significantly improve chemotherapy safety by reducing the number of prescribing errors. Epic's Beacon Oncology Information System of computerized physician order entry and electronic medication administration was implemented in Henry Ford Health System's ambulatory oncology infusion centers on 9 November 2013. Since that time, compliance to the infusion workflow had not been assessed. The objective of this study was to optimize the current workflow and improve the compliance to this workflow in the ambulatory oncology setting. This study was a retrospective, quasi-experimental study which analyzed the composite workflow compliance rate of patient encounters from 9 to 23 November 2014. Based on this analysis, an intervention was identified and implemented in February 2015 to improve workflow compliance. The primary endpoint was to compare the composite compliance rate to the Beacon workflow before and after a pharmacy-initiated intervention. The intervention, which was education of infusion center staff, was initiated by ambulatory-based, oncology pharmacists and implemented by a multi-disciplinary team of pharmacists and nurses. The composite compliance rate was then reassessed for patient encounters from 2 to 13 March 2015 in order to analyze the effects of the determined intervention on compliance. The initial analysis in November 2014 revealed a composite compliance rate of 38%, and data analysis after the intervention revealed a statistically significant increase in the composite compliance rate to 83% ($p < 0.001$). This study supports a pharmacist-initiated educational intervention can improve compliance to an ambulatory, oncology infusion workflow.

Pharmacy

Farhan S, **Pelland D**, **Wautelet S**, **Neme K**, **Mikulandric N**, **Trapp MA**, **Szymanski S**, **Ruemenapp K**, **Peres E**, and **Janakiraman N**. Impact of cytomegalovirus on early chimerism in patients with myeloid disorders undergoing stem cell transplantation using reduced toxicity ablative conditioning regimen *Biol Blood Marrow Transplant* 2016; 22(3):S318-S318. PMID: Not assigned. Abstract

[Farhan, Shatha; Peres, Edward; Janakiraman, Nalini] Henry Ford Hosp, Hematol Oncol & Bone Marrow Transplantat, Detroit, MI 48202 USA. [Pelland, Danielle; Wautelet, Susan; Trapp, Mary Ann; Szymanski, Sarah; Ruemenapp, Kenneth] Henry Ford Hosp, Detroit, MI 48202 USA. [Neme, Klodiana; Mikulandric, Nancy] Henry Ford Hosp, Pharm, Detroit, MI 48202 USA.

Pharmacy

Hencken L, **To L**, **Ly N**, and **Morgan JA**. Serotonin syndrome following methylene blue administration for vasoplegic syndrome *J Card Surg* 2016; 31(4):208-210. PMID: 26934199. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan.
Department of Cardiology, Henry Ford Hospital, Detroit, Michigan.
Department of Cardiac Surgery, Henry Ford Hospital, Detroit, Michigan.

Methylene blue (MB) has been used for additional blood pressure support in patients who develop severe, refractory vasoplegia; however, MB can induce serotonin syndrome, especially when used in conjunction with other serotonergic agents. We describe a case of serotonin syndrome in a patient who received MB for vasoplegic syndrome after left ventricular assist device implantation and discuss its presentation and management.

Pharmacy

Kenney RM, Cole KA, **Perri MB**, Dumkow LE, **Samuel LP**, **Zervos MJ**, and **Davis SL**. Reply to "urinary tract infections: Resistance is futile" *Antimicrob Agents Chemother* 2016; 60(4):2598. PMID: 27016558. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA rkenney1@hfhs.org.
Department of Pharmacy Services, University of Toledo Medical Center, Toledo, Ohio, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Pharmacy Services, Mercy Health Saint Mary's, Grand Rapids, Michigan, USA.
Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, Michigan, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan, USA Wayne State University School of Medicine, Detroit, Michigan, USA.
Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan, USA Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA.

Pharmacy

Zasowski EJ, Claeys KC, Lagnf AM, **Davis SL**, and Rybak MJ. Time is of the essence: The impact of delayed antibiotic therapy on patient outcomes in hospital-onset enterococcal bloodstream infections *Clin Infect Dis* 2016;PMID: 26945013. Full Text

Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University.
Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University Department of Pharmacy Services, Henry Ford Hospital.
Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University Department of Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University Department of Pharmacy Services, Detroit Medical Center, Michigan.

BACKGROUND: With increasing prevalence of vancomycin-resistant enterococci (VRE), appropriate antibiotic therapy for enterococcal bloodstream infections (EBSI) can be delayed. Data regarding the impact of delayed therapy on EBSI outcomes are conflicting, and the time delay most strongly associated with poor outcomes has not been defined. METHODS: This was a single-center, retrospective cohort study of adult, nonneutropenic patients with hospital-onset EBSI from 2010 to 2014. Classification and regression tree (CART) analysis was used to determine the delay in appropriate therapy most predictive of 30-day mortality. Appropriate therapy was defined as antibiotic therapy to which the enterococci and copathogen, where applicable, were susceptible. Outcomes and clinical characteristics were compared between patients receiving early or delayed therapy, defined by CART timepoint. Poisson regression was employed to determine the independent association of delayed therapy on 30-day mortality and predictors of delayed therapy. RESULTS: Overall, 190 patients were included. A breakpoint in time to appropriate therapy was identified at 48.1 hours, where 30-day mortality was substantially increased (14.6% vs 45.3%; P < .001). Patients receiving appropriate therapy after 48.1 hours also experienced higher in-hospital mortality and longer EBSI duration. After adjustment for severity of illness and comorbidity, delayed therapy >/=48.1 hours was associated with a 3-fold increase in 30-day mortality (risk ratio, 3.16 [95% confidence interval, 1.96-5.09]). Vancomycin resistance was the only independent predictor of delayed therapy. CONCLUSIONS: In patients with hospital-onset EBSI, receipt of appropriate therapy within the first 48 hours was associated with reduced mortality, underscoring the potential role of rapid diagnostic testing for early identification of VRE.

Podiatry

Burson LK, and **Schank CH**. Charcot neuroarthropathy of the foot and ankle *Home Healthc Now* 2016; 34(3):135-139. PMID: 26925938. Article Request Form

Lisa K. Burson, DPM, is a Podiatry Resident, Podiatric Surgery, Michigan Surgical Hospital, Warren, Michigan. Christopher H. Schank, DPM, MS, is a Podiatry Resident, Podiatric Surgery, Henry Ford Health System, Clinton TWP, Michigan.

Charcot neuropathy is a painless, progressive, degeneration most notably of the ankle or midfoot joints, seen in patients with diabetes and neuropathy. This article will describe the etiology, diagnosis, and treatment of this potentially debilitating joint disease and provide implications for home care clinicians.

Psychiatry
Ahmedani BK, **Peterson EL**, **Wells KE**, **Henein F**, and **Williams LK**. Long-term management of low back pain with opioids and non-steroidal anti-inflammatory drugs in a health system *Am J Prev Med* 2016;PMID: 26970664. Full Text

Henry Ford Health System, Detroit, Michigan. Electronic address: bahmeda1@hfhs.org.

Public Health Sciences
Ahmedani BK, **Peterson EL**, **Wells KE**, **Henein F**, and **Williams LK**. Long-term management of low back pain with opioids and non-steroidal anti-inflammatory drugs in a health system *Am J Prev Med* 2016;PMID: 26970664. Full Text

Henry Ford Health System, Detroit, Michigan. Electronic address: bahmeda1@hfhs.org.

Public Health Sciences
Bertran EA, Berlie HD, **Taylor A**, **Divine G**, and Jaber LA. Diagnostic performance of HbA for diabetes in Arab vs. European populations: a systematic review and meta-analysis *Diabet Med* 2016;PMID: 26996656. Full Text

Eugene Applebaum College of Pharmacy and Health Sciences, Department of Pharmacy Practice, Wayne State University, Detroit.
Henry Ford Health System, Department of Public Health Sciences, Detroit, USA.

AIM: To examine differences in the performance of HbA1c for diagnosing diabetes in Arabs compared with Europeans. METHODS: The PubMed, Embase and Cochrane library databases were searched for records published between 1998 and 2015. Estimates of sensitivity, specificity and log diagnostic odds ratios for an HbA1c cut-point of 48 mmol/mol (6.5%) were compared between Arabs and Europeans, using a bivariate linear mixed-model approach. For studies reporting multiple cut-points, population-specific summary receiver operating characteristic (SROC) curves were constructed. In addition, sensitivity, specificity and Youden Index were estimated for strata defined by HbA1c cut-point and population type. Database searches yielded 1912 unique records; 618 full-text articles were reviewed. Fourteen studies met the inclusion criteria; hand-searching yielded three additional eligible studies. Three Arab (N = 2880) and 16 European populations (N = 49 127) were included in the analysis. RESULTS: Summary sensitivity and specificity for a HbA1c cut-point of 48 mmol/mol (6.5%) in both populations were 42% (33-51%), and 97% (95-98%). There was no difference in area under SROC curves between Arab and European populations (0.844 vs. 0.847; P = 0.867), suggesting no difference in HbA1c diagnostic accuracy between populations. Multiple cut-point summary estimates stratified by population suggest that Arabs have lower sensitivity and higher specificity at a HbA1c cut-point of 44 mmol/mol (6.2%) compared with European populations. Estimates also suggest similar test performance at cut-points of 44 mmol/mol (6.2%) and 48 mmol/mol (6.5%) for Arabs. CONCLUSIONS: Given the low sensitivity of HbA1c in the high-risk Arab American population, we recommend a combination of glucose-based and HbA1c testing to ensure an accurate and timely diagnosis of diabetes. This article is protected by copyright. All rights reserved.

Public Health Sciences
Cajigal S, **Peterson EL**, **Wells KE**, **Zoratti EM**, **Lanfear DE**, Seibold M, Rajesh K, Burchard EG, and **Williams LK**. Asthma control test composite score may not be superior to assessments of rescue inhaler use for predicting severe asthma exacerbations *J Allergy Clin Immunol* 2016; 137(2):AB207. PMID: Not assigned. Abstract

S. Cajigal, Division of Allergy and Clinical Immunology, Henry Ford Health System, Detroit, United States

RATIONALE: Current U.S. guidelines recommend the Asthma Control Test (ACT) for assessing disease control and selecting treatment. The ACT was initially validated based on concurrence with specialist opinion. The goal of this study was to prospectively assess the ACT and its component questions for their utility in predicting severe exacerbations. METHODS: Study individuals were participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) and had the following characteristics: age ≥18 years, physician diagnosis of asthma, and membership in a health system serving southeastern Michigan. Participants

underwent a baseline evaluation that included the ACT. Severe asthma exacerbations, defined as the need for oral steroids, emergency room visit, or inpatient admission, were identified prospectively using pharmacy claims and patient encounters. Receiver-operator curves were used to assess predictive utility, and the area under the curve (AUC) was used for comparisons. RESULTS: Two hundred thirty two (23.4%) of the 990 participants experienced an asthma exacerbation in the 6 months following their baseline evaluation. The ACT composite score had an AUC of 0.675. With the exception of the rescue inhaler use question, the composite ACT score was significantly better in predicting exacerbations when compared to the 4 other ACT questions. Pharmacy records of concurrent SABA MDI use were equally predictive of exacerbation when compared to the composite ACT score. CONCLUSIONS: Our study demonstrates that while the ACT is predictive for exacerbations, the composite score may not be superior to assessing SABA rescue use alone when predicting risk of serious asthma exacerbations.

Public Health Sciences

Gammon HM, **Shelton CB**, **Siegert C**, **Dawson C**, **Sexton E**, **Burmeister C**, **Gnam G**, and **Siddiqui A**. Self-turning for pressure injury prevention *Wound Medicine* 2016; 12:15-18. PMID: Not assigned Article Request Form

A. Siddiqui, Division of Plastic Surgery, K-16, Henry Ford Hospital, Detroit, United States

The study objective was to determine if hospitalized patients who are designated as self-turn would reposition themselves appropriately in the acute care setting. This was a prospective case series in a general practice unit of an 800-bed urban tertiary care hospital. Patients were instructed on the importance of mobility for pressure ulcer prevention and subsequently monitored on a continuous bedside pressure mapping device. Primary outcomes included intervals of inactivity and pressure ulcer incidence. During the 3-month study interval, only 2 patients had a documented 4-h interval without measurable repositioning. None of the 101 consecutive patients enrolled in the study developed pressure ulcers. General practice unit patients that are given proper instruction and designated as self-turn can reliably be considered low-risk for hospital acquired pressure ulcers. Based on our prospective study, patients designated as self-turn do reposition themselves.

Public Health Sciences

Garcia-Rodriguez L, **Jones L**, **Chen KM**, **Datta I**, **Divine G**, and **Worsham MJ**. Causal network analysis of head and neck keloid tissue identifies potential master regulators *Laryngoscope* 2016;PMID: 26990118. Full Text

Department of Otolaryngology-Head and Neck Surgery, Henry Ford Hospital, Detroit, Michigan, U.S.A.
Department of Public Health Sciences Center for Bioinformatics, Henry Ford Health System, Detroit, Michigan, U.S.A.

OBJECTIVES/HYPOTHESIS: To generate novel insights and hypotheses in keloid development from potential master regulators. STUDY DESIGN: Prospective cohort. METHODS: Six fresh keloid and six normal skin samples from 12 anonymous donors were used in a prospective cohort study. Genome-wide profiling was done previously on the cohort using the Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA). The 190 statistically significant CpG islands between keloid and normal tissue mapped to 152 genes ($P < .05$). The top 10 statistically significant genes (VAMP5, ACTR3C, GALNT3, KCNAB2, LRRC61, SCML4, SYNGR1, TNS1, PLEKHG5, PPP1R13-alpha, false discovery rate <.015) were uploaded into the Ingenuity Pathway Analysis software's Causal Network Analysis (QIAGEN, Redwood City, CA). To reflect expected gene expression direction in the context of methylation changes, the inverse of the methylation ratio from keloid versus normal tissue was used for the analysis. Causal Network Analysis identified disease-specific master regulator molecules based on downstream differentially expressed keloid-specific genes and expected directionality of expression (hypermethylated vs. hypomethylated). RESULTS: Causal Network Analysis software identified four hierarchical networks that included four master regulators (pyroxamide, tributyrin, PRKG2, and PENK) and 19 intermediate regulators. CONCLUSIONS: Causal Network Analysis of differentiated methylated gene data of keloid versus normal skin demonstrated four causal networks with four master regulators. These hierarchical networks suggest potential driver roles for their downstream keloid gene targets in the pathogenesis of the keloid phenotype, likely triggered due to perturbation/injury to normal tissue. LEVEL OF EVIDENCE: NA Laryngoscope, 2016.

Public Health Sciences

Li C, **Zhang Y**, **Levin AM**, **Chopp M**, and **Zhang ZG**. Characterization of micrornas and their target proteins in distal axons of cortical neurons *Stroke* 2016; 47PMID: Not assigned. Abstract

C. Li, Dept of Neurology, Henry Ford Hosp, Detroit, United States

Introduction: Axonal growth is essential for the establishment of a functional neuronal network. Molecular information of axon is limited. MicroRNAs (miRNAs) regulate post-transcriptional gene expression. We hypothesized that axonal miRNAs are locally relevant to their target genes. Methods: Proteins and RNAs were extracted from distal axons of cortical neurons cultured in a microfluidic device. A mass spectrometer and miRNA arrays were used to measure proteins and miRNAs, respectively. Ingenuity Pathway Analysis (IPA) and Database for Annotation, Visualization and Integrated Discovery (DAVID) bioinformatic tools were used to make in silico predictions of functionally relevant miRNA target genes. Results: Proteomic showed that distal axons contained 883 proteins. Bioinformatic analysis showed the presence of 94 proteins that regulate axonal growth. To identify relevant miRNAs to these 94 proteins, miRNAs with 8mer sites that exactly match target genes were considered, based on the fact that 8mer sites efficaciously affect miRNA-target interactions. Of the 94 genes, we found that there were 56 candidate genes that can be targeted by 62 miRNAs enriched in axons. Among them, we validated 13 proteins and 11 miRNAs, respectively, by means of Western blot and RT-PCR. To examine target genes, we treated axons with chondroitin sulfate proteoglycans (CSPGs) that inhibit axonal growth and examined alterations of these proteins and miRNAs in the distal axons. We found that elevation of miR-203a, -133b, -29abc and -92ab were associated with reduced AKT, MTOR, PI3Kp85, DPYSL2, MAP1B, PPP2CA and DCX proteins, whereas decreased miR-15b, -26b, -34b, -376b, -128, -381 and -195 were accompanied by increased proteins of EZR, KIF5A, RTN4, GSK3B, and ROCK2. Bioinformatic analysis revealed that these miRNAs and proteins are highly related to the axonal growth network. These data suggest that miRNAs altered by CSPGs functionally target these genes for mediating the inhibitory effect of CSPGs on axonal growth. Conclusions: Our bioinformatic analyses of miRNAs and proteins in the distal axon identifies an interconnected group of miRNAs and their target genes that regulate axonal growth, which provides new insight into the molecular mechanisms underlying axonal growth.

Public Health Sciences

Luria CJ, **Sitarik AR**, **Havstad S**, **Wegienka GR**, **Kim H**, **Zoratti EM**, **Joseph CLM**, and **Andrea Cassidy B**. Association between asthma symptom scores and increased perceived stress and trait anxiety in asthmatic adolescents *J Allergy Clin Immunol* 2016; 137(2):AB11. PMID: Not assigned. Abstract

C.J. Luria, Division of Allergy and Clinical Immunology, Henry Ford Health System, Detroit, United States

RATIONALE: The relationship between asthma symptoms and perceived stress and trait anxiety is not well understood. METHODS: Adolescents ages 14-17 years were recruited to examine the effect of stress on health measures. They were included in the present analysis if they reported current asthma, defined as self-reported cliniciandiagnosed asthma plus one or more episodes of asthma in the past year. Asthma symptoms were assessed on a 7-point Likert scale using six asthma control questionnaire items targeting nocturnal awakening due to asthma, symptoms upon awakening, activity limitation, shortness of breath, time spent wheezing, and short-acting bronchodilator (SABA) use. Stress was measured using the perceived stress scale (PSS), and trait anxiety was measured using the State-Trait Anxiety Inventory. Linear regression was used to associate asthma symptoms with PSS and trait anxiety. RESULTS: Of 335 adolescents recruited, 38 (11.3%) reported current asthma. Four of the six asthma symptom assessments had significant associations with PSS: symptoms upon awakening (β54.8, p-value<0.001), nocturnal awakening due to asthma (β54.47, p<0.001), activity limitation (β52.78, p=0.005), and shortness of breath (β51.73, p=0.014). These associations remained significant after adjusting for gender, race, and BMI percentile. Time spentwheezing and SABA use were not significantly associated with PSS. Trait anxiety had significant associations with nocturnal awakening (β59.28, p=0.002) and symptoms upon awakening (β58.74, p=0.002). CONCLUSIONS: Asthma symptoms are associated with increased perceived stress and trait anxiety. Asthmatic adolescents may represent a population that is particularly vulnerable to perceived stress and anxiety, highlighting the importance of considering these factors in asthma counseling.

Public Health Sciences

Miller AJ, Bobian M, **Peterson E**, and **Deeb R**. Bleeding risk associated with resection of the middle turbinate during functional endoscopic sinus surgery *Am J Rhinol Allergy* 2016; 30(2):140-142. PMID: 26980395
Article Request Form

Department of Otolaryngology, Henry Ford Health System, Detroit, Michigan, USA.

BACKGROUND: The decision to resect the middle turbinate (MT) during functional endoscopic sinus surgery is controversial. Although there have been a variety of studies that examined the functional outcome related to this maneuver, very few studies evaluated the potential for complications, in particular, epistaxis. OBJECTIVE: We sought to determine if resection of the MT during functional endoscopic sinus surgery leads to an increased risk for postoperative bleeding. METHODS: Patients who underwent functional endoscopic sinus surgery for chronic sinusitis or nasal polyposis between 2004 and 2014 at a single institution were analyzed for bleeding and other complications

after resection of the MT. RESULTS: Between 2004 and 2014, 1185 sinus surgeries were performed by 18 surgeons. A propensity matched set of 228 patients who underwent turbinate resection, and 228 controls were selected based on predicted probabilities from a logistic regression that predicted turbinate resection and that was adjusted for age, sex, and procedure. There were 89 patients with bilateral turbinates removed and 139 with unilateral turbinates removed. There was no significant difference in major bleeding or other complication rates between the two groups. Patients who underwent resection of at least one MT were 3.95 times more likely to have minor bleeding compared with those who did not; this risk increased with the number of turbinates resected (trend p = 0.008). Patients on anticoagulation medications were at a significant risk of bleeding if their MT was removed (p = 0.007), whereas patients on aspirin or antiplatelet therapy were not at a significant risk. CONCLUSION: There was no increased risk of major bleeding or other complication associated with resection of the MT. However, there was a significantly increased minor bleeding rate associated with MT resection, particularly if the patient was on anticoagulants.

Public Health Sciences

Morris D, **Chopp M**, **Cheung WL**, **Cui Y**, **Zhang T**, **Lu M**, **Zhang L**, and **Zhang ZG**. Thymosin β4 for the treatment of sub-acute stroke in aged rats *Stroke* 2016; 47PMID: Not assigned. Abstract

D. Morris, Emergency Medicine, Henry Ford Hosp, Detroit, United States

Introduction: Thymosin β4 (Tβ4) is a 5K peptide which influences cellular migration by inhibiting organization of the actin-cytoskeleton. Tβ4 has neurorestorative properties and is a potential candidate for the treatment of sub-acute stroke. Previous research demonstrated that Tβ4 improved neurological outcome in a young (3 months) rat model of embolic stroke. Hypothesis: We hypothesized that Tβ4 would improve neurological outcome in an aged rat model of embolic stroke when administered 24 hours after embolic stroke. Methods: Aged Male Wistar rats (Charles River, France 18-21 months) were subjected to embolic middle cerebral artery occlusion (MCAo). Rats were randomized to receive Tβ4 (12 mg/kg, Regenerx Biopharmaceuticals, Inc.) or control 24 hrs after MCAo and then every 3 days for 4 additional doses. The dose of 12 mg/kg was the maximal dose of Tβ4 that showed functional improvement in a young rat model of embolic stroke. Functional tests were performed weekly. The rats were sacrificed 56 days after MCAo and lesion volumes measured. Generalized Estimating Equations were used to compare the treatment effect on functional recovery and t-test for lesion volumes. Results and Conclusions: Twenty-three rats were included in the study: control group (n=12) and Tβ4 group (n=11). After randomization, there were three deaths in both the control and Tβ4 groups. The Tβ4 treatment reduced infarct volume by more than 50% (12.8% ± 9.3%, mean ± SE, $p<0.05$) compared to the control group (26.0% ± 4.3%). However, Tβ4 did not show improvement in functional outcome compared to control. Lesion volumes in the treated group showed a correlation to functional testing of ($R=0.85$, $p<0.05$), whereas no correlation was observed in the control group ($R=0.19$). Conclusions: The Tβ4 treatment of stroke aged animals significantly reduces infarct volume compared to vehicle treated stroke. Dissociation between infarct volume and functional outcome in the control group suggests, a ceiling effect of these functional tests in aged animals may obscure proper evaluation of functional outcome between the Tβ4 and control groups. Additional studies and more sensitive behavioral tests are needed to examine the dissociation between infarct volume and functional outcomes in aged ischemic rats.

Public Health Sciences

Munkarah A, Mert I, **Chhina J**, **Hamid S**, **Poisson L**, **Hensley-Alford S**, **Giri S**, and **Rattan R**. Targeting of free fatty acid receptor 1 in EOC: A novel strategy to restrict the adipocyte-EOC dependence *Gynecol Oncol* 2016; 141(1):72-79. PMID: 27016232. Full Text

Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: amunkar1@hfhs.org.
Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: imert@med.wayne.edu.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA. Electronic address: jchhina1@hfhs.org.
Department of Neurology, Henry Ford Hospital, USA. Electronic address: hsuhail1@hfhs.org.
Center for Bioinformatics, Henry Ford Hospital, USA; Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: lpoisso1@hfhs.org.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA. Electronic address: salford1@hfhs.org.
Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA; Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA. Electronic address: sgiri1@hfhs.org.
Department of Women's Health, Obstetrics and Gynecology, Henry Ford Hospital, USA; Josephine Ford Cancer Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: rrattan1@hfhs.org.

OBJECTIVES: Adipocyte derived free fatty acids (FFA) promote epithelial ovarian cancer (EOC) by acting as a fuel source to support the energy requirement of the cancer cells. FFA may also exert biological effects through signaling pathways. Recently, a family of FFA activated G-protein coupled receptors (FFAR/GPCRs) was identified. Our objective was to investigate the role of FFAR/GPCRs in EOC and assess their potential as therapeutic targets. METHODS: The mRNA (RT-PCR) expression of FFAR/GPCR family members (FFAR1/GPR40; FFAR2/GPR43, FFAR3/GPR41, FFAR4/GPR120 and GPR84) was examined in: (1) a syngeneic mouse model of EOC fed high energy diet (60% fat) or regular diet (30% fat), (2) EOC cell lines exposed to free fatty acids and (3) specimens from 13 histologically normal ovaries and 28 high grade ovarian serous carcinomas. The GPR 40 antagonist, GW1100, was used to inhibit FFAR1/GPR40 and cell survival was assayed by MTT in various cell lines. RESULTS: High Grade Serous carcinoma specimens expressed significantly increased GPR40 compared to normal ovaries (p=0.0020). Higher expression was noted in advanced stage disease. ID8 ovarian tumors from mice fed with high fat diet also showed higher GPR40 expression. Exposing EOC cells to FFAs, increased GPR40 expression. Treatment of EOC cell lines with GW100 resulted in growth inhibition and was associated with an alteration in their energy metabolism. CONCLUSION: FFA-induced cancer cell growth may be partly mediated through FFAR1/GPR40. Targeting of FFAR1/GPR40 may be an attractive treatment strategy in EOC, and possibly offers a targeted treatment for a subset of EOC patients.

Public Health Sciences

Wells KE, **Cajigal S**, **Peterson EL**, **Ahmedani BK**, Kumar R, **Lanfear DE**, Burchard EG, and **Williams LK**. Assessing differences in inhaled corticosteroid response by self-reported race-ethnicity and genetic ancestry among asthmatic subjects *J Allergy Clin Immunol* 2016;PMID: 27016472. Full Text

Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich. Electronic address: kewells1@aol.com.
Department of Internal Medicine, Henry Ford Health System, Detroit, Mich.
Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich.
Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Mich.
Department of Pediatrics, The Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Ill.
Department of Bioengineering & Therapeutic Sciences, University of California San Francisco, San Francisco, Calif; Department of Medicine, University of California San Francisco, San Francisco, Calif.
Department of Internal Medicine, Henry Ford Health System, Detroit, Mich; Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Mich.

BACKGROUND: Inhaled corticosteroids (ICSs) are the preferred treatment for achieving asthma control. However, little is known regarding the factors contributing to treatment response and whether treatment response differs by population group. OBJECTIVE: We sought to assess behavioral, sociodemographic, and genetic factors related to ICS response among African American and European American subjects with asthma. METHODS: Study participants were part of the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE). The analytic sample included asthmatic subjects aged 12 to 56 years with greater than 12% bronchodilator reversibility and percent predicted FEV1 of between 40% and 90%. Participants received 6 weeks of inhaled beclomethasone dipropionate. The primary measure of ICS response was a change in Asthma Control Test (ACT) score; the secondary measure was a change in prebronchodilator FEV1. Adherence was measured with electronic monitors. Genetic ancestry was estimated for African American participants by using genome-wide genotype data. RESULTS: There were 339 study participants; 242 self-identified as African American and 97 as European American. Baseline ACT score, percent predicted FEV1, degree of bronchodilator response, and ICS adherence were significantly associated with ICS response. A baseline ACT score of 19 or less was useful in identifying those who would respond, as evidenced by the significant dose-response relationship with ICS adherence. Neither self-reported race-ethnicity among all participants nor proportion of African ancestry among African American participants was associated with ICS responsiveness. CONCLUSIONS: Our findings suggest that baseline lung function measures and self-reported asthma control predict ICS response, whereas self-reported race-ethnicity and genetic ancestry do not.

Public Health Sciences

Zhu L, **Yang XP**, **Janic B**, **Rhaleb NE**, **Harding P**, **Nakagawa P**, **Peterson EL**, and **Carretero OA**. Ac-SDKP suppresses TNFalpha-induced ICAM-1 expression in endothelial cells via inhibition of IkappaB kinase and NF-kappaB activation *Am J Physiol Heart Circ Physiol* 2016:ajpheart.00252.02015. PMID: 26945075. Full Text

Henry Ford Hospital.
Henry Ford Health System.

Henry Ford Hospital Ocarret1@hfhs.org.

N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a naturally occurring tetrapeptide that prevents inflammation and fibrosis in hypertension and other cardiovascular diseases. We previously showed that in angiotensin II-induced hypertension, Ac-SDKP decreased the activation of nuclear transcription factor NF-kappaB, while in experimental autoimmune myocarditis and hypertension animal models it also reduced the expression of endothelial leukocyte adhesion molecule ICAM-1. However, the mechanisms by which Ac-SDKP down-regulated ICAM-1 expression are still unclear. TNFalpha is a pro-inflammatory cytokine that induces ICAM-1 expression in various cell types via TNF receptor 1 and activation of the classical NF-kappaB pathway. We hypothesized that in endothelial cells Ac-SDKP suppresses TNFalpha-induced ICAM-1 expression by decreasing IkappaB kinase (IKK) phosphorylation that as a consequence leads to a decrease of IkappaB phosphorylation, and NF-kappaB activation. To test this hypothesis, human coronary artery endothelial cells were treated with Ac-SDKP and then stimulated with TNFalpha. We found that TNFalpha-induced ICAM-1 expression was significantly decreased by Ac-SDKP in a dose-dependent manner. Ac-SDKP also decreased TNF-alpha-induced NF-kappaB translocation from cytosol to nucleus, as assessed by electrophoretic mobility shift assay, which correlated with a decrease in IkappaB phosphorylation. In addition, we found that Ac-SDKP decreased TNFalpha-induced IKK phosphorylation and IKKbeta expression. However, Ac-SDKP had no effect on TNFalpha-induced phosphorylation of p38 MAP kinase or ERK. Thus, we conclude that Ac-SDKP inhibition of TNFalpha activation of canonical, i.e. IKKbeta dependent, NF-kappaB pathway and subsequent increase in ICAM-1 expression is achieved via inhibition of IKKbeta.

Pulmonary

Chasteen K, **Awdish R**, **Mendez M**, **Buick D**, and **Kokas M**. Clear conversations: A comprehensive curriculum to facilitate translation of skills learned in simulated settings to improve communication in real clinical encounters *J Pain Symptom Manage* 2016; 51(2):384-385. PMID: Not assigned. Abstract

K. Chasteen, Henry Ford Hospital, Detroit, United States

Objectives • Apply a protocol for deliberate practice of communication skills in real encounters with the aid of a mobile app and online template. • Demonstrate at least two communication skills learned in simulation (eg, ask-tell-ask, empathic response, open-ended question to elicit patient values) in a real clinical encounter. Background. Communication skills training with simulated patients has gained traction in many academic centers as a way to improve communication skills. However, the optimal method to facilitate translation of skills learned in simulated settings to improve communication in real clinical encounters has not been described. Methods. We developed a comprehensive communication skills curriculum for physicians in the ICU that consists of (1) simulation-based communication skills workshops for ICU fellows, residents, and attending physicians; (2) standardized pre- and postfamily meeting team huddles following a template in a mobile app, which includes setting a communication goal and getting specific feedback; (3) online evaluation template to record family meeting feedback as a procedure; and (4) mandatory family meetings within 72 hours for all patients in the ICU with APACHE IV mortality >30%. We conducted a prospective cohort 2-week pilot study. We implemented the curriculum in one ICU unit and compared it to another geographically distinct ICU unit where the attending, fellow, and residents had not received simulation training or training on other aspects of the curriculum. Our main outcome measure was family satisfaction with physician communication in the ICU using a 10-question modified HCAPS survey. A secondary outcome was trainee self-perceived preparedness for end-of-life communication tasks in the ICU pre and post intervention. Results. Patients in the intervention group (n=15) scored significantly higher on satisfaction with physician communication than the control group (n=16) (p=0.0178). Trainees in the intervention group showed significant improvement in self-perceived preparedness in communication skills between pre and post intervention in expressing empathy, responding to families who deny the seriousness of their loved one's illness, and discussing spiritual issues. There were no significant differences pre and post intervention in the control group. Discussion. This comprehensive communication curriculum combining simulation-based training, deliberate practice at the bedside with the aid of a mobile app and online evaluation template, and mandatory early family meetings for high risk patients was associated with improved patient satisfaction with physician communication in the ICU and increased trainee preparedness for difficult communication tasks. Conclusion. This communication curriculum could serve as a model for optimal inpatient communication skills training for residents and fellows across all disciplines.

Radiation Oncology

Meyer JE, Dilling TJ, Amdur RJ, Strasser JF, Tendulkar R, Lee WR, Jani AB, **Elshaikh M**, Poppe MM, Takita C, Currey A, Cheng SK, Jagsi R, Kuo JV, Chen AM, Dragun AE, Bradley K, Beriwal S, Smith RP, Chen RC, Rosenzweig K, Kim S, and Mehta K. In regard to Wu and Vapiwala et al *Int J Radiat Oncol Biol Phys* 2016; 94(4):858-859. PMID: 26972659. Full Text

Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania.
Department of Radiation Oncology, Moffitt Cancer Center, Tampa, Florida.
Department of Radiation Oncology, University of Florida, Gainseville, Florida.
Department of Radiation Oncology, Helen F. Graham Cancer Center, Newark, Delaware.
Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio.
Department of Radiation Oncology, Duke University School of Medicine, Durham, North Carolina.
Department of Radiation Oncology, Emory University, Atlanta, Georgia.
Department of Radiation Oncology, Henry Ford Hospital, Wayne State University School of Medicine, Detroit, Michigan.
Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, Salt Lake City, Utah.
Department of Radiation Oncology, Jackson Memorial Hospital, University of Miami, Miami, Florida.
Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin.
Department of Radiation Oncology, New York Presbyterian Hospital, Columbia University College of Physicians and Surgeons, New York City, New York.
Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan.
Department of Radiation Oncology, University of California-Irvine, Irvine, California.
Department of Radiation Oncology, Jonsson Comprehensive Cancer Center, University of California-Los Angeles, Los Angeles, California.
Department of Radiation Oncology, James Graham Brown Cancer Center, University of Louisville School of Medicine, Louisville, Kentucky.
Department of Radiation Oncology, University of Wisconsin, Madison, Wisconsin.
Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.
Department of Radiation Oncology, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina.
Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York City, New York.
Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ.
Department of Radiation Oncology, Montefiore Medical Center, The Bronx, New York.

Radiaiton Oncology
Siddiqui F, **Bentley GA**, **McLean SA**, and **Ryu S**. Inflammatory pseudotumor of the pharynx: A rare entity *Indian J Cancer* 2015; 52(4):668-669. PMID: 26960513. Full Text

Department of Radiation Oncology, Henry Ford Health Systems, Detroit, MI-48202, USA.
Department of Otolaryngology, Head and Neck Surgery, Henry Ford Health Systems, Detroit, MI-48202, USA.

Radiology
Harkness BA, and Fahey FH. A report on the current state of nuclear medicine physics training: The findings of the AAPM/SNMMI joint task force *J Nucl Med* 2016;PMID: 26966159. Full Text

Henry Ford Hospital, United States;
Boston Children's Hospital, United States.

Radiology
Keller RA, **Marshall NE**, **Bey MJ**, **Ahmed H**, **Scher CE**, **van Holsbeeck M**, and **Moutzouros V**. Pre- and postseason dynamic ultrasound evaluation of the pitching elbow *Arthroscopy* 2015; 31(9):1708-1715. PMID: 26354194. Full Text

Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan, U.S.A.. Electronic address: robkeller23@gmail.com.
Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, Michigan, U.S.A.
Bone and Joint Center, Henry Ford Health System, Detroit, Michigan, U.S.A.
Department of Radiology, Henry Ford Health System, Detroit, Michigan, U.S.A.

PURPOSE: To use ultrasound imaging to document changes over time (i.e., preseason v postseason) in the pitching elbow of high school baseball pitchers. METHODS: Twenty-two high school pitchers were prospectively followed. Pitchers were evaluated after a 2-month period of relative arm rest via preseason physical exams, dynamic ultrasound imaging of their throwing elbow, and the Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) assessment. Players were reevaluated within 1 week of their last game. Dynamic ultrasound images were then randomized, blinded to testing time point, and evaluated by 2 fellowship-trained musculoskeletal radiologists. RESULTS: Average pitcher age was 16.9 years. Average pitches thrown was 456.5, maximum velocity 77.7 mph,

games pitched 7.3, and days off between starts 6.6. From preseason to postseason, there were significant increases in ulnar collateral ligament (UCL) thickness (P = .02), ulnar nerve cross-sectional area (P = .001), UCL substance heterogeneity (P = .001), and QuickDASH scores (P = .03). In addition, there was a nonsignificant increase in loaded ulnohumeral joint space (P = .10). No pitchers had loose bodies on preseason exam, while 3 demonstrated loose bodies postseason. The increase in UCL thickness was significantly associated with the number of bullpen sessions per week (P = .01). The increase in ulnar nerve cross-sectional area was significantly associated with the number of pitches (P = .04), innings pitched (P = .01), and games pitched (P = .04). CONCLUSIONS: The stresses placed on the elbow during only one season of pitching create adaptive changes to multiple structures about the elbow including UCL heterogeneity and thickening, increased ulnohumeral joint space laxity, and enlarged ulnar nerve cross-sectional area. LEVEL OF EVIDENCE: Level II prospective observational study.

Radiology

Rezaeian MR, Hossein-Zadeh GA, and **Soltanian-Zadeh H**. Simultaneous optimization of power and duration of radio-frequency pulse in PARACEST MRI *Magn Reson Imaging* 2016;PMID: 26956610. Full Text

Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and Computer Engineering, College of Eng., Univ. of Tehran, Tehran, Iran. Electronic address: mrrezaeian@ut.ac.ir.
Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and Computer Engineering, College of Eng., Univ. of Tehran, Tehran, Iran. Electronic address: ghzadeh@ut.ac.ir.
Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and Computer Engineering, College of Eng., Univ. of Tehran, Tehran, Iran; Medical Image Analysis Laboratory, Radiology Department, Henry Ford Hospital, Detroit, Michigan, USA. Electronic address: hszadeh@ut.ac.ir.

Chemical exchange saturation transfer (CEST) MRI is increasingly used to probe mobile proteins and microenvironment properties, and shows great promise for tumor and stroke diagnosis. The CEST effect is complex and depends not only on the CEST agent concentration, exchange rates, the characteristic of the magnetization transfer (MT), and the relaxation properties of the tissue, but also varies with the experimental conditions such as radio-frequency (RF) pulse power and duration. The RF pulse is one of the most important factors that promote the CEST effect for biological properties such as pH, temperature and protein content, especially for contrast agents with intermediate to fast exchange rates. The CEST effect is susceptible to the RF duration and power. The present study aims at determining the optimal power and the corresponding optimal duration (that maximize the CEST effect) using an off-resonance scheme through a new definition of the CEST effect. This definition is formulated by solving the Bloch-McConnell equation through the R1rho method (based on the eigenspace solution) for both of the MT and CEST effects as well as their interactions. The proposed formulations of the optimal RF pulse power and duration are the first formulations in which the MT effect is considered. The extracted optimal RF pulse duration and power are compared with those of the MTR asymmetry model in two- and three-pool systems, using synthetic data that are similar to the muscle tissue. To validate them further, the formulations are compared with the empirical formulation of the CEST effect and other findings of the previous researches. By extending our formulations, the optimal power and the corresponding optimal duration (in the biological systems with many chemical exchange sites) can be determined.

Radiology

Shankar A, Borin TF, Iskander A, Varma NR, Achyut BR, Jain M, **Mikkelsen T**, Guo AM, Chwang WB, Ewing JR, **Bagher-Ebadian H**, and Arbab AS. Combination of vatalanib and a 20-HETE synthesis inhibitor results in decreased tumor growth in an animal model of human glioma *Onco Targets Ther* 2016; 9:1205-1219. PMID: 27022280. Full Text

Tumor Angiogenesis Laboratory, Cancer Center, Georgia Regents University, Augusta, GA, USA.
Laboratory of Molecular Investigation of Cancer (LIMC), Faculty of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Brazil.
Department of Radiology, Cellular and Molecular Imaging Laboratory, Detroit, MI, USA.
Department of Neurosurgery, Henry Ford Health System, Detroit, MI, USA.
Department of Pharmacology, New York Medical College, Valhalla, NY, USA.
Department of Neurology and Radiology, Henry Ford Health System, Detroit, MI, USA.

BACKGROUND: Due to the hypervascular nature of glioblastoma (GBM), antiangiogenic treatments, such as vatalanib, have been added as an adjuvant to control angiogenesis and tumor growth. However, evidence of progressive tumor growth and resistance to antiangiogenic treatment has been observed. To counter the unwanted effect of vatalanib on GBM growth, we have added a new agent known as N-hydroxy-N'-(4-butyl-2 methylphenyl)formamidine (HET0016), which is a selective inhibitor of 20-hydroxyeicosatetraenoic acid (20-HETE) synthesis. The aims of the studies were to determine 1) whether the addition of HET0016 can attenuate the unwanted effect of vatalanib on tumor growth and 2) whether the treatment schedule would have a crucial impact on

controlling GBM. METHODS: U251 human glioma cells (4x10(5)) were implanted orthotopically. Two different treatment schedules were investigated. Treatment starting on day 8 (8-21 days treatment) of the tumor implantation was to mimic treatment following detection of tumor, where tumor would have hypoxic microenvironment and well-developed neovascularization. Drug treatment starting on the same day of tumor implantation (0-21 days treatment) was to mimic cases following radiation therapy or surgery. There were four different treatment groups: vehicle, vatalanib (oral treatment 50 mg/kg/d), HET0016 (intraperitoneal treatment 10 mg/kg/d), and combined (vatalanib and HET0016). Following scheduled treatments, all animals underwent magnetic resonance imaging on day 22, followed by euthanasia. Brain specimens were equally divided for immunohistochemistry and protein array analysis. RESULTS: Our results demonstrated a trend that HET0016, alone or in combination with vatalanib, is capable of controlling the tumor growth compared with that of vatalanib alone, indicating attenuation of the unwanted effect of vatalanib. When both vatalanib and HET0016 were administered together on the day of the tumor implantation (0-21 days treatment), tumor volume, tumor blood volume, permeability, extravascular and extracellular space volume, tumor cell proliferation, and cell migration were decreased compared with that of the vehicle-treated group. CONCLUSION: HET0016 is capable of controlling tumor growth and migration, but these effects are dependent on the timing of drug administration. The addition of HET0016 to vatalanib may attenuate the unwanted effect of vatalanib.

Research Administration

Wolf B. First microdeletion involving only the biotinidase gene that can cause biotinidase deficiency: A lesson for clinical practice *Mol Genet Metab Rep* 2016; 6:74-76. PMID: 27014582. 27014582

Department of Research Administration, Henry Ford Hospital, Detroit, MI 48202, USA.

We report the first microdeletion (26 kb) of the biotinidase gene (BTD) that involves three of the four exons of the gene. This deletion further exemplifies the importance of performing microarray analysis or other methodologies for a deletion of the BTD gene when the enzymatic activity indicates lower activity than can be attributed to the mutations identified by DNA sequencing.

Sleep Medicine

Cheng P, and **Drake C**. Occupational sleep medicine *Sleep Med Clin* 2016; 11(1):65-79. PMID: 26972034. Full Text

Sleep Disorders and Research Center, Henry Ford Health System, Detroit, MI, USA.
Sleep Disorders and Research Center, Henry Ford Health System, Detroit, MI, USA. Electronic address: cdrake1@hfhs.org.

Sleep and circadian rhythms significantly impact almost all aspects of human behavior and are therefore relevant to occupational sleep medicine, which is focused predominantly around workplace productivity, safety, and health. In this article, 5 main factors that influence occupational functioning are reviewed: (1) sleep deprivation, (2) disordered sleep, (3) circadian rhythms, (4) common medical illnesses that affect sleep and sleepiness, and (5) medications that affect sleep and sleepiness. Consequences of disturbed sleep and sleepiness are also reviewed, including cognitive, emotional, and psychomotor functioning and drowsy driving.

Sleep Medicine

Connor KM, Mahoney E, Jackson S, Hutzelmann J, Zhao X, Jia N, Snyder E, Snavely D, Michelson D, **Roth T**, and Herring WJ. A phase II dose-ranging study evaluating the efficacy and safety of the orexin receptor antagonist filorexant (mk-6096) in patients with primary insomnia *Int J Neuropsychopharmacol* 2016;PMID: 26979830. Full Text

Merck & Co., Inc., Kenilworth, NJ, USA kathryn.connor@merck.com.
Merck & Co., Inc., Kenilworth, NJ, USA Biogen.
Merck & Co., Inc., Kenilworth, NJ, USA.
Merck & Co., Inc., Kenilworth, NJ, USA Janssen Pharmaceutical Research and Development.
Merck & Co., Inc., Kenilworth, NJ, USA Eli Lilly and Company.
Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: Filorexant (MK-6096) is an orexin receptor antagonist; here, we evaluate the efficacy of filorexant in the treatment of insomnia in adults. METHODS: A double-blind, placebo-controlled, randomized, two 4-week-period, adaptive crossover polysomnography study was conducted at 51 sites worldwide. Patients (18-<65 years) with insomnia received one of four doses of oral filorexant (2.5, 5, 10, 20 mg) once daily at bedtime during one period and matching placebo in the other period in one of eight possible treatment sequences. Polysomnography was performed

on Night 1 and end of Week 4 of each period. Primary endpoint was sleep efficiency (SE) at Night 1 and end of Week 4. Secondary endpoints included wakefulness after persistent sleep onset (WASO) and latency to onset of persistent sleep (LPS). RESULTS: A total of 324 patients received study treatment, 315 received >/=1 dose of placebo and 318 >/=1 dose of filorexant (2.5 mg, n=79; 5 mg, n=78; 10 mg, n=80; 20 mg, n=81). All filorexant doses (2.5/5/10/20 mg) were significantly superior to placebo in improving sleep among patients with insomnia as measured by SE and WASO on Night 1 and end of Week 4. The two higher filorexant doses (10/20 mg) were also significantly more effective than placebo in improving sleep onset as measured by LPS at Night 1 and end of Week 4. Filorexant was generally well tolerated. CONCLUSIONS: Orexin receptor antagonism by filorexant significantly improved SE in non-elderly patients with insomnia. Dose-related improvements in sleep onset and maintenance outcomes were also observed with filorexant.

Sleep Medicine
Palagini L, Bruno RM, **Cheng P**, Mauri M, Taddei S, **Ghiadoni L**, **Drake CL**, and Morin CM. Relationship between insomnia symptoms, perceived stress and coping strategies in subjects with arterial hypertension: Psychological factors may play a modulating role *Sleep Med* 2016; 19:108-115. PMID: Not yet assigned. Abstract

L. Palagini, Department of Clinical and Experimental Medicine, Psychiatric Unit, University of Pisa, School of Medicine, Pisa, Italy

Objective: The aim of the study was to evaluate perceived stress and coping strategies in people with hypertension, according to the presence of insomnia symptoms and by using a set of variables that included anxiety and depressive symptoms evaluation. Methods: A total of 371 hypertensive patients were enrolled during their first visit to the Hypertension Outpatient Unit. The Perceived Stress Scale (PSS), Brief-COPE, Insomnia Severity Index (ISI), Beck Depression Inventory (BDI), Self-rating Anxiety Scale (SAS), and State-Trait Anxiety Inventory (STAI) were administered. Patients with other sleep disorders or with incomplete data (n = 41) were excluded. Results: Data from 330 hypertensive patients were analyzed (males 51%, mean age 57 ± 13 years). Those with insomnia symptoms (n = 70, 21%) were older ($p = 0.02$), more frequently females ($p = 0.01$), and presented with higher PSS ($p < 0.001$), BDI ($p < 0.0001$), SAS ($p = 0.0003$), and STAI ($p < 0.0001$) scores than those without insomnia symptoms. In a linear regression trait, anxiety ($p < 0.0001$) and depressive symptoms ($p < 0.05$) were independent predictors of high PSS. Patients with insomnia symptoms showed lower scores in coping strategies, such as positive reframing ($p = 0.03$) and emotional support ($p = 0.04$), and an increased score in behavioral disengagement ($p = 0.03$). Trait anxiety and insomnia severity were independent predictors of less effective coping strategies. Conclusions: People with hypertension and insomnia symptoms showed higher perceived stress and less effective coping strategies than non-insomniacs; psychological factors such as trait anxiety and depressive symptoms may play a modulating role in these relationships. Prevention and treatment of insomnia symptoms and psychological factors should receive high attention for people with hypertension.

Sleep Medicine
Wickwire EM, Williams SG, **Roth T**, Capaldi VF, Jaffe M, Moline M, Motamedi GK, Morgan GW, Mysliwiec V, Germain A, Pazdan RM, Ferziger R, Balkin TJ, MacDonald ME, Macek TA, Yochelson MR, Scharf SM, and Lettieri CJ. Sleep, sleep disorders, and mild traumatic brain injury. What we know and what we need to know: Findings from a national working group *Neurotherapeutics* 2016;PMID: 27002812. Article Request Form

Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA. ewickwire@medicine.umaryland.edu.
Sleep Disorders Center, Division of Pulmonary and Critical Care, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA. ewickwire@medicine.umaryland.edu.
Department of Medicine, Walter Reed National Military Medical Center, Bethesda, MD, USA.
Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.
Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI, USA.
Department of Behavioral Biology, Walter Reed Army Institute of Research, Center for Military Psychiatry and Neuroscience Research, Silver Spring, MD, USA.
Department of Neurology, University of Florida, Gainesville, FL, USA.
Concussion and Sports Program, University of Florida Trauma, Gainesville, FL, USA.
UF Health Sleep Disorders Center, Gainesville, FL, USA.
Eisai, Inc., Woodcliff Lake, NJ, USA.
Department of Neurology, Georgetown University Hospital, Washington, DC, USA.
Sleep Disorders Center, National Intrepid Center of Excellence, Bethesda, MD, USA.
Department of Sleep Medicine, San Antonio Military Medical Center, San Antonio, TX, USA.
Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

U.S. Public Health Service, Fort Carson, CO, USA.
Merck and Co, Kenilworth, NJ, USA.
Defense and Veterans Brain Injury Center, (Contractor, General Dynamics Health Solutions), Evans Army Community Hospital, Fort Carson, CO, USA.
Department of Clinical Science, CNS, Takeda Development Center - Americas, Deerfield, IL, USA.
Medstar National Rehabilitation Network, Washington, DC, USA.
Departments of Neurology and Rehabilitation Medicine, Georgetown University School of Medicine, Washington, DC, USA.
Sleep Disorders Center, Division of Pulmonary and Critical Care, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA.

Disturbed sleep is one of the most common complaints following traumatic brain injury (TBI) and worsens morbidity and long-term sequelae. Further, sleep and TBI share neurophysiologic underpinnings with direct relevance to recovery from TBI. As such, disturbed sleep and clinical sleep disorders represent modifiable treatment targets to improve outcomes in TBI. This paper presents key findings from a national working group on sleep and TBI, with a specific focus on the testing and development of sleep-related therapeutic interventions for mild TBI (mTBI). First, mTBI and sleep physiology are briefly reviewed. Next, essential empirical and clinical questions and knowledge gaps are addressed. Finally, actionable recommendations are offered to guide active and efficient collaboration between academic, industry, and governmental stakeholders.

Surgery
Bunnapradist S, Rostaing L, Alloway RR, West-Thielke P, **Denny J**, Mulgaonkar S, and Budde K. LCPT Once-Daily Extended-Release Tacrolimus Tablets Vs. Twice-Daily Capsules: A Pooled Analysis of Two Phase 3 Trials in Important De Novo and Stable Kidney Transplant Recipient Subgroups *Transpl Int* 2016;PMID: 26953629. Full Text

David Geffen School of Medicine at UCLA, Los Angeles, CA.
Hopital de Rangueil/Larrey, Toulouse, France.
University of Cincinnati Medical Center & The Christ Hospital, Cincinnati, OH.
University of Illinois at Chicago, Chicago, IL.
Henry Ford Health System, Detroit, MI.
St. Barnabas Medical Center, Livingston, NJ.
Charite University, Berlin, Germany.

African-American and elderly kidney transplant recipients (KTR) have increased risk for poor clinical outcomes posttransplant. Management of immunosuppression may be challenging in these patients and contribute to worse outcomes. A novel once-daily formulation of tacrolimus (LCPT) has demonstrated non-inferiority, similar safety, improved bioavailability, a consistent concentration time profile, and less peak and peak-trough fluctuations vs. tacrolimus twice-daily (Tac BID). This pooled analysis of two phase 3 randomized, controlled trials, including 861 (LCPT N=428; Tac BID N=433; 38% of patients were stable KTR, and 62% were de novo KTR) patients, examined the efficacy of LCPT in KTR subgroups (blacks, females and age >/=65). Overall, treatment failure (death, graft failure, centrally read biopsy-proven acute rejection [BPAR], or lost to follow-up) at 12 months was: LCPT: 11.9%, BID Tac: 13.4% (-1.48% [-5.95%, 2.99%]). BPAR rates were: LCPT: 8.2%, Tac BID: 9.5% (-1.29% [-5.14%, 2.55%]). Numerically fewer treatment failure events with LCPT were found in the majority of subgroups, with significantly less treatment failure associated with LCPT among black KTR (-13.82% [-27.22%, -0.31%]) and KTR >/=65 (-13.46% [-25.27%, -0.78%]). This pooled analysis suggests numerically lower efficacy failure rates associated with LCPT amongst high-risk subgroups, in particular black KTR and KTR >/=65 years old.

Surgery
Gammon HM, **Shelton CB**, **Siegert C**, **Dawson C**, **Sexton E**, **Burmeister C**, **Gnam G**, and **Siddiqui A**. Self-turning for pressure injury prevention *Wound Medicine* 2016; 12:15-18. PMID: Not assigned Article Request Form

A. Siddiqui, Division of Plastic Surgery, K-16, Henry Ford Hospital, Detroit, United States

The study objective was to determine if hospitalized patients who are designated as self-turn would reposition themselves appropriately in the acute care setting. This was a prospective case series in a general practice unit of an 800-bed urban tertiary care hospital. Patients were instructed on the importance of mobility for pressure ulcer prevention and subsequently monitored on a continuous bedside pressure mapping device. Primary outcomes included intervals of inactivity and pressure ulcer incidence. During the 3-month study interval, only 2 patients had a documented 4-h interval without measurable repositioning. None of the 101 consecutive patients enrolled in the study developed pressure ulcers. General practice unit patients that are given proper instruction and designated as self-turn

can reliably be considered low-risk for hospital acquired pressure ulcers. Based on our prospective study, patients designated as self-turn do reposition themselves.

Surgery

Hencken L, **To L**, **Ly N**, and **Morgan JA**. Serotonin syndrome following methylene blue administration for vasoplegic syndrome *J Card Surg* 2016; 31(4):208-210. PMID: 26934199. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, Michigan.
Department of Cardiology, Henry Ford Hospital, Detroit, Michigan.
Department of Cardiac Surgery, Henry Ford Hospital, Detroit, Michigan.

Methylene blue (MB) has been used for additional blood pressure support in patients who develop severe, refractory vasoplegia; however, MB can induce serotonin syndrome, especially when used in conjunction with other serotonergic agents. We describe a case of serotonin syndrome in a patient who received MB for vasoplegic syndrome after left ventricular assist device implantation and discuss its presentation and management. doi: 10.1111/jocs.12705 (J Card Surg 2016;31:208-210).

Surgery

Kakkos SK, Kouri AK, Tsolakis IA, **Haddad GK**, Lampropoulos GC, and Karnabatidis D. Surgical and endovascular revision of brachio-basilic vein fistula *J Vasc Access* 2016; 17 Suppl 1:6-11. PMID: 26951896. Article Request Form

Department of Vascular Surgery, University Hospital of Patras, Patras - Greece.
Division of Vascular Surgery, Department of Surgery, Henry Ford Hospital, Detroit, Michigan - USA.
Department of Interventional Radiology, University Hospital of Patras, Patras - Greece.

PURPOSE: The brachio-basilic vein fistula (BBVF) is currently the third vascular access option for patients on hemodialysis, following radio-cephalic and brachio-cephalic arterio-venous fistulas. Like all types of hemodialysis vascular access, a variety of procedures may have to be performed in order to maintain long-term use of the BBVF. The aim of the present study was to perform a literature review of endovascular or surgical revisions of BBVFs. METHODS: On Pubmed search, 676 records were obtained and reviewed for relevance with the aim of the search. RESULTS: A variety of endovascular and surgical revision techniques has been described to manage BBVF poor maturation, dysfunction manifested as failing BBVF (most often the result of a stenosis at the transposed/swing segment), thrombosis, aneurysm formation and hemodialysis access-induced hand ischemia (steal syndrome). The role of revision is crucial in BBVF maintenance, taking into account that around 70% of these fistulas will require some intervention by 18 months and as a result of revision, secondary patency is preserved in the vast majority, according to the results of one study. Endovascular revision is the treatment of choice for most cases of BBVF dysfunction or thrombosis, with redo surgery reserved for failures of endovascular techniques or other specific indications. CONCLUSIONS: BBVF revision, more often in the form of endovascular surgery, plays a crucial role in BBVF maintenance and its continued use for hemodialysis, necessary for reducing graft and catheter use and the associated morbidity.

Surgery

Karamanos E, Van Esbroeck A, **Mohanty S**, Syed Z, and **Rubinfeld I**. Quality and outcomes reporting in trauma using international statistical classification for diseases, ninth revision codes *J Surg Res* 2015; 199(2):529-535. PMID: 26119273. Full Text

Department of Surgery, Henry Ford Hospital, Detroit, Michigan.
Department of EECS, University of Michigan, Ann Arbor, Michigan.
Department of Surgery, Henry Ford Hospital, Detroit, Michigan. Electronic address: irubinf1@hfhs.org.

BACKGROUND: Use of the trauma and injury severity score (TRISS) for quality and outcomes assessment is challenged by the need for laborious collection of demographic and physiological data. We hypothesize that a novel stratification approach based on International Statistical Classification for Diseases, Ninth Revision (ICD-9) data that are readily available for trauma patients provides a more accurate and more easily obtainable alternative to TRISS with the potential for widespread use. METHODS: Data from the ACS National Trauma Data Bank were used to train and evaluate a regularized logistic regression model for mortality and linear regression models for hospital length of stay (HLOS) and intensive care unit length of stay (ILOS) using ICD-9 diagnostic and procedural codes. Model training was performed on data from 2008 (n = 124,625) and evaluation on data from 2009 (n = 120,079). The discrimination and calibration of each model based on ICD-9 codes were compared with those of TRISS. RESULTS:

The mortality model using ICD-9 codes was comparable with that of TRISS in terms of the area under the receiver operating characteristic curve (0.922 versus 0.921, P = not significant.) and achieved better results in terms of both integrated discrimination improvement (0.106, P < 0.001) and Hosmer-Lemeshow chi-squared value (294.15 versus 2043.20). The HLOS and ILOS models using ICD-9 codes also demonstrated improvements in both R(2) (0.64 versus 0.30 for HLOS, 0.68 versus 0.34 for ILOS) and root mean-squared error (7.06 versus 8.62 for HLOS, 4.15 versus 9.54 for ILOS). CONCLUSIONS: Use of ICD-9 codes for stratification provides a more accurate and more broadly applicable approach to quality and outcomes assessment in trauma patients than the labor-intensive gold standard of TRISS.

Surgery
Likosky DS, Zhang M, **Paone G**, Collins J, DeLucia A, 3rd, Schreiber T, Theurer P, Kazziha S, Leffler D, Wunderly DJ, Gurm HS, and Prager RL. Impact of institutional culture on rates of transfusions during cardiovascular procedures: The Michigan experience *Am Heart J* 2016; 174:1-6. PMID: 26995363. Full Text

Department of Cardiac Surgery, University of Michigan, Ann Arbor, MI. Electronic address: likosky@umich.edu.
Department of Biostatistics, University of Michigan, Ann Arbor, MI.
Department of Surgery, Division of Cardiac Surgery, Henry Ford Hospital, Detroit, MI.
St Mary's of Michigan Saginaw, Saginaw, MI.
Department of Cardiothoracic Surgery, Bronson Methodist Hospital, Bronson, MI.
Detroit Medical Center-Cardiovascular Institute, Detroit, MI.
Department of Cardiac Surgery, University of Michigan, Ann Arbor, MI.
Crittenton Hospital, Rochester, MI.
Thoracic & Cardiovascular Institute, Sparrow Hospital, Lansing, MI.
Department of Cardiology, Bronson Methodist Hospital, Bronson, MI.
Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI.

BACKGROUND: Red blood cell (RBC) transfusions have been associated with morbidity and mortality in both coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI). As a mechanism for identifying determinants of RBC practice, we quantified the relationship between a center's PCI and CABG transfusion rate. METHODS: We identified all patients undergoing CABG (n = 16,568) or PCI (n = 94,634) at each of 33 centers from 2010 through 2012 in the state of Michigan and compared perioperative RBC transfusion rates for CABG and PCI at each center. Crude and adjusted transfusion rates were modeled separately. We adjusted for common preprocedural risk factors (12 for CABG and 23 for PCI) and reported Pearson correlation coefficients based on the crude and risk-adjusted rates. RESULTS: As expected, RBC transfusion was more common after CABG (mean 46.5%) than PCI (mean 3.3%), with wide variation across centers for both (CABG min:max 26.5:71.3, PCI min:max 1.6:6.0). However, RBC transfusion rates were significantly correlated between CABG and PCI in both crude, 0.48 (P = .005), and adjusted, 0.53 (P = .001), analyses. These findings were consistent when restricting to nonemergent cases (radj = 0.44, P = .001). CONCLUSIONS: Red blood cell transfusion rates were significantly correlated between the CABG and PCI at individual hospitals in Michigan, independent of patient case mix. Future work should explore institutional practice patterns, philosophies, and guidelines for RBC transfusions.

Surgery
Xuereb L, **Go PH**, **Kaur B**, Akrawe S, **Borgi J**, **Paone G**, and Morgan JA. Should patients with hepatic fibrosis undergo LVAD implantation: A comparative analysis *Asaio j* 2016;PMID: 27014788. Full Text

1. Wayne State University School of Medicine, Detroit, MI 2. Division of Cardiothoracic Surgery, Henry Ford Hospital, Heart and Vascular Institute, Detroit, MI 3. Division of Cardiothoracic Transplant and Assist Devices, Texas Heart Institute, Baylor College of Medicine, Houston, TX.

The purpose of our study was to evaluate outcomes in patients with hepatic fibrosis at the time of LVAD implantation. There were 5 (2.1%) patients with preoperative hepatic fibrosis with a mean age of 51.2 + 16.8 years. Survival at 180 days was significantly reduced in patients with hepatic fibrosis - 40.0% vs. 88.0%; p=0.001. Hepatic fibrosis was a significant independent predictor of mortality in multivariate analysis (HR 2.27, p=0.036).

Urology
Abdullah N, **Rahbar H**, **Barod R**, **Dalela D**, Larson J, Johnson M, Mass A, Zargar H, Allaf M, Bhayani S, Stifelman M, Kaouk J, and **Rogers C**. Multicentre outcomes of robot-assisted partial nephrectomy after major open abdominal surgery *BJU International* 2016;PMID: Not yet assigned.
Full Text

C. Rogers, Vattikuti Urology Institute, Henry Ford Health System, 2799 West Grand Boulevard, Detroit, MI 48202, USA

Objective: To evaluate the outcomes of robot-assisted partial nephrectomy RAPN after major prior abdominal surgery (PAS) using a large multicentre database. Patients and methods: We identified 1 686 RAPN from five academic centres between 2006 and 2014. In all, 216 patients had previously undergone major PAS, defined as having an open upper midline/ipsilateral incision. Perioperative outcomes were compared with those 1 470 patients who had had no major PAS. The chi-squared test and Mann-Whitney U-test were used for categorical and continuous variables, respectively. Results: There was no statistically significant difference in Charlson comorbidity index, tumour size, R.E.N.A.L. nephrometry score or preoperative estimated glomerular filtration rate (eGFR) between the groups. Age and body mass index were higher in patients with PAS. The PAS group had a higher estimated blood loss (EBL) but this did not lead to a higher transfusion rate. A retroperitoneal approach was used more often in patients with major PAS (11.2 vs 5.4%), although this group did not have a higher percentage of posterior tumours (38.8 vs 43.3%, P = 0.286). Operative time, warm ischaemia time, length of stay, positive surgical margin, percentage change in eGFR, and perioperative complications were not significantly different between the groups. Conclusions: RAPN in patients with major PAS is safe and feasible, with increased EBL but no increased rate of transfusion. Patients with major PAS had almost twice the likelihood of having a retroperitoneal approach.

Urology
Cole AP, **Abdollah F**, and Trinh QD. Observational studies to contextualize surgical trials *Eur Urol* 2016;PMID: 26992277. Full Text

Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
Henry Ford Hospital, Vattikuti Institute of Urology, Center for Outcomes Research, Analytics and Evaluation, Detroit, MI, USA.
Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
Electronic address: qtrinh@bwh.harvard.edu.

Urology
Hsu L, **Li H**, **Pucheril D**, Hansen M, **Littleton R**, **Peabody J**, and **Sammon J**. Use of percutaneous nephrostomy and ureteral stenting in management of ureteral obstruction *World J Nephrol* 2016; 5(2):172-181. PMID: 26981442. Full Text

Linda Hsu, Hanhan Li, Daniel Pucheril, Raymond Littleton, James Peabody, Jesse Sammon, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI 48202-2689, United States.

The management options for ureteral obstruction are diverse, including retrograde ureteral stent insertion or antegrade nephrostomy placement, with or without eventual antegrade stent insertion. There is currently no consensus on the ideal treatment or treatment pathway for ureteral obstruction owing, in part, to the varied etiologies of obstruction and diversity of institutional practices. Additionally, different clinicians such as internists, urologists, oncologists and radiologists are often involved in the care of patients with ureteral obstruction and may have differing opinions concerning the best management strategy. The purpose of this manuscript was to review available literature that compares percutaneous nephrostomy placement vs ureteral stenting in the management of ureteral obstruction from both benign and malignant etiologies.

Urology
Jeong W, **Kumar R**, and **Menon M**. Past, present and future of urological robotic surgery *Investig Clin Urol* 2016; 57(2):75-83. PMID: 26981588. Full Text

Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA.

The first urologic robotic program in the world was built at the Vattikuti Urology Institute, Henry Ford Hospital Detroit, Michigan, in 2000 under the vision of surgical innovator, Dr. Mani Menon for the radical prostatectomy. The robot-assisted radical prostatectomy continues being modified with techniques to improve perioperative and surgical outcomes. The application of robotic surgical technique has since been expanded to the bladder and upper urinary tract surgery. The evolution of surgical technique and its expansion of application will continue to improve quality, outcome parameters and experience for the patients.

Urology
Ng AM, Shah PH, and **Leavitt DA**. Headache and facial swelling *JAMA Surg* 2016;PMID: 27008236. Full Text

Hofstra North Shore-LIJ School of Medicine, Hempstead, New York.
Department of Urology, Smith Institute for Urology, North Shore-LIJ Health System, New Hyde Park, New York.
Department of Urology, Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan.