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Henry Ford Health System Publication List – June 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 July, and then imported into EndNote for formatting.There are 113 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.

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Cardiology / Cardiovascular Research

Collins SP, Levy PD, Martindale JL, Dunlap ME, Storrow AB, Pang PS, Albert NM, Felker GM, Fermann GJ, Fonarow GC, Givertz MM, Hollander JE, **Lanfear DJ**, Lenihan DJ, Lindenfeld JM, Frank Peacock W, Sawyer DB, Teerlink JR, and Butler J. Clinical and research considerations for patients with hypertensive acute heart failure a consensus statement from the society for academic emergency medicine and the heart failure society of america acute heart failure working group *Acad Emerg Med* 2016;PMID: 27286136. Full Text

Vanderbilt University, Department of Emergency Medicine.
Wayne State University, Department of Emergency Medicine.
SUNY Downstate, Department of Emergency Medicine.
Case Western University, Department of Medicine.
Indiana University, Department of Emergency Medicine.
Cleveland Clinic, Department of Medicine.
Duke University, Department of Medicine.
University of Cincinnati, Department of Emergency Medicine.
University of California, Los Angeles, Department of Medicine.
Harvard Medical School, Department of Medicine.
Thomas Jefferson University, Department of Emergency Medicine.
Henry Ford Health System, Department of Medicine.
Vanderbilt University, Department of Medicine.
Baylor College of Medicine, Department of Emergency Medicine.
Maine Medical Center, Department of Medicine.
San Francisco VA Medical Center, Department of Medicine.
Stony Brook University, Department of Medicine.

Management approaches for patients in the emergency department (ED) who present with acute heart failure (AHF) have largely focused on intravenous diuretics. Yet, the primary pathophysiological derangement underlying AHF in many patients is not solely volume overload. Patients with hypertensive AHF (H-AHF) represent a clinical phenotype with distinct pathophysiologic mechanisms that result in elevated ventricular filling pressures. To optimize treatment response and minimize adverse events in this subgroup, we propose clinical management be tailored to a conceptual model of disease that is based on these mechanisms. This consensus statement reviews the relevant pathophysiology, clinical characteristics, approach to therapy, and considerations for clinical trials in ED patients with H-AHF. This article is protected by copyright. All rights reserved.

Cardiology / Cardiovascular Research

Hani Sabbah HN, **Gupta RC**, and **Sing-Gupta V**. Circulating blood levels of growth differentiation factor 11 are decreased in dogs with heart failure and restored after long-term therapy with elamipretide (Bendavia, MTP-131) *Eur J Heart Fail* 2016; 18:424. PMID: Not assigned. Abstract

H.N. Hani Sabbah, Henry Ford Hospital, Detroit, United States

Introduction: Growth differentiation factor 11 (GDF11), a member of the transforming growth factor beta superfamily, has been shown to decrease with advanced age. GDF11 is implicated as having a role in the stem cell differentiation into cardiomyocytes, in reducing brain natriuretic peptide (BNP) and increasing expression of SERCA-2a, an enzyme necessary for myocardial contraction and relaxation. Supplementation of GDF11 protein in mice has been shown to ameliorate age-related dysfunction of skeletal muscle (SM). Many of the abnormalities seen with advanced age also manifest in heart failure (HF) including cardiomyocyte dysfunction and loss, SM dysfunction and reduced SERCA-2a activity and expression. We previously showed that these abnormalities can be reversed in dogs with HF following long-term therapy with elamipretide (Bendavia, MTP-131), a novel mitochondria targeting peptide.
Purpose/Hypothesis: In the present study, we tested the hypothesis that plasma level of GDF11 is reduced in dogs with chronic HF and are restored following long-term therapy with elamipretide. Methods: Venous blood samples were obtained from 14 dogs at baseline (normal state) prior to induction of HF, after the induction of HF by intracoronary microembolizations but prior to any therapy and again at 3months after initiating therapy with either subcutaneous elamipretide (0.5 mg/kg/day, n=7) or saline v/v (Control, n=7). Plasma levels of GDF11 were measured using a dog specific commercially available (MyBiosource, San Diego, CA) enzyme-linked immunosorbent assay (ELISA) kit. Results: In control dogs, plasma level of GDF11 was 61.3±3.8 pg/ml at baseline and decreased to 36.2±0.9 pg/ml ($p<0.05$) when dogs were in HF and remained lower at 3 months after initiating therapy with saline (36.1±0.7 pg/ml). In dogs treated with elamipretide, plasma level of GDF11 was 62.9±5.6 pg/ml at baseline, decreased to 37.4±1.0 pg/ml ($p<0.05$) when dogs were in HF and increased to near normal levels (59.3±4.0 pg/ml) at 3 months after initiating therapy with elamipretide. Conclusions: As in aging, circulating plasma levels of GDF11 are decreased in HF dogs. Long-term treatment with elamipretide reverses this decline. These findings are consistent with previous observations of improved cardiomyocyte function, increased SERCA-2a activity, decreased circulating levels of BNP and improved SM structure in dogs with HF treated with elamipretide.

Cardiology / Cardiovascular Research

Hani Sabbah HN, **Gupta RC**, **Sing-Gupta V**, and **Zhang K**. Elamipretide (Bendavia, MTP-131) normalizes cGMP levels in left ventricular myocardium of dogs with advanced heart failure *Eur J Heart Fail* 2016; 18:296. PMID: Not assigned. Abstract

H.N. Hani Sabbah, Henry Ford Hospital, Detroit, United States

Background: The second messenger cyclic guanosine monophosphate (cGMP) is reduced in heart failure (HF) and is implicated in the progressive deterioration of both LV systolic and diastolic function that characterizes the HF state in patients with reduced ejection fraction (HFrEF). cGMP is also reduced in patients with HF and preserved ejection fraction (HFpEF) and can contribute to progressive worsening of LV relaxation. cGMP generated by guanylyl cyclases (GC) produces its effects by activation of several downstream effectors that include cGMP-dependent protein kinase and cGMP-regulated phosphodiesterases (PDEs). It is well known that the nitric oxide (NO)/soluble GC (NO-sGC) system, once activated, results in the formation of cGMP. In HF, NO generated by endothelial nitric oxide synthase (eNOS) is reduced leading to reduced activation of NO-sGC and, hence, reduced formation of cGMP. Limited activation of eNOS as a result of reduction in cGMP can also negatively impact mitochondrial biogenesis. We previously showed that elamipretide (Bendavia, MTP-131), a novel mitochondria-targeting peptide, improves LV systolic and diastolic function in HF dogs with reduced EF (HFrEF), normalizes maximum rate of ATP synthesis and levels of eNOS. Purpose / Hypothesis: This study tested the hypothesis that chronic therapy with elamipretide normalizes cGMP levels in LV myocardium of dogs with HFrEF (LV EF ~30%). Methods: Studies were performed in LV tissue of 14 HF dogs randomized to 3 months therapy with subcutaneous injections of elamipretide (0.5 mg/kg once daily, n=7) or saline (HF-Control, n=7). LV tissue from 6 normal (NL) dogs was used for comparisons. cGMP level (pmol/mg protein) was determined using commercially available Elisa kits. Protein level of eNOS was assessed in LV tissue homogenate by Western Blotting and bands quantified in densitometric units (du). Results: cGMP level in NL dogs was 1.02±0.1 pg/ml and decreased significantly in HF-Control dogs to 0.47±0.05 pg/ml ($p<0.05$). Treatment with elamipretide restored tissue levels of GMP to near normal (0.77±0.05 pg/ml) ($p<0.05$ vs. HF-Controls). eNOS level in NL dogs was 0.68±0.07 du and decreased to 0.19±0.02 du in HF-Controls ($p<0.05$). Treatment with elamipretide significantly increased protein levels of eNOS to levels closer to normal (0.38±0.03 du) ($p<0.05$ vs. HF-Controls). Conclusions: cGMP and eNOS levels are reduced in LV of dogs with advanced HF. Chronic therapy with elamipretide restores cGMP and eNOS levels to near normal. These findings suggest that elamipretide, in addition to being potentially useful for the treatment of HFrEF, may also be useful in the treatment of patients with HFpEF.

Cardiology / Cardiovascular Research

Hani Sabbah HN, **Gupta V**, **Gupta V**, and Emanuele M. Vepoloxamer (purified poloxamer-188) improves LV function, limits cardiomyocyte calcium overload and restores integrity of calciu cycling proteins in myocardium of dogs with advanced heart failure *European Journal of Heart Failure* 2016; 18:9. PMID: Not assingned. Abstract

H.N. Hani Sabbah, Henry Ford Hospital, Detroit, United States

Background: Calcium overload occurs in cardiomyocytes (CMs) of the failing heart and contributes to cell death and progressive LV dysfunction. Vepoloxamer (VEPO), purified poloxamer-188, is a rheologic agent that improves microvascular blood flow and repairs damaged cell membranes. It is under investigation in a phase-3 trial in patients with acute sickle cell crisis and in phase-2a trial in patients with heart failure (HF). Purpose: We examined the effects of multiple acute infusions of VEPO on LV function in dogs with (HF) (LV ejection fraction, EF~30%) and tested the hypothesis that the membrane reparative properties of VEPO attenuate calcium overload in failing CMs by inhibiting unregulated calcium entry into cells and, in doing so, reverses abnormalities of sarcoplasmic reticulum (SR) calcium cycling proteins. Methods: 14 HF dogs were randomized to 2, 2 hrs infusions of VEPO (450 mg/kg, n=7) or saline (control, n=7) given 3 weeks (W) apart. LV EF and plasma troponin-I (TnI) were measured at baseline, at end of infusion and at 1 and 3W after each infusion. LV tissue obtained at end of study was used to assess calcium ATPase activity (CaAA) and protein levels of phosphorylated (p) ryanodine receptors at serine-2808 (p-RYR-s2808) and p-sodium-calcium-exchanger 1 (p-NCX-1) by Western blotting. Tissue from 7 normal (NL) dogs was used for comparisons. Separately, freshly isolated CMs from 6 control dogs were incubated for 2 hrs with VEPO (4.5 mg/ml) or saline and then treated with 10 μM Fura-2 AM to flourometrically assess intracellular calcium concentration. Results: VEPO increased EF by 6.0±0.7%∗ at 2 hrs; 7.0±0.7%∗% at 1W; 1.0±0.6% at 3W; 6.0±1.3%∗ at 4W and 5.9±1.3%∗ at 6W and reduced TnI by 0.02±0.04 ng/ml at 2hrs; 0.18±0.04∗ ng/ml at 1W; 0.13±0.03∗ ng/ml at 3W; 0.23±0.03∗ ng/ml at 4W and 0.17±0.03∗ ng/ml at 6W(∗=p<0.05 vs. control). CaAA was reduced and p-RYR-s2808 and p-NCX-1 levels increased in HF-Controls compared to NL. VEPO therapy normalized all SR proteins (Table). Treatment of isolated CMs with VEPO reduced intracellular calcium compared to saline (2.32±0.05 vs. 3.14±0.32 relative flourometric units, p<0.05). Conclusions: VEPO attenuates calcium overload and normalizes SR calcium cycling. This leads to lowering of TnI along with improvement of LV function. The results support the development of VEPO for treatment of patients with HF. (Table Presented).

Cardiology / Cardiovascular Research

Karmpaliotis D, Karatasakis A, **Alaswad K**, Jaffer FA, Yeh RW, Wyman RM, Lombardi WL, Grantham JA, Kandzari DE, Lembo NJ, Doing A, Patel M, Bahadorani JN, Moses JW, Kirtane AJ, Parikh M, Ali ZA, Kalra S, Nguyen-Trong PK, Danek BA, Karacsonyi J, Rangan BV, Roesle MK, Thompson CA, Banerjee S, and Brilakis ES. Outcomes with the use of the retrograde approach for coronary chronic total occlusion interventions in a contemporary multicenter US registry *Circ Cardiovasc Interv* 2016; 9(6)PMID: 27307562. Full Text

From the Center for Interventional Vascular Therapy at New York-Presbyterian Hospital/Columbia University Medical Center, New York (D.K., J.W.M., A.J.K., M.P., Z.A.A., S.K.); Department of Cardiology, VA North Texas Healthcare System and University of Texas Southwestern Medical Center, Dallas (A.K., P.-K.J.N.-T., B.A.D., J.K., B.V.R., M.K.R., S.B., E.S.B.); Department of Cardiology, Henry Ford Hospital, Detroit, MI (K.A.); Department of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston (F.A.J.); CardioVascular Institute at Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA (R.W.Y.); Lundquist Cardiovascular Institute, Torrance Memorial Medical Center, CA (R.M.W.); Cardiovascular Center, PeaceHealth St. Joseph Medical Center, Bellingham, WA (W.L.L.); Department of Interventional Cardiology, Mid America Heart Institute, Kansas City, MO (J.A.G.); Department of Interventional Cardiology, Piedmont Heart Institute, Atlanta, GA (D.E.K., N.J.L.); Department of Cardiology, Medical Center of the Rockies, Loveland, CO (A.D.); Division of Cardiovascular Medicine, VA San Diego Healthcare System and University of California (M.P., J.N.B.); and Boston Scientific, Natick, MA (C.A.T.). From the Center for Interventional Vascular Therapy at New York-Presbyterian Hospital/Columbia University Medical Center, New York (D.K., J.W.M., A.J.K., M.P., Z.A.A., S.K.); Department of Cardiology, VA North Texas Healthcare System and University of Texas Southwestern Medical Center, Dallas (A.K., P.-K.J.N.-T., B.A.D., J.K., B.V.R., M.K.R., S.B., E.S.B.); Department of Cardiology, Henry Ford Hospital, Detroit, MI (K.A.); Department of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston (F.A.J.); CardioVascular Institute at Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA (R.W.Y.); Lundquist Cardiovascular Institute, Torrance Memorial Medical Center, CA (R.M.W.); Cardiovascular Center, PeaceHealth St. Joseph Medical Center, Bellingham, WA (W.L.L.); Department of Interventional Cardiology, Mid America Heart Institute, Kansas City, MO (J.A.G.); Department of Interventional Cardiology, Piedmont Heart Institute, Atlanta, GA (D.E.K., N.J.L.); Department of Cardiology, Medical Center of the Rockies, Loveland, CO (A.D.); Division of Cardiovascular Medicine, VA San Diego Healthcare System and University of California (M.P., J.N.B.); and Boston Scientific, Natick, MA (C.A.T.). esbrilakis@gmail.com.

BACKGROUND: We sought to examine the efficacy and safety of chronic total occlusion percutaneous coronary intervention using the retrograde approach. METHODS AND RESULTS: We compared the outcomes of the retrograde versus antegrade-only approach to chronic total occlusion percutaneous coronary intervention among 1301 procedures performed at 11 experienced US centers between 2012 and 2015. The mean age was 65.5+/-10 years, and 84% of the patients were men with a high prevalence of diabetes mellitus (45%) and previous coronary

artery bypass graft surgery (34%). Overall technical and procedural success rates were 90% and 89%, respectively, and in-hospital major adverse cardiovascular events occurred in 31 patients (2.4%). The retrograde approach was used in 539 cases (41%), either as the initial strategy (46%) or after a failed antegrade attempt (54%). When compared with antegrade-only cases, retrograde cases were significantly more complex, both clinically (previous coronary artery bypass graft surgery prevalence, 48% versus 24%; P<0.001) and angiographically (mean Japan-chronic total occlusion score, 3.1+/-1.0 versus 2.1+/-1.2; P<0.001) and had lower technical success (85% versus 94%; P<0.001) and higher major adverse cardiovascular events (4.3% versus 1.1%; P<0.001) rates. On multivariable analysis, the presence of suitable collaterals, no smoking, no previous coronary artery bypass graft surgery, and left anterior descending artery target vessel were independently associated with technical success using the retrograde approach. CONCLUSIONS: The retrograde approach is commonly used in contemporary chronic total occlusion percutaneous coronary intervention, especially among more challenging lesions and patients. Although associated with lower success and higher major adverse cardiovascular event rates in comparison to antegrade-only crossing, retrograde percutaneous coronary intervention remains critical for achieving overall high success rates.

Cardiology / Cardiovascular Research

Nakagawa P, **Xu J**, **Bordcoch G**, **Janic B**, and **Carretero OA**. Inhibition of neutrophil chemotaxis by N-acetyl-seryl-aspartyl-lysyl-proline and thymosin β4 *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

P. Nakagawa, Hypertension and Vasc. Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, United States

The role of neutrophils in heart failure has been extensively analyzed and it has been shown that they are the first cells that massively invade the myocardium after myocardial infarction (MI). N-Acetyl-Seryl-Aspartyl-Lysyl-Proline (Ac-SDKP) is a natural tetrapeptide that is released from its precursor thymosin β4 (TB4). Ac-SDKP and TB4 are shown to have beneficial effect in post MI cardiac healing by decreasing cardiac rupture and mortality in mice. Therefore we explored whether neutrophils play a role in the mechanism of AcSDKP and TB4 cardiac protection. We hypothesized that Ac-SDKP and TB4 contribute to heart healing in MI by inhibiting neutrophil chemotaxis. To test neutrophil chemotaxis we performed transwell chemotaxis assay using neutrophil differentiated HL-60 cells. We measured the migration of a) vehicle, b) Ac-SDKP (10, 100 nM), or c) TB4 (20 nM) pre-treated cells towards to a chemotactic bacterial formylated tripeptide N-formyl-met-leu-phe (fMLP) at 1nM. We also measured the effect of Ac-SDKP on neutrophil infiltration post-MI in mice. Ac-SKDP or vehicle were infused subcutaneously using osmotic minipumps at a dose of 1.6 mg/kg/day. Two days after minipump implantation, MI was induced by permanent ligation of the left descending coronary artery. Neutrophil infiltration was measured at 24 hrs post-MI by immunohistochemistry. At a dose of 100 nM Ac-SDKP reduced fMLP-induced neutrophil chemotaxis by 20 %. However, at 10 nM Ac-SDKP failed to inhibit neutrophil chemotaxis. TB4 at 20 nM completely inhibited neutrophil migration. In vivo, Ac-SDKP decreased neutrophil cardiac infiltration (veh: 44 vs Ac-SDKP: 13 cells/mm2; $p < 0.05$). We conclude that TB4 is a potent inhibitor of neutrophil chemotaxis, while Ac-SDKP exerts mild inhibitory effects. Inhibition of neutrophil chemotaxis could explain some of the beneficial effects of Ac-SDKP and TB4 in post MI cardiac inflammation and fibrosis.

Cardiology / Cardiovascular Research

Nguyen-Trong PK, **Alaswad K**, Karmpaliotis D, Lombardi W, Grantham JA, Lembo N, Kandzari D, Karatasakis A, Karacsonyi J, Danek BA, Rangan BV, Roesle M, Ayers CR, Thompson CA, Banerjee S, and Brilakis ES. Use of saphenous vein bypass grafts for retrograde recanalization of coronary chronic total occlusions: Insights from a multicenter registry *J Invasive Cardiol* 2016; 28(6):218-224. PMID: 27236005. Full Text

Dallas VA Medical Center (111A), 4500 South Lancaster Road, Dallas, TX 75216 USA. esbrilakis@gmail.com.

BACKGROUND: The use of saphenous vein grafts (SVGs) for retrograde native-vessel chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. METHODS: We retrospectively reviewed the medical records and coronary angiograms of retrograde CTO-PCI performed through an SVG at four United States institutions between 2012 and 2013. RESULTS: During the study period, retrograde CTO-PCI was performed in 144 of 572 cases (25.2%) and retrograde CTO-PCI via SVG in 21 patients (14.6% of all retrograde cases). Mean age was 71 +/- 7 years and 95.2% of the patients were men. The CTO target vessel was the right coronary (38%), circumflex (38%), and left anterior descending (24%) artery. Mean J-CTO score was 3.5 +/- 1.0. The most common reentry technique was reverse controlled antegrade dissection and reentry. Technical and procedural success rates were 86% and 81%, respectively, with retrograde SVG-PCI attempts being successful in 67%. A major adverse cardiac event occurred in 2 patients (1 periprocedural myocardial infarction and 1 tamponade resulting in death). Median contrast volume, fluoroscopy time, and procedure time were 250 mL, 91.6 minutes, and 214 minutes, respectively. Two SVGs were coiled due to competitive flow after CTO recanalization. CONCLUSION: Retrograde native-vessel

CTO-PCI via SVG represents a small proportion of retrograde CTO-PCIs and was associated with high technical success rates, but may carry increased risk for complications.

Cardiology / Cardiovascular Research
Shah J, **Jain T**, **Shah S**, **Mawri S**, and **Ananthasubramaniam K**. Rare case of unileaflet mitral valve *J Cardiovasc Ultrasound* 2016; 24(2):168-169. PMID: 27358711. Full Text

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

Unileaflet mitral valve is the rarest of the congenital mitral valve anomalies and is usually life threatening in infancy due to severe mitral regurgitation (MR). In most asymptomatic individuals, it is mostly due to hypoplastic posterior mitral leaflet. We present a 22-year-old male with palpitations, who was found to have an echocardiogram revealing an elongated anterior mitral valve leaflet with severely hypoplastic posterior mitral valve leaflet appearing as a unileaflet mitral valve without MR. Our case is one of the 11 reported cases in the literature so far. We hereby review those cases and conclude that these patients are likely to be at risk of developing worsening MR later in their lives.

Cardiology / Cardiovascular Research
Shavelle DM, Kirtane AJ, Schreiber TL, Kapasi NK, **O'Neill WW**, Moses JW, Popma J, and Matthews RV. Impact of surgical consultation on outcomes in hemodynamically supported high-risk percutaneous coronary intervention: Insights from protect ii randomized study *J Invasive Cardiol* 2016; 28(5):187-192. PMID: 26887029. Full Text

Division of Cardiovascular Medicine, University of Southern California, 1510 San Pablo Street, Suite 322, Los Angeles, CA 90033 USA. shavelle@usc.edu.

BACKGROUND: In observational studies of patients undergoing percutaneous coronary intervention (PCI), surgical ineligibility is associated with increased mortality. Whether the use of hemodynamic support during PCI can mitigate the adverse prognostic importance of surgical ineligibility is unknown. METHODS AND RESULTS: We sought to evaluate the association between request for surgical consultation (presumed surgical ineligibility) prior to PCI and clinical outcomes in 427 patients with multivessel coronary artery disease or unprotected left main disease and severely reduced left ventricular systolic function undergoing PCI assisted by hemodynamic support (intraaortic balloon pump or Impella) from the PROTECT II randomized trial. Patients in whom surgical consultation was requested prior to PCI (n = 201) were compared with those in whom surgical consultation was not requested (n = 226). The primary endpoint of this analysis was the composite of 90-day major adverse cardiac and cerebrovascular events (MACCE). Demographic and procedural variables were similar between patients receiving surgical consultation and patients not receiving surgical consultation, with the exception that the prevalence of prior coronary artery bypass graft surgery was significantly higher in patients not receiving surgical consultation (42.0% vs 25.4%; P<.001); these patients also had a higher proportion of lesions within a saphenous vein graft, and a greater prevalence of moderate/severe vessel calcification. MACCE rate at 90 days was similar in patients receiving surgical consultation compared with patients not receiving surgical consultation (23.4% vs 29.0%, respectively; P=.19). CONCLUSIONS: In this high-risk cohort of patients undergoing hemodynamically supported PCI, clinical outcome was not associated with an antecedent request for surgical consultation (presumed surgical ineligibility). Whether the use of hemodynamically supported PCI can lessen the risk conferred by surgical ineligibility requires further study.

Center for Health Policy and Health Services Research
Jaffee KD, **Shires DA**, and **Stroumsa D**. Discrimination and delayed health care among transgender women and men: Implications for improving medical education and health care delivery *Med Care* 2016;PMID: 27314263. Full Text

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BACKGROUND: The transgender community experiences health care discrimination and approximately 1 in 4 transgender people were denied equal treatment in health care settings. Discrimination is one of the many factors significantly associated with health care utilization and delayed care. OBJECTIVES: We assessed factors associated with delayed medical care due to discrimination among transgender patients, and evaluated the relationship between perceived provider knowledge and delayed care using Anderson's behavioral model of health services utilization. RESEARCH DESIGN: Multivariable logistic regression analysis was used to test whether predisposing, enabling, and health system factors were associated with delaying needed care for transgender women and transgender men.

SUBJECTS: A sample of 3486 transgender participants who took part in the National Transgender Discrimination Survey in 2008 and 2009. MEASURES: Predisposing, enabling, and health system environment factors, and delayed needed health care. RESULTS: Overall, 30.8% of transgender participants delayed or did not seek needed health care due to discrimination. Respondents who had to teach health care providers about transgender people were 4 times more likely to delay needed health care due to discrimination. CONCLUSIONS: Transgender patients who need to teach their providers about transgender people are significantly more likely to postpone or not seek needed care. Systemic changes in provider education and training, along with health care system adaptations to ensure appropriate, safe, and respectful care, are necessary to close the knowledge and treatment gaps and prevent delayed care with its ensuing long-term health implications.

Center for Health Policy and Health Services Research

Li J, **Gordon S**, **Rupp L**, **Zhang T**, Boscarino J, Trinacty C, Schmidt M, Moorman A, Holmberg S, and **Lu M**. Long-term fibrosis and viral level progression among treated and untreated patients with chronic hepatitis B *J Hepatol* 2016; 64(2):S371. PMID: Not assigned. Abstract

J. Li, Department of Public Health Sciences, Detroit, United States

Background and Aims: The temporal relationship between HBV DNA viral load and liver fibrosis progression remains controversial. Using data from in the Chronic Hepatitis Cohort Study (CHeCS), a longitudinal study of patients from four large US health systems, we investigated long-term trajectories of viral load and FIB4 among HBV patients with and without antiviral therapy. Methods: Observation for each patient commenced at the “index date,” either the date of first treatment initiation (treated) or the earliest date of viral load measurement (untreated). Median FIB4 scores and viral load levels derived from routine testing were summarized in 30-day intervals for up to 5 years after index. Propensity scores for inverse probability of treatment weighting (IPTW) were used to control for bias in treatment selection. The propensity scores were derived using multiple logistic regression with a large selection of baseline covariates. Changes in FIB4 and viral load over time were modeled using a bivariate piecewise linear spline mixed effects model. Results: 1,126 untreated and 928 treated patients were included. The five-year dynamics of viral load and FIB4 exhibited a bi-phasic pattern. Viral load declined 31% ($p < 0.001$) per month for the first 5 months after treatment initiation, then slowed to a 2.3% ($p < 0.001$) decline per month thereafter. A non-significant viral load decline was observed for untreated patients. FIB4 began to decline 0.4% per month ($p < 0.001$) at 5 months post-treatment initiation and stabilized at 28 months. Starting at approximately 28 months after index, FIB4 significantly increased by 0.6% per month ($p < 0.001$) among untreated patients. FIB4 trajectories were consistent across baseline FIB4 levels. Conclusions: Antiviral therapy results in a rapid HBV DNA viral load decline followed by a delayed decline in FIB4. In untreated patients, viral load remains stable and significantly higher than in treated patients, and FIB4 gradually increases over time, suggesting fibrosis progression. (Figure presented).

Center for Health Policy and Health Services Research

Rossom RC, Shortreed S, Coleman KJ, Beck A, Waitzfelder BE, Stewart C, **Ahmedani BK**, Zeber JE, and Simon GE. Antidepressant adherence across diverse populations and healthcare settings *Depress Anxiety* 2016;PMID: 27320786. Full Text

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BACKGROUND: Early adherence is key to successful depression treatment, but nearly 60% of patients discontinue antidepressants within 3 months. Our study aimed to determine factors associated with poor early adherence to antidepressants in a large diverse sample of patients. METHODS: Six Mental Health Research Network healthcare systems contributed data for adults with depression and a new antidepressant start, defined by a washout period of at least 270 days, between January 1, 2010 and December 31, 2012. Pharmacy fill and self-reported race/ethnicity data were obtained from the electronic medical record. Patients had early adherence if they had a second antidepressant fill within 180 days of the first. We used logistic regression to investigate the relationship between early adherence and patient characteristics. RESULTS: A total of 177,469 adult patients had 184,967 new episodes of depression with a filled antidepressant prescription. Patients refilled their antidepressants within 180 days in 71% of episodes.

Race/ethnicity was a strong predictor of early adherence, with patients from racial/ethnic minorities other than Native Americans/Alaskan Natives less likely (adjusted odd ratios 0.50-0.59) to refill their antidepressants than non-Hispanic whites. Age, neighborhood education, comorbidity burden, provider type and engagement in psychotherapy were also associated with adherence. Other apparent predictors of early adherence, including neighborhood income, gender, and prior mental health hospitalizations, were no longer significant in the fully adjusted model. CONCLUSIONS: Race/ethnicity was a robust predictor of early antidepressant adherence, with minority groups other than Native Americans/Alaskan Natives less likely to be adherent. Further research is needed to determine whether early nonadherence in specific minority populations is intentional, due to side effects or patient preference, or unintentional and appropriate for targeted interventions to improve adherence.

Center for Health Promotion and Disease Prevention

Holm AL, **Rowe Gorosh M**, **Brady M**, and **White-Perkins D**. Recognizing privilege and bias: An interactive exercise to expand health care providers' personal awareness *Acad Med* 2016;PMID: 27355785. Full Text

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PROBLEM: Despite increasing awareness of the social determinants of health, health care disparities among sociocultural groups persist. Health care providers' unconscious bias resulting from unrecognized social privilege is one contributor to these disparities. APPROACH: In 2009, Henry Ford Health System initiated the Healthcare Equity Campaign both to raise employees' awareness of inequalities related to the social determinants of health and to increase their motivation to reduce them. After conducting awareness-raising activities to increase employees' understanding of the social determinants of health, a curriculum team developed the interactive Privilege and Responsibility Curricular Exercise (PRCE) and incorporated it into a series of trainings. The team designed the exercise to enhance participants' awareness of privilege in their lives and work, to improve their understanding of the impact of privilege on their own and others' lived experiences as a step beyond cultural competence toward cultural humility, and to encourage them to leverage their advantages to reduce health care inequities. OUTCOMES: About 300 participants of diverse professional and personal backgrounds from across the health system completed the training between the spring of 2009 and the spring of 2012, and many provided qualitative feedback about the exercise. Evaluations showed the exercise's potential as a powerful learning experience that might enhance a variety of equity- or diversity-related trainings, and also showed that participants considered the PRCE a highlight of the training. NEXT STEPS: The PRCE is worthy of additional study and could prove valuable to other organizations.

Dermatology

Foley P, **Stein-Gold L**, Kircik L, Fowler J, Jackson M, Tan J, Draleos Z, Fleischer A, Appell M, Steinhoff M, Lynde C, Hong L, and Jacovella J. Ivermectin 1% Cream, an effective and safe topical treatment of inflammatory lesions of papulopustular rosacea *Australas J Dermatol* 2016; 57:32. PMID: Not assigned. Abstract

P. Foley, Department of Dermatology, St Vincent's Hospital, Melbourne, Australia

Background: Treatments for papulopustular rosacea (PPR) are limited. The objective was to demonstrate the efficacy and safety of once-daily application of ivermectin 1% cream in subjects with moderate to severe PPR. Methods: Two identical 12-week, randomized, double-blind, parallel group, vehicle controlled studies were conducted with ivermectin 1% cream (IVM 1%) in subjects with moderate to severe PPR. Main efficacy assessments were Investigator's Global Assessment (IGA) of disease severity and inflammatory lesion counts. Safety assessments included incidence of adverse events (AEs)andlocal tolerance parameters. Subjects evaluated their rosacea and completed satisfaction and quality of life(QoL) questionnaires. Results: In both studies, a greater proportion of subjects in the IVM 1% group achieved treatment success (IGA “clear” or “almost clear”): 38.4% and 40.1% vs. 11.6% and 18.8% for vehicle (both $p < 0.001$), respectively. IVM 1% was superior to vehicle in terms of reduction from baseline in inflammatory lesion counts (76.0% and 75.0% vs. 50.0% for both vehicle groups, respectively). For all endpoints, starting at week 4 and continuing through the end of the study (week 12), IVM 1% was statistically significantly superior ($p < 0.001$). Fewer subjects treated by IVM 1% reported dermatologic AEs, and a higher proportion of subjects were observed to have no skin dryness or itching compared to vehicle. Significantly more

subjects receiving IVM 1% reported having an “excellent” or “good” improvement, along with an improved QoL. Conclusions: Ivermectin 1% cream was effective and safe in treating inflammatory lesions of papulopustular rosacea.

Dermatology
Mohammad TF, and **Hamzavi IH**. Practice and educational gaps in abnormal pigmentation *Dermatol Clin* 2016; 34(3):291-301. PMID: 27363886. Full Text

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Dyschromia refers to abnormal pigmentation and is one of the most common diagnoses in dermatology. However, there are many educational and practice gaps in this area, specifically in melasma, postinflammatory hyperpigmentation, and vitiligo. This article aims to review the gold standard of care for these conditions as well as highlight common educational and practice gaps in these areas. Finally, possible solutions to these gaps are addressed.

Dermatology
Ozog DM, Rkein AM, Fabi SG, Gold MH, Goldman MP, Lowe NJ, Martin GM, and Munavalli GS. Photodynamic therapy: A clinical consensus guide *Dermatol Surg* 2016; 42(7):804-827. PMID: 27336945. Full Text

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BACKGROUND: The American Society of Dermatologic Surgery (ASDS) periodically develops consensus documents for its members concerning various aspects of dermatologic surgery. Advances in photodynamic therapy (PDT) have been many and PDT use has been established in a variety of skin conditions. OBJECTIVE: The ASDS board of directors proposed a committee of experts in the field to develop consensus documents on different treatments. An expert panel reviewed the literature on PDT and discussed the findings. The consensus was reached with evidence-based recommendations on different clinical applications for PDT. PATIENTS AND METHODS: This consensus document includes discussions regarding PDT, including different photosensitizers and various light source activators, historical perspective, mechanism of action, various therapeutic indications and expected outcomes, pre- and post-care, and management of adverse outcomes. RESULTS: Photodynamic therapy is highly effective for pre-cancerous lesions, superficial nonmelanoma skin cancers, inflammatory acne vulgaris and other conditions. New protocols including laser mediated PDT significantly improve results for several indications. CONCLUSION: The ASDS consensus document on PDT will be helpful for educating members on safe and effective PDT for a variety of indications.

Dermatology
Yin C, **Weiland M**, **Li J**, **She R**, **Zhou L**, and **Mi Q**. Serum miRNAs as potential biomarkers for early prediction of type 1 diabetes *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

C. Yin, Immunology/Dermatology Department, Henry Ford Health System, Detroit, United States

Background The incidence of type 1 diabetes (T1D), a T cell-mediated beta cell destructive autoimmune disease, has been increasing about 3-4% annually for several decades. Individuals at risk for T1D are diagnosed at a late stage when the possibility for disease prevention is absent. Autoantibodies (AA) to islet antigens such as islet antigen (IA)-2, IA-2b, and glutamate decarboxylase (GAD65) appear earlier before T1D onset and are used for early T1D prediction. However, the appearance of islet AA marks a relatively late stage of the autoimmune process and therefore is not suitable for early disease intervention. More importantly AA lack causal relationship with the pathogenesis of T1D. Therefore, there is an urgent need for better (increased specificity/sensitivity) and earlier (predating autoantibodies) markers for the prediction of AA development. MicroRNAs (miRNAs) have emerged as an important regulatory factors in pancreatic β-cell development, homeostasis, function, and in a variety of immune cell development, differentiation and function. Our recent study showed that miRNAs regulate T1D development and serum miRNAs are potential biomarkers for T1D progression in mouse models. Our objective here is to identify

specific serum miRNA biomarkers for earlier and better prediction of individuals at risk for T1D in human. Method We performed serum miRNA expressions profiles in 35 AA positive (IAA and ICA) non-T1D subjects and 40 AA negative relative subjects from the Diabetes Prevention Trial-Type 1 (DPT-1) cohort, using the TaqMan low-density arrays. miRNAs with changed expression level were further confirmed by a single TaqMan RT-PCR. Result 9 miRNAs (miR-146a, miR-561 and miR-548a-3p, miR-184 and miR-200a) were down-regulated and 2 miRNAs (miR-30c and miR-487a) are up-regulated in the serum of AA+ non-T1D subjects compared to that from AA- subjects (two-sample t-test $P<0.05$). In addition, a cluster of five miRNAs (miR-146a, miR-197, miR-193b, miR-574-3p, and miR-561) was identified to clearly separate AA+ subjects from AA- subjects with higher sensitivity and specificity (LASSO logistic regression). miRNA target and pathway prediction analyses revealed that some of these miRNAs are related to immune function and beta-cell homeostasis and potentially involved in autoimmune processes. Conclusion We have identified distinct serum miRNA expressions profiles in AA+ subjects compared to AA- subjects. These serum miRNAs could serve as potential biomarkers for early prediction of autoimmune processes in individuals at risk for T1D, which need to be further confirmed in the future studies.

Dermatology

Zane LT, Chanda S, Jarnagin K, Nelson DB, Spelman L, and **Gold LS**. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies *Immunotherapy* 2016;PMID: 27283509. Article Request Form

Anacor Pharmaceuticals, Inc., 1020 East Meadow Circle, Palo Alto, CA, USA.
Veracity Clinical Research, Queensland, Australia.
Henry Ford Health System, Detroit, MI, USA.

Atopic dermatitis (AD), a chronic, relapsing, inflammatory skin disease that is characterized by intense pruritus and eczematous lesions with up to 90% of patients presenting with mild to moderate disease. Current topical treatments for AD have not changed in over 15 years and are associated with safety concerns. In AD, overactivity of phosphodiesterase 4 (PDE4), leads to inflammation and disease exacerbation. Crisaborole Topical Ointment, 2%, is a novel, nonsteroidal, topical anti-inflammatory PDE4 inhibitor currently being investigated for the treatment of mild to moderate AD. Preliminary studies in children and adults demonstrated favorable efficacy and safety profiles. Crisaborole may represent an anti-inflammatory option that safely minimizes the symptoms and severity of AD and that can be used for both acute and long-term management.

Dermatology

Zane LT, Eichenfield LF, Call RS, Forsha DW, Fowler JF, Hebert AA, Spellman M, **Gold LFS**, Van Syoc M, and Tschen EH. Long-term safety of Crisaborole Topical Ointment, 2%, in children and adults with mild-to-moderate atopic dermatitis *J Immunol* 2016; 196PMID: Not assigned. Abstract

L.T. Zane, Anacor Pharmaceuticals, Inc, United States

Atopic dermatitis (AD) is a chronic inflammatory skin disease that often requires long-term topical treatment. Crisaborole Topical Ointment, 2% (Anacor Pharmaceuticals, Inc., Palo Alto, CA), a novel nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 (PDE4) inhibitor, is currently being investigated for the treatment of AD. Herein we present the long-term safety results of patients ≥2 years of age with mild-to-moderate AD. A multicenter, open-label, long-term, 48-week, extension safety study was conducted in patients (N = 517) who opted to continue treatment after completing a 28-day Phase 3 pivotal study. Patients were assessed for AD severity every 4 weeks and treated with 4-week cycles of crisaborole as needed (Investigator's Static Global Assessment ≥2 [Mild]). During the open-label extension and the pivotal studies, 65% of patients reported at least 1 treatment-emergent adverse event (TEAE), most of which were mild (51.2%) or moderate (44.6%) in severity and considered unrelated to treatment (93.1%). Treatment-related AEs occurred in 10.2% of patients; the most frequently reported events were atopic dermatitis (3.1%), application site pain (burning/stinging, 2.3%), and application site infection (1.2%). None of the 7 treatment-emergent serious AEs that occurred in the extension study were considered treatment related. During the long-term study, only 9 patients (1.7%) discontinued the study because of TEAEs. No cutaneous adverse reactions such as application site atrophy, telangiectasia, or hypopigmentation were reported. The safety profile of crisaborole was similar across age groups. Crisaborole Topical Ointment, 2%, has a favorable safety profile for the long-term treatment of patients with AD.

Dermatology

Zane LT, Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL, **Gold LFS**, Zaenglein AL, and Hebert AA. Two phase 3 study results of children and adults

with mild-to-moderate atopic dermatitis treated with Crisaborole Topical Ointment, 2%, a novel, nonsteroidal, topical, anti-inflammatory, phosphodiesterase 4 inhibitor *J Immunol* 2016; 196PMID: Not assigned Abstract

L.T. Zane, Anacor Pharmaceuticals, Inc, United States

Up to 90% of children and adults with atopic dermatitis (AD), a chronic inflammatory skin disease, present with mild-to-moderate disease. Crisaborole Topical Ointment, 2%, is a novel, nonsteroidal, topical, anti-inflammatory, phosphodiesterase 4 inhibitor being studied for the treatment of AD. The efficacy and safety of crisaborole was assessed in 2 identically designed, multicenter, vehicle-controlled, double-blind Phase 3 studies (301 and 302) that enrolled patients ≥2 years old with mild-to-moderate AD affecting ≥5% of body surface area (BSA). Patients were randomized 2:1 to receive crisaborole or vehicle twice daily and evaluated on Days 8, 15, 22, and 29. The primary endpoint defined success in the Investigator's Static Global Assessment (ISGA) as “almost clear/1” or “clear/0” with ≥2-grade improvement from baseline at Day 29. Secondary endpoints analyzed the time to success and the percentage of patients achieving “almost clear/1” or “clear/0” on ISGA. At Day 29, more crisaborole-treated patients achieved ISGA success than vehicle (301: 32.8% vs 25.4%, P = 0.038; 302: 31.4% vs 18.0%, P < 0.001), with a greater percentage of “almost clear/1” or “clear/0” ISGA scores (301: 51.7% vs 40.6%, P = 0.005; 302: 48.5% vs 29.7%, P < 0.001). Success in ISGA scores was achieved earlier with crisaborole than vehicle (P < 0.001). Treatment-related adverse events (AEs) were usually mild and included upper respiratory tract infection (pooled data, crisaborole vs vehicle: 3.0% vs 3.0%) and application site pain (4.4% vs 1.2%). AE-related discontinuation rates were low for both groups (1.2%). 2 large Phase 3 studies demonstrated crisaborole may represent a novel, safe, and efficacious treatment for patients with mild-to-moderate AD.

Dermatology

Zhang L, **Yang M**, **Mayer T**, Johnstone B, **Les C**, **Frisch N**, **Parsons T**, **Mi QS**, and **Gibson G**. Use of MicroRNA biomarkers to distinguish enchondroma from low-grade chondrosarcoma *Connect Tissue Res* 2016:1-7. PMID: 27267924. Article Request Form

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b Department of Pathology , Henry Ford Hospital , Detroit , MI , USA.
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d Department of Orthopaedic Surgery , Henry Ford Hospital , Detroit , MI , USA.
e Department of Dermatology , Henry Ford Hospital , Detroit , MI , USA.

Establishing a definitive diagnosis between benign enchondroma versus low-grade chondrosarcoma presents a potential challenge to both clinicians and pathologists. microRNAs (small non-coding RNAs) have proven to be effective biomarkers for the identification of tumors and tumor progression. We present analysis, both array and quantitative PCR, that shows consistently and substantially increased expression of two microRNAs, miRs-181a and -138, in low-grade chondrosarcomas compared with enchondromas. The data suggest these microRNAs would provide an analytical distinction between the chondrosarcoma and benign neoplasms that can be performed in formalin-fixed paraffin-embedded specimens. Together with recent publications, these data indicate that miRs-181a and -138 also play a role in tumor development and homeostasis and may provide new targets for the development of much needed therapeutic intervention.

Emergency Medicine

Nguyen HB, **Jaehne AK**, Jayaprakash N, Semler MW, **Hegab S**, Yataco AC, **Tatem G**, Salem D, **Moore S**, Boka K, **Gill JK**, **Gardner-Gray J**, **Pflaum J**, **Domecq JP**, **Hurst G**, Belsky JB, **Fowkes R**, Elkin RB, Simpson SQ, Falk JL, Singer DJ, and **Rivers EP**. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE *Crit Care* 2016; 20(1):160. PMID: 27364620. Full Text

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Department of Emergency Medicine, Orlando Regional Medical Center, Orlando, Florida, USA.
University of Central Florida College of Medicine, Orlando, Florida, USA.
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Prior to 2001 there was no standard for early management of severe sepsis and septic shock in the emergency department. In the presence of standard or usual care, the prevailing mortality was over 40-50 %. In response, a systems-based approach, similar to that in acute myocardial infarction, stroke and trauma, called early goal-directed therapy was compared to standard care and this clinical trial resulted in a significant mortality reduction. Since the publication of that trial, similar outcome benefits have been reported in over 70 observational and randomized controlled studies comprising over 70,000 patients. As a result, early goal-directed therapy was largely incorporated into the first 6 hours of sepsis management (resuscitation bundle) adopted by the Surviving Sepsis Campaign and disseminated internationally as the standard of care for early sepsis management. Recently a trio of trials (ProCESS, ARISE, and ProMISe), while reporting an all-time low sepsis mortality, question the continued need for all of the elements of early goal-directed therapy or the need for protocolized care for patients with severe and septic shock. A review of the early hemodynamic pathogenesis, historical development, and definition of early goal-directed therapy, comparing trial conduction methodology and the changing landscape of sepsis mortality, are essential for an appropriate interpretation of these trials and their conclusions.

Emergency Medicine

Rooney KP, Lahham S, Lahham S, Anderson CL, Bledsoe B, Sloane B, Joseph L, Osborn MB, and Fox JC. Pre-hospital assessment with ultrasound in emergencies: implementation in the field *World J Emerg Med* 2016; 7(2):117-123. PMID: 27313806. Full Text

Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan 48202, USA.
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BACKGROUND: Point-of-care ultrasound (US) is a proven diagnostic imaging tool in the emergency department (ED). Modern US devices are now more compact, affordable and portable, which has led to increased usage in austere environments. However, studies supporting the use of US in the prehospital setting are limited. The primary outcome of this pilot study was to determine if paramedics could perform cardiac ultrasound in the field and obtain images that were adequate for interpretation. A secondary outcome was whether paramedics could correctly identify cardiac activity or the lack thereof in cardiac arrest patients. METHODS: We performed a prospective educational study using a convenience sample of professional paramedics without ultrasound experience. Eligible paramedics participated in a 3-hour session on point-of-care US. The paramedics then used US during emergency calls and saved the scans for possible cardiac complaints including: chest pain, dyspnea, loss of consciousness, trauma, or cardiac arrest. RESULTS: Four paramedics from two distinct fire stations enrolled a total of 19 unique patients, of whom 17 were deemed adequate for clinical decision making (89%, 95%CI 67%-99%). Paramedics accurately recorded 17 cases of cardiac activity (100%, 95%CI 84%-100%) and 2 cases of cardiac standstill (100%, 95%CI 22%-100%). CONCLUSION: Our pilot study suggests that with minimal training, paramedics can use US to obtain cardiac images that are adequate for interpretation and diagnose cardiac standstill. Further large-scale clinical trials are needed to determine if prehospital US can be used to guide care for patients with cardiac complaints.

Emergency Medicine

Wilson S, **Dev S**, **Mahan M**, **Malhotra M**, and **Miller J**. Identifying disparity in emergency department length of stay and admission likelihood *World J Emerg Med* 2016; 7(2):111-116. PMID: 27313805. Full Text

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BACKGROUND: To assess whether insurance status has an effect on emergency department (ED) length of stay (LOS) and likelihood for admission or transfer to an operating room. METHODS: This was a retrospective cross-sectional study of all encounters from January 2011 through October 2013 at an urban, academic trauma center. Analysis included multi-variable linear regression for ED LOS and logistic regression for the likelihood of admission. RESULTS: Overall, 201 535 patients met the inclusion criteria, for which the mean age was 43.8 years, 55.9% were female, 23.4% were uninsured and 8% were of non-black race. Admission rate was 24.5% and operative rate was 1.4%. After adjusting for age, sex, triage acuity and race, the presence of insurance coverage was associated with an increased ED LOS of 575 (95%CI 552-598) vs. 567 (95%CI 543-591) minutes (P<0.01) among admitted patients and a decreased ED LOS of 456 (95%CI 381-531) vs. 499 (95%CI 423-575) minutes (P<0.01) among those transferred to an operating room. Adjusting for these same predictors, insured status remained a predictor for admission (odds ratio 1.24, 95%CI 1.20-1.28, P<0.01) and a negative predictor for transfer to the operating room (odds ratio 0.84, 95%CI 0.77-0.92, P<0.01). CONCLUSION: The insured experienced a clinically insignificant increase in ED LOS when admitted and a 43-minute decrease in ED LOS when being transferred to the operating room. The insured were more likely to be admitted and less likely to be transferred to an operating room.

Family Medicine

Holm AL, **Rowe Gorosh M**, **Brady M**, and **White-Perkins D**. Recognizing privilege and bias: An interactive exercise to expand health care providers' personal awareness *Acad Med* 2016;PMID: 27355785. Full Text

A.L. Holm is project manager, Center for Health Promotion and Disease Prevention, Henry Ford Health System, Detroit, Michigan. M. Rowe Gorosh is senior staff, Department of Family Medicine, organizational and educational consultant, Institute on Multicultural Health, Henry Ford Health System, and associate clinical professor, Wayne State University School of Medicine, Detroit, Michigan. M. Brady is manager, Stroke Program, Department of Neuroscience, Henry Ford Hospital, Detroit, Michigan. At the time of this project, she was project manager, Institute on Multicultural Health, Henry Ford Health System, Detroit, Michigan. D. White-Perkins is director, Institute on Multicultural Health, Henry Ford Health System, senior staff and faculty member, Department of Family Medicine, and associate clinical professor, Wayne State University School of Medicine, Detroit, Michigan.

PROBLEM: Despite increasing awareness of the social determinants of health, health care disparities among sociocultural groups persist. Health care providers' unconscious bias resulting from unrecognized social privilege is one contributor to these disparities. APPROACH: In 2009, Henry Ford Health System initiated the Healthcare Equity Campaign both to raise employees' awareness of inequalities related to the social determinants of health and to increase their motivation to reduce them. After conducting awareness-raising activities to increase employees' understanding of the social determinants of health, a curriculum team developed the interactive Privilege and Responsibility Curricular Exercise (PRCE) and incorporated it into a series of trainings. The team designed the exercise to enhance participants' awareness of privilege in their lives and work, to improve their understanding of the impact of privilege on their own and others' lived experiences as a step beyond cultural competence toward cultural humility, and to encourage them to leverage their advantages to reduce health care inequities. OUTCOMES: About 300 participants of diverse professional and personal backgrounds from across the health system completed the training between the spring of 2009 and the spring of 2012, and many provided qualitative feedback about the exercise. Evaluations showed the exercise's potential as a powerful learning experience that might enhance a variety of equity- or diversity-related trainings, and also showed that participants considered the PRCE a highlight of the training. NEXT STEPS: The PRCE is worthy of additional study and could prove valuable to other organizations.

Gastroenterology

Gane EJ, Nguyen M, Kwo P, Kowdley K, Reau N, Jacobson I, Curry M, Pearlman B, Khalid O, Everson G, **Gordon S**, Poulos J, Sheikh A, Bernstein D, Yang JC, Stamm LM, An D, Dvory-Sobol H, Brainard DM, McHutchison JG, Tong M, Tsai N, Beavers KL, Rabinovitz M, Shiffman M, Stedman C, and Lawitz E. Short duration treatment with sofosbuvir/velpatasvir plus GS-9857 in treatment-naive genotype 1-6 HCV-infected patients with or without cirrhosis *J Hepatol* 2016; 64(2):S758-S759. PMID: Not assigned. Abstract

E.J. Gane, Auckland Clinical Studies, Auckland, New Zealand

Background and Aims: Sofosbuvir (SOF), velpatasvir (VEL), and GS- 9857 target 3 distinct viral proteins: NS5B, NS5A, and NS3, respectively. All 3 of these DAAs are pangenotypic, with high barriers to resistance. The combination of these DAAs could reduce treatment duration across all patient populations, without reducing efficacy. Two Phase 2 studies, GS-US-367-1168 and GS-US-367-1169, evaluated whether short duration SOF/VEL (400

mg/100 mg) + GS- 9857 (100 mg) can effectively treat genotype (GT) 1-6 HCV-infected, treatment-naïve patients with or without cirrhosis. Methods: Patients were assigned SOF/VEL + GS-9857 administered orally once daily for 6 or 8weeks based on the absence or presence of cirrhosis, respectively. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12) as assessed by the CAP/ CTM HCV 2.0 assay (LLOQ = 15 IU/mL). NS5B, NS5A, and NS3 regions were amplified and deep sequenced (<1% cutoff) at baseline and at the time of virologic failure. Results: A total of 130 patients (52% GT1, 9% GT2, 30% GT3, 8% GT4, and 1% GT6) were treated: 58% male, 82% white, 68% with non-CC IL28B allele(s), and 48% had documented cirrhosis. SVR12 rates are shown in the Table. Baseline resistance-associated variants (RAVs) were detected in 55% of patients (22% NS5A; 22% NS3, 4% NS5B [no S282T], and 8% with resistance to multiple classes of DAA). All treatment failures (n = 18) were due to virologic relapse. Final NS5B, NS5A, and NS3 RAVs detected at the time of relapse will be presented. Frequent adverse events (AE, >10%) were headache, fatigue, diarrhea, and nausea; most were mild or moderate in severity. Two (2%) patients had treatment-emergent SAEs of atrial flutter (n = 1) and vertigo (n = 1); and both were considered not related to study drug by the investigator. Two (2%) patients discontinued therapy due to AE(s) of asthenia, diarrhea, vomiting, and dehydration (n = 1) at Week 7; and fatigue (n = 1) at Week 5; both achieved SVR12. No clinically significant laboratory abnormalities were observed. Conclusions: Treatment with SOF/VEL + GS-9857 administered once daily for 8 weeks is safe, well tolerated, and highly effective in treatment-naïve, genotype 1-6 HCV-infected patients with cirrhosis. The 6 week treatment duration was associated with a higher relapse rate. This 3 drug combination is being further evaluated in Phase 3 trials, as a single tablet regimen for 8 weeks in treatment-naïve patients, with or without cirrhosis. (Table Presented).

Gastroenterology
Li J, **Gordon S**, **Rupp L**, **Zhang T**, Boscarino J, Trinacty C, Schmidt M, Moorman A, Holmberg S, and **Lu M**. Long-term fibrosis and viral level progression among treated and untreated patients with chronic hepatitis B *J Hepatol* 2016; 64(2):S371. PMID: Not assigned. Abstract

J. Li, Department of Public Health Sciences, Detroit, United States

Background and Aims: The temporal relationship between HBV DNA viral load and liver fibrosis progression remains controversial. Using data from in the Chronic Hepatitis Cohort Study (CHeCS), a longitudinal study of patients from four large US health systems, we investigated long-term trajectories of viral load and FIB4 among HBV patients with and without antiviral therapy. Methods: Observation for each patient commenced at the “index date,” either the date of first treatment initiation (treated) or the earliest date of viral load measurement (untreated). Median FIB4 scores and viral load levels derived from routine testing were summarized in 30-day intervals for up to 5 years after index. Propensity scores for inverse probability of treatment weighting (IPTW) were used to control for bias in treatment selection. The propensity scores were derived using multiple logistic regression with a large selection of baseline covariates. Changes in FIB4 and viral load over time were modeled using a bivariate piecewise linear spline mixed effects model. Results: 1,126 untreated and 928 treated patients were included. The five-year dynamics of viral load and FIB4 exhibited a bi-phasic pattern. Viral load declined 31% ($p < 0.001$) per month for the first 5 months after treatment initiation, then slowed to a 2.3% ($p < 0.001$) decline per month thereafter. A non-significant viral load decline was observed for untreated patients. FIB4 began to decline 0.4% per month ($p < 0.001$) at 5 months post-treatment initiation and stabilized at 28 months. Starting at approximately 28 months after index, FIB4 significantly increased by 0.6% per month ($p < 0.001$) among untreated patients. FIB4 trajectories were consistent across baseline FIB4 levels. Conclusions: Antiviral therapy results in a rapid HBV DNA viral load decline followed by a delayed decline in FIB4. In untreated patients, viral load remains stable and significantly higher than in treated patients, and FIB4 gradually increases over time, suggesting fibrosis progression. (Figure presented).

Gastroenterology
O'Leary JG, **Brown K**, Burton Jr J, Firpi-Morell R, Fontana RJ, Muir A, O'Brien C, Rabinovitz M, Rajender Reddy K, Ryan R, Shprecher A, Villadiego S, Prabhakar A, and Brown Jr RS. Efficacy and safety of simeprevir and sofosbuvir with and without ribavirin for 12 weeks in subjects with recurrent genotype 1 hepatitis C post-orthotopic liver transplant: The galaxy study *Journal of Hepatology* 2016; 64(2):S540. PMID: Not assigned. Abstract

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Background and Aims: Simeprevir (SMV) is a hepatitis C virus (HCV) protease inhibitor approved as part of a combination antiviral regimen to treat non-transplant patients with chronic hepatitis C genotype 1 infection. Methods: This is an ongoing, prospective, partially-randomised, phase 2, open-label study of once-daily SMV 150 mg + sofosbuvir (SOF; HCV nucleotide polymerase inhibitor) 400 mg with and without ribavirin (RBV) 1000 mg (1200 mg for subjects ≥75 kg) in subjects with recurrent genotype 1 HCV post-orthotopic liver transplant; the primary endpoint was the proportion of subjects with wk 12 sustained virologic response (SVR12). Choice of immunosuppression was

at the investigator's discretion, excluding cyclosporine due to the drug interaction with SMV. The first 33 subjects without cirrhosis were randomised 1:1:1 into three arms and stratified by genotype subtype and presence of Q80K: 1) SMV + SOF + RBV ×12 wks, 2) SMV + SOF ×12 wks, and 3) SMV + SOF ×24 wks; 13 additional subjects (2 with, 11 without cirrhosis) were enrolled in the SMV + SOF 24-wk arm. An interim analysis was performed when all subjects in the 12-wk arms reached the SVR12 timepoint. The final analysis (including pharmacokinetics) will be presented at the congress. Results: All 46 subjects received at least one dose of study drug; median age, 60 y; 74% male; 80% white; mean (standard deviation) baseline HCV RNA level, 6.4 (0.8) log10 IU/mL; 72% genotype 1a (three subjects/arm had Q80K). Median time since liver transplant was 4.5 y. At the time of analysis, five subjects in the 24-wk arm (without cirrhosis) and 22 subjects in the 12-wk arms had reached the SVR12 timepoint; 93% (25/27) achieved SVR12 (82% in RBV arm and 100% in arms without RBV). Two subjects did not achieve SVR12 (one had viral relapse at follow-up wk 4, one did not have wk 12 data [death by suicide]; both were in the RBV arm). Four (9%) subjects had a serious adverse event, considered unrelated to treatment per investigator. No episodes of acute rejection were reported. Conclusions: In liver transplant recipients with recurrent HCV infection, SMV + SOF treatment for 12-24 wks with or without RBV resulted in a high SVR12 rate (93%) and was well tolerated; SVR12was achieved by 100% of subjects with available data in both SMV + SOF arms without ribavirin, suggesting that 12 wks of SMV + SOF therapy is adequate for genotype 1 liver transplant subjects without cirrhosis.

Gastroenterology

Poordad F, **Gordon SC**, Asatryan A, Felizarta F, Reindollar RW, Landis C, Fried MW, Bernstein DE, Ng TI, Lin CW, Liu R, Kort J, and Mensa FJ. High efficacy of ABT-493 and ABT-530 in HCV genotype 1 infected patients who have failed direct-acting antiviral-containing regimens: The Magellan-i study *J Hepatol* 2016; 64(2):S160-S161. PMID: Not assigned. Abstract

F. Poordad, Texas Liver Institute, University of Texas, Health Science Center, San Antonio, United States

Introduction: There are limited HCV treatment options for patients with prior DAA treatment failure. We evaluated the efficacy and safety of the combination regimen of the NS3/4A protease inhibi ABT-493 plus the NS5A inhibitor ABT-530 with or without ribavirin (RBV) in HCV genotype 1 (GT1)-infected patients without cirrhosis who have failed DAA-containing regimens that included a protease inhibitor and/or NS5A inhibitor, with or without an NS5B polymerase inhibitor. Material and Methods: MAGELLAN-I is an ongoing phase 2, randomised, open-label study. Patients were randomized to receive once-daily ABT-493 (identified by AbbVie and Enanta) and ABT-530 at doses of 200 + 80 mg(Arm A), 300 + 120 mg + 800 mgRBV (Arm B), or 300 + 120 mg (Arm C), respectively, for 12 weeks. Patients who failed previous treatment for reasons other than breakthrough or relapse were excluded. Efficacy was assessed by sustained virologic response (HCV RNA < 15 IU/mL) at post-treatment week 12 (SVR12). Deep sequencing (Illumina MiSeq) was performed on HCV NS3 and NS5A genes from samples collected from all patients at baseline, and at the time of virologic failure. Results: Fifty patients were randomised, of whom 42 (84%) had GT1a infection and 33 (66%) had treatment experience with regimens that contained 2 or 3 DAAs. Deep sequencing revealed baseline resistanceassociated variants (RAVs) in 41 (82%) patients, 15 in NS3, 10 in NS5A, and 16with RAVs in both targets (Table). ArmAenrolment was stopped early to investigate higher doses of study drugs in other arms. Among patients with SVR12 data, SVR12 was achieved in 6/6 (100%) Arm A patients, 20/21 (95%) Arm B patients, and 19/20 (95%) Arm C patients. Twovirologic failures were observed; 1 relapse inanArmBpatient with baseline NS5A RAVs, and 1 breakthrough at treatmentweek 8 in ArmC in a patient with Crohn's disease on immune suppressant therapy, and with baseline NS3 and NS5A RAVs. The most common adverse events (AEs) were headache (28%), fatigue (26%), and nausea (20%). Two patients experienced serious AEs assessed as unrelated to study drug or RBV (breast cancer and femoral fracture). There were no grade 3 laboratory abnormalities or treatment discontinuations due to AE. Conclusion: The regimen of ABT-493 + ABT-530 with or without RBV for 12 weeks was well tolerated and achieved high SVR12 rates in non-cirrhotic HCV GT1-infected DAA-experienced patients, most of whom had baseline NS3 and/or NS5A RAVs. The addition of RBV did not appear to impact SVR. (Table Presented).

Hematology, Oncology and the Josephine Ford Cancer Institute

Penner LA, Dovidio JF, Gonzalez R, Albrecht TL, **Chapman R**, Foster T, Harper FW, Hagiwara N, Hamel LM, Shields AF, Gadgeel S, Simon MS, Griggs JJ, and Eggly S. The effects of oncologist implicit racial bias in racially discordant oncology interactions *J Clin Oncol* 2016;PMID: 27325865. Full Text

Louis A. Penner, Terrance L. Albrecht, Tanina Foster, Felicity W.K. Harper, Lauren M. Hamel, Anthony F. Shields, Shirish Gadgeel, Michael S. Simon, and Susan Eggly, Wayne State University; Robert Chapman, Henry Ford Health Care System, Detroit; Richard Gonzalez and Jennifer J. Griggs, University of Michigan, Ann Arbor, MI; John F. Dovidio, Yale University, New Haven, CT; and Nao Hagiwara, Virginia Commonwealth University, Richmond, VA. pennerl@karmanos.org.

Louis A. Penner, Terrance L. Albrecht, Tanina Foster, Felicity W.K. Harper, Lauren M. Hamel, Anthony F. Shields, Shirish Gadgeel, Michael S. Simon, and Susan Eggly, Wayne State University; Robert Chapman, Henry Ford Health Care System, Detroit; Richard Gonzalez and Jennifer J. Griggs, University of Michigan, Ann Arbor, MI; John F. Dovidio, Yale University, New Haven, CT; and Nao Hagiwara, Virginia Commonwealth University, Richmond, VA.

PURPOSE: Health providers' implicit racial bias negatively affects communication and patient reactions to many medical interactions. However, its effects on racially discordant oncology interactions are largely unknown. Thus, we examined whether oncologist implicit racial bias has similar effects in oncology interactions. We further investigated whether oncologist implicit bias negatively affects patients' perceptions of recommended treatments (i.e., degree of confidence, expected difficulty). We predicted oncologist implicit bias would negatively affect communication, patient reactions to interactions, and, indirectly, patient perceptions of recommended treatments. METHODS: Participants were 18 non-black medical oncologists and 112 black patients. Oncologists completed an implicit racial bias measure several weeks before video-recorded treatment discussions with new patients. Observers rated oncologist communication and recorded interaction length of time and amount of time oncologists and patients spoke. Following interactions, patients answered questions about oncologists' patient-centeredness and difficulty remembering contents of the interaction, distress, trust, and treatment perceptions. RESULTS: As predicted, oncologists higher in implicit racial bias had shorter interactions, and patients and observers rated these oncologists' communication as less patient-centered and supportive. Higher implicit bias also was associated with more patient difficulty remembering contents of the interaction. In addition, oncologist implicit bias indirectly predicted less patient confidence in recommended treatments, and greater perceived difficulty completing them, through its impact on oncologists' communication (as rated by both patients and observers). CONCLUSION: Oncologist implicit racial bias is negatively associated with oncologist communication, patients' reactions to racially discordant oncology interactions, and patient perceptions of recommended treatments. These perceptions could subsequently directly affect patient-treatment decisions. Thus, implicit racial bias is a likely source of racial treatment disparities and must be addressed in oncology training and practice.

Hematology, Oncology and the Josephine Ford Cancer Institute

Schering J, and **Donthireddy V**. Paraneoplastic syndrome in splenic marginal zone lymphoma: A rare phenomenon of paraplegia as an atypical presenting manifestation *Case Rep Hematol* 2016; 2016:7034167. PMID: 27293921. Full Text

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We describe a case presenting complaint of complete lower body paraparesis, which was discovered to have splenic marginal zone lymphoma (SMZL). While paraneoplastic syndromes are more common in tumors, such as small cell lung cancer, very few reports exist on this condition with SMZL. We describe such a rare entity with a clinical course spanning twenty-four months after diagnosis.

Hypertension and Vascular Research

Bryson TD, **Szandzik D**, and **Harding P**. Prostaglandin E2 inhibits monocyte chemotactic protein 5 production and secretion in mouse cardiac fibroblasts via EP4 receptor *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

T.D. Bryson, Hypertension and Vascular Research Division, Henry Ford Health System, Detroit, United States

Monocyte Chemotactic Protein 5 (MCP-5) is a chemokine that recruits monocytes and macrophages to sites of inflammation. Prostaglandin E2 (PGE2) is a local hormone that signals through four distinct G protein-coupled receptors (EP1, EP2, EP3 and EP4) and was recently shown to have both pro and anti- inflammatory actions depending on which receptor sub type is stimulated. Although all four EP receptors are expressed in the heart, it is unclear what role they play in physiological and pathological conditions. Previously, we have shown that cardiomyocyte-specific EP4 knockout (KO) mice have a phenotype of dilated cardiomyopathy coupled with elevated MCP-5 mRNA in the left ventricle, suggesting that MCP-5 may be regulated by PGE2 via its EP4 receptor and play a role in cardiac remodeling. Therefore, we hypothesized that PGE2 via EP4 receptor is anti-inflammatory; inhibiting MCP-5 in cardiac fibroblasts, which are a key cell type in the cardiac remodeling process. Primary cultures of cardiac fibroblasts from male C57 Bl/6 mice (16-21 weeks) were treated with vehicle, PGE2 (1 μM) or the EP4 receptor agonist (ONO-AE1-329; 1μM), in the presence or absence of lipopolysaccharide (LPS; 10 μg/μL), a known stimulator of MCP-5 release. Media and cells were harvested after 1 hr, 2 hrs, 4 hrs, and 24 hrs of treatment. MCP-5 secretion was determined by ELISA. LPS treatment for 4 hrs stimulated MCP-5 secretion 2.3-fold compared to vehicle ($p<0.05$, $n=7$) and this stimulation persisted for at least 24 hrs ($p < 0.001$). PGE2 treatment significantly attenuated this increase at both 4 hr and 24 hrs and reduced MCP-5 to baseline levels ($p<0.05$). Similarly, the EP4 receptor agonist reduced LPS-induced MCP-5 secretion at both 4 hrs and 24 hrs. To determine if the decrease in production/secretion

of MCP-5 was due to PGE2 affecting gene expression, MCP-5 mRNA was measured using real time RT-PCR. MCP-5 mRNA levels were markedly increased after LPS stimulation as early as 1 hour after treatment (3.8 fold that of vehicle, n=4) and remained elevated for 24 hrs. PGE2 treatment reduced LPS stimulation of MCP-5 mRNA by 48% at 2 hours (n=5) and continued to diminish MCP-5 mRNA throughout 24 hrs. Similarly, treatment with EP4 agonist attenuated the LPS-induced increase in MCP-5 mRNA at 2 hrs by 17% and continued to reduce MCP-5 mRNA throughout 24 hrs. To elucidate how PGE2 and the EP4 agonist inhibit LPS-induced MCP-5 secretion or production, we treated cells with dibutyryl cAMP (100 μM) since the EP4 receptor is coupled to increases in cAMP. LPS-stimulated MCP-5 secretion was not altered by co-treatment with dibutyryl cAMP. In conclusion, these data suggest that PGE2 acts through its EP4 receptor to affect MCP-5 production, but this appears to be independent of cAMP. This inhibitory effect of PGE2 and the EP4 agonist may reduce cell migration to sites of inflammation during various cardiac pathologies and could potentially exert a cardioprotective effect.

Hypertension and Vascular Research
Caceres PS, and **Ortiz PA**. Role of the novel kinase TNIK on NKCC2 surface expression, phosphorylation and na reabsorption in the thick ascending limb *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

P.S. Caceres, Hypertension and Vascular Research, Henry Ford Hospital, Detroit, United States

NaCl reabsorption by the thick ascending limb (TAL) of the loop of Henle maintains NaCl balance and is important for blood pressure regulation. The apical cotransporter NKCC2 mediates NaCl reabsorption in the TAL. In animal models of hypertension, NKCC2 phosphorylation at amino-terminal Thr-96,101 and its trafficking to the plasma membrane are enhanced. The kinases SPAK and OSR1 bind NKCC2 and phosphorylate Thr-96,101 and are important for blood pressure control. In addition to these, we recently showed that a novel kinase, Traf2 and NCK-interacting kinase (TNIK), also binds and phosphorylates Thr-96,101 in NKCC2. However, the role of TNIK on NKCC2 trafficking, activity and blood pressure regulation is unknown. We hypothesized that TNIK enhances NKCC2 phosphorylation, surface NKCC2 expression and NKCC2-dependent water and Na transport. To test this, we generated TNIK knockout (TNIK-/-) mice and measured phosphorylation of NKCC2 and surface expression in isolated TALs. We observed that NKCC2 phosphorylation at Thr-96,101 was decreased by 23 ± 6% ($p<0.05$) in TALs from TNIK-/- mice on a normal Na diet. Feeding mice a low-Na diet increased NKCC2 phosphorylation by 179 ± 38% in WT mice, but only by 56 ± 5% in TNIK-/- mice ($p<0.05$). The NKCC2 surface-to-intracellular ratio was decreased by 58 ± 4% in TALs from TNIK-/- on a normal diet and by 55 ± 16% on a low-Na diet. When placed in metabolic cages TNIK-/- mice excreted 99% more urine (WT = 1.03 ± 0.01 ml vs. TNIK-/- = 2.05 ± 0.13 ml; $p<0.05$). Baseline Na excretion was similar between strains on normal Na diet. However, after 48 hours of switching to low-Na diet, TNIK-/- mice excreted 75% more Na compared to WT (WT = 15 ± 0.7 μmol/day vs. TNIK-/- = 26 ± 5 μmol/day; $p<0.05$). To test whether TNIK mediates NKCC2-dependent Na excretion, we measured bumetanide-induced diuresis and natriuresis in TNIK-/- mice over a six-hour period following oral administration of bumetanide (1.66 mg/g food). On a normal diet, we did not observe any difference between strains. However, when placed on a low-Na diet, TNIK-/- mice showed decreased bumetanide-induced diuresis (WT = 2.66 ± 0.12 ml vs. TNIK-/- = 2.14 ± 0.11 ml; $p<0.05$) and natriuresis (WT = 239 ± 9 μmol vs. TNIK-/-= 201 ± 7 μmol; $p<0.05$). Finally, TNIK-/- mice had lower systolic blood pressure than WT mice when fed a low-Na diet (WT = 123 ± 3.9 mmHg vs. TNIK-/-= 105 ± 3 mmHg; $p<0.05$). We conclude that TNIK mediates NKCC2 phosphorylation, surface expression and is involved in NKCC2-mediated Na reabsorption during adaptation to low salt diet. TNIK-mediated activation of NKCC2 may also be involved in blood pressure control.

Hypertension and Vascular Research
Deshpande M, **Mali VR**, **Pan G**, **Xu J**, **Yang XP**, Thandavarayan RA, and **Palaniyandi SS**. Increased 4-hydroxy-2-nonenal-induced proteasome dysfunction is correlated with cardiac damage in streptozotocin-injected rats with isoproterenol infusion *Cell Biochem Funct* 2016; 34(5):334-342. PMID: 27273517. Full Text

Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Health System, Detroit, MI, USA.
Department of Cardiovascular Sciences, Center for Cardiovascular Regeneration, Houston Methodist Research Institute, Houston, TX, USA.

Increase in 4-hydroxy-2-nonenal (4HNE) due to oxidative stress has been observed in a variety of cardiac diseases such as diabetic cardiomyopathy. 4HNE exerts a damaging effect in the myocardium by interfering with subcellular organelles like mitochondria by forming adducts. Therefore, we hypothesized that increased 4HNE adduct formation in the heart results in proteasome inactivation in isoproterenol (ISO)-infused type 1 diabetes mellitus (DM) rats. Eight-week-old male Sprague Dawley rats were injected with streptozotocin (STZ, 65 mg kg(-1)). The rats were infused with ISO (5 mg kg(-1)) for 2 weeks by mini pumps, after 8 weeks of STZ injection. We studied normal control (n = 8)

and DM + ISO (n = 10) groups. Cardiac performance was assessed by echocardiography and Millar catheter at the end of the protocol at 20 weeks. Initially, we found an increase in 4HNE adducts in the hearts of the DM + ISO group. There was also a decrease in myocardial proteasomal peptidase (chymotrypsin and trypsin-like) activity. Increases in cardiomyocyte area (446 +/- 32.7 vs 221 +/- 10.83) (microm(2)), per cent area of cardiac fibrosis (7.4 +/- 0.7 vs 2.7 +/- 0.5) and cardiac dysfunction were also found in DM + ISO ($P < 0.05$) relative to controls. We also found increased 4HNE adduct formation on proteasomal subunits. Furthermore, reduced aldehyde dehydrogenase 2 activity was observed in the myocardium of the DM + ISO group. Treatment with 4HNE (100 muM) for 4 h on cultured H9c2 cardiomyocytes attenuated proteasome activity. Therefore, we conclude that the 4HNE-induced decrease in proteasome activity may be involved in the cardiac pathology in STZ-injected rats infused with ISO.

Hypertension and Vascular Research
Gordish KL, **Ortiz PA**, Garvin JL, and **Beierwaltes WH**. Enhanced dietary fructose rapidly induces salt-sensitive hypertension in rats *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

K.L. Gordish, Hypertension Res Div, Henry Ford Hospital, Detroit, United States

Fructose consumption is associated with increased sodium reabsorption, increased formation of reactive oxygen species, and the development of hypertension. In normal rats, 20% dietary fructose supplementation induces hypertension within 8-12 weeks. We hypothesized a diet combining 20% fructose supplemented with high salt (4% NaCl) would induce abnormal sodium retention, increased oxidative stress, and accelerate the development of elevated blood pressure. Rats weighing 200-225 g were pre-trained for 2 weeks for non-invasive tail cuff blood pressure measurements and then placed in metabolic caging. Rats were pair-fed for 2 weeks with one of 4 different diets: 1) control group (0.4% NaCl), 2) high salt chow group (4% NaCl), 3) 20% fructose group (in the drinking water), and 4) 20% fructose plus high salt group (n's = 9,5,9,18). Blood pressure, urinary sodium excretion and cumulative sodium balance were measured over 2 weeks and urinary 8-Isoprostane excretion, as a marker for reactive oxygen species, during the final two days. High salt chow replaced normal chow at the beginning of the second week. By the end of the protocol, systolic blood pressure was unchanged in control group (121±2 to 122±2 mmHg) as well as the high salt group (122±2 to 122±1 mmHg). 20% fructose alone had no effect on blood pressure over the 2 weeks (121±1 to 125±1 mmHg). However, blood pressure significantly increased in the 20% fructose plus high salt group (125 to 140 mmHg $p<0.001$). The increased blood pressure was concomitant with increased positive cumulative sodium balance. During the final week mean urinary sodium excretion in the high salt and 20% fructose plus high salt groups were 5-6 fold higher than normal salt controls ($p<0.001$): 1.13±0.07, 7.67±0.31, 1.20±0.10, 5.33±0.21 µmol/24 hrs, respectively. Despite similar consumption, urinary sodium excretion in the 20% fructose plus high salt group was significantly lower than the high salt group ($p<0.0001$). Urinary 8-Isoprostane excretion was significantly higher in the high salt, 20% fructose, and 20% fructose plus high salt groups compared to control: 16.4±1.3, 29.5±2.5, 32.2±3.9, 31.2±2.5 ng/24 hrs, ($p<0.001$). Our results suggests enhanced fructose and salt consumption increases sodium retention and oxidative stress. High salt can induce elevations in blood pressure in 20% fructose-fed rats within just one week. Increased blood pressure appears to associate with increased sodium retention and positive cumulative sodium balance. Overall, fructose combined with high salt in the diet contributes to the accelerated development of salt-sensitive hypertension.

Hypertension and Vascular Research
Gutierrez A, Goleva SB, Rhoads MK, Weaver CC, **Beierwaltes WH**, and Osborn JL. Altered renal and circulating renin-angiotensin system does not cause spontaneous hypertension in the african green monkey *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

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The renin-angiotensin system (RAS) is important in the long-term regulation of, sodium balance, body fluid volumes and blood pressure. The African Green Monkey, (AGM, Chlorocebus aethiops sabaeus) is a translational model of hypertension (HT) due to its close genetic similarity, behavioral activities and significant upright posture similar to humans. We hypothesized that upregulation of the RAS occurs in HT AGMs which may decrease Na+ excretion leading to Na+ retention and expansion of extracellular fluid volume. AGMs were phenotyped by systolic blood pressure (SBP) as HT (SBP>140 mmHg) or normotensive (NT, SBP<120 mmHg). Plasma and renal tissue samples were obtained from adult male AGMs with NT (n=26) having SBP of 98.2 ± 2.1 mmHg, HT AGMs (n=27) averaging 169.9 ± 6.1 mmHg. Plasma renin activity (PRA) and renal cortical renin content were determined by radioimmunoassay. Circulating PRA of NT (3.27 ± 0.36 ng AngI/ml/hr, n=15) and HT (3.34 ± 0.48 ng AngI/ml/hr, n=16) AGMs were not different ($p>0.05$). Renal cortex tissue was homogenized and incubated with excess renin substrate to measure renal cortical renin content (RCRC). Similar to PRA, RCRC of NT (10.73 ± 2.98 µg AngI/ml/hr/mg protein, n=11) and HT (8.94 ± 1.56 µg AngI/ml/hr/mg protein, n=13) AGMs were similar. Next,

angiotensinogen (AGT) expression was assessed from renal cortex, outer medulla and liver using qRT-PCR from extracted tissue RNA. Gene expression was normalized using RPS32 for kidney and RPS13A for liver. AGT expression was similar between NT and HT AGMs in the renal cortex (NT; 1 ± 0.55 vs HT; 1.74 ± 0.91), in the renal outer medulla (NT; 1 ± 0.16 vs HT; 0.59 ± 0.21) and liver (NT; 1 ± 0.14 vs HT; 1.19 ± 0.17, $p > 0.05$ for all tissues). To assess renal Na+ handling in HT (n=4) and NT (n=3) AGMs, animals were housed individually in pens and urine collected at 24 hour intervals for 5 consecutive days. Daily urinary sodium excretion of HT AGM's was greater than that of NT animals (HT; 2.86±0.40 mmol/day vs NT; 1.17±0.16 mmol/day, $p<0.05$) but urine osmolality was not different. The similar quantities of plasma and tissue renin, combined with unchanged gene expression of AGT, indicate that renin activity and renin substrate (angiotensinogen) in the RAS do not contribute to hypertension in the AGM. Thus, the long term altered blood pressure regulation and hypertension may result from elevated peripheral resistance due to other pressor mechanisms, as our data rules out any abnormal expression or activity of the renin-angiotensin system in this nonhuman primate model of heritable, genetic hypertension.

Hypertension and Vascular Research
Jaykumar AB, Caceres P, Ares G, **Beierwaltes W**, and **Ortiz P**. ALMS1 (Alstrom Syndrome 1), a new interacting protein of NKCC2, regulates apical NKCC2 trafficking, urinary concentration and blood pressure *FASEB Journal* 2016; 30 PMID: Not assigned. Abstract

A.B. Jaykumar, Henry Ford Hospital, Detroit, United States

NaCl absorption by the Thick Ascending Limb (TAL) is mediated by the apical Na/K/2Cl cotransporter, NKCC2. Increased NKCC2 activity and apical trafficking are associated to hypertension. However, only few proteins are known to bind and regulate NKCC2 trafficking. A 150 amino acid region in the carboxyl terminus of NKCC2 (C-NKCC2) was shown to be important for apical trafficking of NKCC2. We hypothesized that proteins which bind to this C-terminus region in NKCC2 play a role in regulating NKCC2 trafficking in the TAL. To identify new TAL proteins that bind C-NKCC2, we performed a proteomics-based screening of TAL proteins which interacted with Glutathione-S-Transferase-C-NKCC2, and identified Alstrom syndrome 1 (ALMS1) as an interacting partner. ALMS1 has been linked to human hypertension and renal function in Genome Wide Association Studies. Thus, we hypothesized that ALMS1 is involved in NKCC2 trafficking in the TAL, sodium reabsorption and blood pressure regulation. First, we confirmed that ALMS1 is expressed in TALs by Western blot and immuno-labeling of isolated perfused TALs. To study the role of ALMS1 we obtained ALMS1 KO rats in collaboration with the Genome Editing Rat Resource Consortium. To study the effect of ALMS1 deletion on NKCC2 trafficking we isolated outer medullary TALs and measured surface and total NKCC2 expression. In TALs from ALMS1 KO, the percentage of total NKCC2 at the surface was higher compared to WT (13.8 ± 1.2% vs 9.1 ± 1.0%, $p<0.05$, n=6). Total NKCC2 expression was not different between strains. Urine osmolality was 45% higher in ALMS1 KO rats (2800±37 vs. 1927±167 mOsm/kg H2O, $p<0.001$, n=5), whereas urinary volume was lower in ALMS1 KO (ALMS1: 10.1±0.5 vs. WT: 14.4± 1.7 ml/day, $p< 0.05$, n=5). Water intake was also lower in ALMS1 KO rats (18.4±1.1 vs. 28.2±1.5 ml/day, $p<0.001$, n=5). At three months of age, ALMS1 KO rats had higher mean arterial pressure (ALMS1: 141±5 vs WT: 99 ±6 mmHg, $p< 0.001$). Combined, these data indicate that ALMS1 binds and regulates NKCC2 trafficking and suggest that higher urine concentration is in part due to increased NKCC2 activity in the TAL of ALMS1 KO rats. We conclude that ALMS1 plays a role in NKCC2 trafficking and regulates blood pressure. The mechanism causing hypertension in ALMS1 KO rats may involve an increase in NKCC2 activity and higher sodium reabsorption by the TAL.

Hypertension and Vascular Research
Kumar N, **Nakagawa P**, **Janic B**, **Romero CA**, **Worou ME**, **Peterson EL**, Ongeri EE, Niyitegeka JMV, **Rhaleb NE**, and **Carretero OA**. The anti-inflammatory peptide AC-SDKP is released from thymosin β4 by meprin α and prolyl oligopeptidase *FASEB Journal* 2016; 30 PMID: Not assigned. Abstract

N. Kumar, Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, United States

N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a natural tetrapeptide with anti-inflammatory and anti-fibrotic properties. We have previously shown that prolyl oligopeptidase (POP) is involved in the Ac-SDKP release from thymosin β4 (Tβ4). However, POP can only hydrolyze peptides shorter than 30 amino acids and Tβ4 is 43 amino acids long. This suggests that Tβ4 must be hydrolyzed by another peptidase that releases N-terminal intermediate peptide(s) <30 amino acids before POP hydrolysis takes place. Our search in peptidase database for potential candidate(s) gave high score for meprin α metalloprotease. Therefore, we hypothesize that Tβ4 is hydrolyzed by meprin α prior to POP hydrolysis. To test this, in vitro and in vivo studies were performed. In vitro, we found that the incubation of Tβ4 with both, meprin α and POP releases Ac-SDKP, whereas it failed when Tβ4 is incubated with either meprin α or POP alone. Incubation of Tβ4 with rat kidney homogenate increases Ac-SDKP, which is blocked

by actinonin (meprin α inhibitor). In addition, kidney from meprin α knockout mice showed a significantly lower Ac-SDKP as compared to its wild type control. In vivo, we observed that rat treated with captopril (ACE inhibitor) increased plasma concentrations of Ac-SDKP, which is inhibited by the co-administration of actinonin (vehicle 3.1±0.22 nmol/L; captopril 15.1±0.7 nmol/L; captopril + actinonin 6.1±0.3 nmol/L; vehicle versus captopril, P<0.002; captopril versus captopril + actinonin, P<0.002). Similar results were obtained with urinary Ac-SDKP excretion. We conclude that Ac-SDKP is released from Tβ4 by the successive action of meprin α and POP.

Hypertension and Vascular Research

Mendez M. Renal cortical hydrogen peroxide (H2O2) stimulates renin release from juxtaglomerular (JG) cells and increases blood pressure: Role of JG cell NOX4 *FASEB Journal* 2016; 30 PMID: Not assigned. Abstract

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Renin plays an essential role in blood pressure control and the development of hypertension. Enhanced hydrogen peroxide (H2O2) levels in the kidney are associated with hypertension. This is thought to be due to direct stimulation of tubular salt transport and enhanced vascular reactivity. However, we previously found that H2O2 can directly stimulate renin release from renal juxtaglomerular (JG) cells suggesting that this pathway may also be responsible for the hypertension. However, it is not clear whether enhanced H2O2 in the renal cortex stimulates renin release and increases blood pressure. We hypothesized that enhancing renal cortical H2O2 stimulates renin release and increases blood pressure. To enhance renal cortical H2O2 in mice, we placed a subcapsular renal catheter connected to an osmotic minipump to reach a concentration of 1 μM, and measured blood pressure by radio telemetry and plasma renin concentration (PRC). Two days after infusion of H2O2, systolic blood pressure increased by 22±2 mmHg ($p<0.05$) and PRC doubled (from 110± 7 to 214±39 ngAngI/hr/ml, $p<0.05$). In control mice, with renal cortical infusion of saline, blood pressure and PRC were not different from baseline, indicating that renal cortical H2O2 increased renin release and blood pressure. In vivo, H2O2 produced by surrounding cells or endogenously produced, could enhance renin release. We found that in freshly isolated mouse JG cells, decreasing endogenous H2O2 with catalase (100U/ml) decreased baseline renin release by 45±9% ($n = 6$; $p < 0.05$) indicating that endogenously produced H2O2 tonically stimulates renin release. To start dissecting the enzymatic sources of H2O2 production, we studied the NADPH oxidase isoforms present in JG cells. By Western blot, we found that NOX1, NOX2 and NOX4 are expressed in JG cell lysates (n=3). By immunofluorescence and confocal imaging, we observed that NOX4 isoform is highly expressed in JG cell renin granules (n=3). Treating JG cells with apocynin (120 μM), a general inhibitor of NADPH oxidases, decreased renin release by 28±7% ($p<0.04$). To identify whether NOX4 mediates the endogenous H2O2 production, we used adenovirus mediated gene silencing of NOX4. Silencing NOX4 in JG cells decreased renin release by 34 ±4% ($p < 0.05$). We concluded that renal cortical H2O2 is a potent stimuli for renin release in vivo. Endogenously produced H2O2 from NOX4 expressed in mouse JG cells stimulates renin release. Our data suggest that enhanced renal cortical reactive oxygen species may induce hypertension by enhancing renin release. NOX4 inhibition in JG cells might be a candidate for renin release and blood pressure control.

Hypertension and Vascular Research

Nakagawa P, **Xu J**, **Bordcoch G**, **Janic B**, and **Carretero OA**. Inhibition of neutrophil chemotaxis by N-acetyl-seryl-aspartyl-lysyl-proline and thymosin β4 *FASEB Journal* 2016; 30 PMID: Not assigned. Abstract

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The role of neutrophils in heart failure has been extensively analyzed and it has been shown that they are the first cells that massively invade the myocardium after myocardial infarction (MI). N-Acetyl-Seryl-Aspartyl-Lysyl-Proline (Ac-SDKP) is a natural tetrapeptide that is released from its precursor thymosin β4 (TB4). Ac-SDKP and TB4 are shown to have beneficial effect in post MI cardiac healing by decreasing cardiac rupture and mortality in mice. Therefore we explored whether neutrophils play a role in the mechanism of AcSDKP and TB4 cardiac protection. We hypothesized that Ac-SDKP and TB4 contribute to heart healing in MI by inhibiting neutrophil chemotaxis. To test neutrophil chemotaxis we performed transwell chemotaxis assay using neutrophil differentiated HL-60 cells. We measured the migration of a) vehicle, b) Ac-SDKP (10, 100 nM), or c) TB4 (20 nM) pre-treated cells towards to a chemotactic bacterial formylated tripeptide N-formyl-met-leu-phe (fMLP) at 1nM. We also measured the effect of Ac-SDKP on neutrophil infiltration post-MI in mice. Ac-SKDP or vehicle were infused subcutaneously using osmotic minipumps at a dose of 1.6 mg/kg/day. Two days after minipump implantation, MI was induced by permanent ligation of the left descending coronary artery. Neutrophil infiltration was measured at 24 hrs post-MI by immunohistochemistry. At a dose of 100 nM Ac-SDKP reduced fMLP-induced neutrophil chemotaxis by 20 %.

However, at 10 nM Ac-SDKP failed to inhibit neutrophil chemotaxis. TB4 at 20 nM completely inhibited neutrophil migration. In vivo, Ac-SDKP decreased neutrophil cardiac infiltration (veh: 44 vs Ac-SDKP: 13 cells/mm2; $p < 0.05$). We conclude that TB4 is a potent inhibitor of neutrophil chemotaxis, while Ac-SDKP exerts mild inhibitory effects. Inhibition of neutrophil chemotaxis could explain some of the beneficial effects of Ac-SDKP and TB4 in post MI cardiac inflammation and fibrosis.

Hypertension and Vascular Research

Zhu L, **Xu J**, **Harding P**, and **Yang XP**. Role of ACE2 in the cardioprotective effects of angiotensin II type 2 receptors *FASEB Journal* 2016; 30 PMID: Not assigned. Abstract

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Blockade of angiotensin II (Ang II) type 1 receptors with angiotensin receptor blockers (ARBs) activates the Ang II type 2 receptors (AT2) and also increases angiotensin-converting enzyme 2 (ACE2) expression and Ang 1-7 levels. However, it is not known whether activation of AT2 and ACE2 are synergistically associated to exert cardioprotection. We hypothesize that activation of AT2 increases the expression and activity of ACE2, leading to cardioprotection. Transgenic mice with cardiac overexpression of AT2 (Tg-AT2) were subjected to myocardial infarction (MI) for 12 weeks. We found that Tg-AT2 mice had cardiac ACE2 protein expression 2.36±0.07-fold higher than the wild-type (WT) controls, associated with better preserved cardiac function compared with WT controls (ejection fraction: 41.6±2.3% vs 27.6±1.8%). In AT2-stimulated coronary artery endothelial cells, ACE2 protein expression was increased by 1.79±0.04-fold and ACE2 activity was enhanced from 0.61± 0.05 (basal) to 0.95±0.03 pg/μl/h/μg protein. These effects were blunted by AT2 antagonist. Furthermore, activation of AT2 increased cGMP by 1.71±0.12-fold, which was diminished by Mas receptors antagonist. AT2 activation also increased Ang 1-7 from 0.1±0.05 (basal) to 15.6±0.5 (pg/ml/μg protein) and this effect was diminished by the AT2 antagonist. Our data suggest that the cardioprotective effects of AT2 is in part mediated via activation of ACE2, enhancing the release of Ang 1-7 and leading to cardioprotection.

Infectious Diseases

Murphy MV, Du DT, Hua W, Cortez KJ, Butler MG, Davis RL, DeCoster TA, **Johnson L**, Li L, Nakasato C, Nordin JD, **Ramesh M**, Schum M, Von Worley A, Zinderman C, Platt R, and Klompas M. Risk factors for surgical site infections following anterior cruciate ligament reconstruction *Infect Control Hosp Epidemiol* 2016; 37(7):827-833. PMID: 27340734. Full Text

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OBJECTIVE To determine the effect of graft choice (allograft, bone-patellar tendon-bone autograft, or hamstring autograft) on deep tissue infections following anterior cruciate ligament (ACL) reconstructions. DESIGN Retrospective cohort study. SETTING AND POPULATION Patients from 6 US health plans who underwent ACL reconstruction from January 1, 2000, through December 31, 2008. METHODS We identified ACL reconstructions and potential postoperative infections using claims data. A hierarchical stratified sampling strategy was used to identify patients for medical record review to confirm ACL reconstructions and to determine allograft vs autograft tissue implanted, clinical characteristics, and infection status. We estimated infection rates overall and by graft type. We used logistic regression to assess the association between infections and patients' demographic characteristics, comorbidities, and choice of graft. RESULTS On review of 1,452 medical records, we found 55 deep wound infections. With correction for sampling weights, infection rates varied by graft type: 0.5% (95% CI, 0.3%-0.8%) with allografts, 0.6% (0.1%-1.5%) with bone-patellar tendon-bone autografts, and 2.5% (1.9%-3.1%) with hamstring autograft. After adjusting for potential confounders, we found an increased infection risk with hamstring autografts compared with allografts (odds ratio, 5.9; 95% CI, 2.8-12.8). However, there was no difference in infection risk among bone-patellar tendon-bone

autografts vs allografts (odds ratio, 1.2; 95% CI, 0.3-4.8). CONCLUSIONS The overall risk for deep wound infections following ACL reconstruction is low but it does vary by graft type. Infection risk was highest in hamstring autograft recipients compared with allograft recipients and bone-patellar tendon-bone autograft recipients. Infect Control Hosp Epidemiol 2016;37:827-833.

Infectious Diseases

Petrie JG, Ohmit SE, Cheng CK, Martin ET, Malosh RE, Lauring AS, **Lamerato LE**, **Reyes KC**, Flannery B, Ferdinands JM, and Monto AS. Influenza vaccine effectiveness against antigenically drifted influenza higher than expected in hospitalized adults: 2014-2015 *Clin Infect Dis* 2016; PMID: 27369320. Full Text

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BACKGROUND: The 2014-2015 influenza season was severe, with widespread circulation of influenza A (H3N2) viruses that were antigenically drifted from the vaccine virus. Reported vaccine effectiveness (VE) estimates from ambulatory care settings were markedly decreased. METHODS: Adults, hospitalized at two hospitals in southeast Michigan for acute respiratory illnesses, defined by admission diagnoses, of </=10 days duration were prospectively enrolled. Throat and nasal swab specimens were collected, combined, and tested for influenza by RT-PCR. VE was estimated by comparing the vaccination status of those who tested positive for influenza with those who tested negative in logistic regression models adjusted for age, sex, hospital, calendar time, time from illness onset to specimen collection, frailty score, and Charlson Comorbidity Index (CCI). RESULTS: Among 624 patients included in the analysis, 421 (68%) were considered vaccinated, 337 (54%) were female, 220 (35%) were age >/=65 years, and 92% had CCI >0 indicating >/=1 comorbid conditions. 98 (16%) patients tested positive for influenza A (H3N2); among 60 (61%) A (H3N2) viruses tested by pyrosequencing, 53 (88%) belonged to the drifted 3C.2a genetic group. Adjusted VE was 43% (95% CI: 4 to 67) against influenza A (H3N2); 40% (95% CI: -13 to 68) for those <65 years of age and 48% (95% CI: -33 to 80) for those >/=65. Sensitivity analyses largely supported these estimates. CONCLUSIONS: VE estimates appeared higher than reports from similar studies in ambulatory care settings, suggesting that the 2014-15 vaccine may have been more effective in preventing severe illness requiring hospitalization.

Internal Medicine

Abed F, Baniya R, and Bachuwa G. Quinine-induced disseminated intravascular coagulation *Case Rep Med* 2016; 2016:9136825. PMID: 27293443. Full Text

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Every drug comes with some side effect. It is the benefit/risk ratio that determines the medical use of the drug. Quinine, a known antimalarial drug, has been used for nocturnal leg cramps since the 1930s; it is associated with severe life-threatening hematological and cardiovascular side effects. Disseminated intravascular coagulation (DIC), albeit rare, is a known coagulopathy associated with Quinine. It is imperative to inquire about the Quinine intake in medication history in patients with coagulopathy, as most patients still consider it a harmless home remedy for nocturnal leg cramps. In this report, we present a case of coagulopathy in a middle-aged woman, who gave a history of taking Quinine for nocturnal leg cramps, as her home remedy. Early identification of the offending agent led to the diagnosis, prompt discontinuation of the medication, and complete recovery and prevented the future possibility of recurrence.

Internal Medicine

Barnes G, Cole D, Gu X, Haymart B, Kline-Rogers E, Almany S, Dahu M, Ekola M, Kozlowski J, **Krol G**, McNamara M, Kaatz S, and Froehlich J. Effectiveness of implementing an extended INR testing interval for stable warfarin patients: Results from the MAQI2 collaborative of anticoagulation clinics *J Thromb Haemost* 2016; 14:20-21. PMID: Not assigned Abstract

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Background: Warfarin-treated patients traditionally have INRs checked at least every 4 weeks. Based on randomized trial data, guidelines support the use of extended INR testing intervals of up to 12 weeks in stable patients. Aims: To assess the effectiveness of implementing an extended INR testing interval for stable warfarin-treated patients. Methods: Uncomplicated warfarin-treated patients at six anticoagulation clinics who had stable INR values and warfarin dosing for at least 10-24 weeks were eligible for extended INR testing (up to 6-8 weeks between INR tests). The number of eligible patients and the rate of extended INR testing utilization were assessed quarterly in 2014 (IRB approved). Follow up INR values were compared between eligible patients who did and did not receive an extended INR testing interval. Results: Of the 3221 patients in our cohort, 644 (20.0%) had stable INRs and warfarin dosing and were eligible for an extended INR testing interval and 380/644 (59%) had their INR interval extended 941 times. Extended INR testing interval patients more often had atrial fibrillation (65.5% vs. 55.3%, P = 0.01) and less often had venous thromboembolism (24.2% vs. 32.6%, P = 0.02) than eligible patients with standard INR testing intervals (up to 4 weeks). Eligible patients using an extended testing interval had a larger median number of days between INR values (42) than eligible patients with a standard testing interval (28; P < 0.01). The percent of eligible patients whose INR testing interval was extended beyond 4 weeks increased from 39.1% in 2014/Q1 to 58.6% in 2014/Q4 (P < 0.001 for trend; see Figure). Equal numbers of next INR values were out of range (28.5% vs. 26.0%; P = 0.73) as well as bleeding and thromboembolic events were documented between the eligible patients with a standard testing interval and an extended testing interval. (Figure presented) Conclusions: A concerted implementation effort can increase the adoption of an extended INR testing interval for stable warfarin patients without safety concerns.

Internal Medicine

Fahs F, **Bi XL**, **Yu FS**, **Zhou L**, and **Mi QS**. Small rnas play big roles: Micrornas in diabetic wound healing *Curr Mol Med* 2016;PMID: 27280494. Article Request Form

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Skin and corneal wounds in diabetics are a major healthcare burden. MicroRNAs are small, non-coding RNAs that post-transcriptionally regulate the expression of protein-coding genes. Studies have identified microRNAs involved in all phases of wound healing. The dysregulation of microRNAs can contribute to impaired or delayed skin and corneal wound healing in diabetics. Here, we present a comprehensive review of the literature involving microRNAs in diabetic skin and corneal wound healing as well as those serving as potential biomarkers for diabetic wound healing.

Internal Medicine

Kueht M, **Bebko S**, Helmick R, and Awad S. Hepatitis C status and infectious complications in the surgical intensive care unit: a retrospective analysis of 1,941 consecutive patients *Am J Surg* 2016; 211(6):1064-1070. PMID: 26746567. Full Text

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BACKGROUND: Hepatitis C virus (HCV) infection is thought to be associated with immune dysfunction. We hypothesized that HCV status would be associated with increased infectious complications in the surgical intensive care unit (SICU). METHODS: All patients admitted to our SICU between 2008 and 2012 were included. We evaluated 90-day mortality and infectious complications in the SICU. Multivariate logistic regression was performed to identify predictors of infectious complications and 90-day mortality. RESULTS: A total of 1,941 patients were included. The HCV-positive group had a higher overall incidence of infectious complications (25% vs 18%), particularly ventilator-associated pneumonia (VAP) and bacteremia. The increased incidences of VAP and bacteremia persisted when cirrhotic patients were excluded. Prolonged intubation (Odds Ratio [OR] = 2.1), abdominal surgery (OR = 1.6), and model for end-stage liver disease >/= 15 (OR = 1.4) were independent predictors of SICU infectious complications. CONCLUSIONS: The HCV-positive group had an increased incidence of infectious complications in the SICU, particularly VAP and bacteremia. This effect persisted when cirrhotic patients were excluded.

Internal Medicine

Nguyen HB, **Jaehne AK**, Jayaprakash N, Semler MW, **Hegab S**, Yataco AC, **Tatem G**, Salem D, **Moore S**, Boka K, **Gill JK**, **Gardner-Gray J**, **Pflaum J**, **Domecq JP**, **Hurst G**, Belsky JB, **Fowkes R**, Elkin RB, Simpson SQ, Falk JL, Singer DJ, and **Rivers EP**. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE *Crit Care* 2016; 20(1):160. PMID: 27364620. Full Text

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Prior to 2001 there was no standard for early management of severe sepsis and septic shock in the emergency department. In the presence of standard or usual care, the prevailing mortality was over 40-50 %. In response, a systems-based approach, similar to that in acute myocardial infarction, stroke and trauma, called early goal-directed therapy was compared to standard care and this clinical trial resulted in a significant mortality reduction. Since the publication of that trial, similar outcome benefits have been reported in over 70 observational and randomized controlled studies comprising over 70,000 patients. As a result, early goal-directed therapy was largely incorporated into the first 6 hours of sepsis management (resuscitation bundle) adopted by the Surviving Sepsis Campaign and disseminated internationally as the standard of care for early sepsis management. Recently a trio of trials (ProCESS, ARISE, and ProMISe), while reporting an all-time low sepsis mortality, question the continued need for all of the elements of early goal-directed therapy or the need for protocolized care for patients with severe and septic shock. A review of the early hemodynamic pathogenesis, historical development, and definition of early goal-directed therapy, comparing trial conduction methodology and the changing landscape of sepsis mortality, are essential for an appropriate interpretation of these trials and their conclusions.

Internal Medicine

Shah J, **Jain T**, **Shah S**, **Mawri S**, and **Ananthasubramaniam K**. Rare case of unileaflet mitral valve *J Cardiovasc Ultrasound* 2016; 24(2):168-169. PMID: 27358711. Full Text

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Unileaflet mitral valve is the rarest of the congenital mitral valve anomalies and is usually life threatening in infancy due to severe mitral regurgitation (MR). In most asymptomatic individuals, it is mostly due to hypoplastic posterior mitral leaflet. We present a 22-year-old male with palpitations, who was found to have an echocardiogram revealing an elongated anterior mitral valve leaflet with severely hypoplastic posterior mitral valve leaflet appearing as a unileaflet mitral valve without MR. Our case is one of the 11 reported cases in the literature so far. We hereby review those cases and conclude that these patients are likely to be at risk of developing worsening MR later in their lives.

Internal Medicine

Yessayan L, **Moore C**, **Lu M**, and **Yee J**. Bone-specific alkaline phosphatase and bone turnover in African American hemodialysis patients *Hemodial Int* 2016;PMID: 27350216. Full Text

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Introduction Noninvasive measures of bone activity include intact parathyroid hormone (iPTH) and bone-specific alkaline phosphatase (BSAP). Whether BSAP measurement alone or in combination with other biochemical data provides more reliable information about bone turnover than iPTH alone in African Americans on hemodialysis is unknown. Methods This cross-sectional study aimed to determine the optimal predictor and cutoff points for BSAP, iPTH, calcium and phosphorus in classifying bone biopsy findings. Forty-three African American hemodialysis patients were available for analysis. Biochemical data on the day of biopsy across a spectrum of qualitative histologic bone features were compared. Classification and regression tree analysis was used to determine both the optimal predictor and cutoff points for BSAP, iPTH, calcium and phosphorus in identifying bone turnover status. Findings Seven subjects had adynamic disease, 31 had mild/moderate hyperparathyroid bone features, and five had severe hyperparathyroid bone disease. BSAP was the optimal predictor of bone biopsy with a cutoff point of 22 ng/mL. Calcium and phosphorus had no predictive value. At BSAP </= 22 ng/mL, subjects had either adynamic bone disease or mild/moderate hyperparathyroid bone disease but iPTH was not useful in further classifying biopsy findings. When BSAP was >22 ng/mL, subjects had either mild/moderate or severe hyperparathyroid bone disease, and iPTH was useful in further classifying biopsy findings. With BSAP > 22 ng/mL and iPTH < 726 pg/mL, all subjects had mild/moderate bone turnover features. Discussion Compared to iPTH, BSAP was shown to be the optimal predictor of biopsy findings with an optimal cutoff at 22 ng/mL.

Nephrology

Neyra JA, Li X, Canepa-Escaro F, Adams-Huet B, Toto RD, **Yee J**, and Hedayati SS. Cumulative fluid balance and mortality in septic patients with or without acute kidney injury and chronic kidney disease *Crit Care Med* 2016;PMID: 27352125. Full Text

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OBJECTIVE: Incident acute kidney injury and prevalent chronic kidney disease are commonly encountered in septic patients. We examined the differential effect of acute kidney injury and chronic kidney disease on the association between cumulative fluid balance and hospital mortality in critically ill septic patients. DESIGN: Retrospective cohort study. SETTING: Urban academic medical center ICU. PATIENTS: ICU adult patients with severe sepsis or septic shock and serum creatinine measured within 3 months prior to and 72 hours of ICU admission. Patients with estimated glomerular filtration rate less than 15 mL/min/1.73 m or receiving chronic dialysis were excluded. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: A total of 2,632 patients, 1,211 with chronic kidney disease, were followed up until hospital death or discharge. Acute kidney injury occurred in 1,525 patients (57.9%), of whom 679 (44.5%) had chronic kidney disease. Hospital mortality occurred in 603 patients (22.9%). Every 1-L increase in cumulative fluid balance at 72 hours of ICU admission was independently associated with hospital mortality in all patients (adjusted odds ratio, 1.06 [95% CI] 1.04-1.08; p < 0.001), and in each acute kidney injury/chronic kidney disease subgroup (adjusted odds ratio, 1.06 [1.03-1.09] for acute kidney injury+/chronic kidney disease+; 1.09 [1.05-1.13] for acute kidney injury-/chronic kidney disease+; 1.05 [1.03-1.08] for acute kidney injury+/chronic kidney disease-; and 1.07 [1.02-1.11] for acute kidney injury-/chronic kidney disease-). There was a significant interaction between acute kidney injury and chronic kidney disease on cumulative fluid balance (p =0.005) such that different cumulative fluid balance cut-offs with the best prognostic accuracy for hospital mortality were identified: 5.9 L for acute kidney injury+/chronic kidney disease+; 3.8 L for acute kidney injury-/chronic kidney disease+; 4.3 L for acute kidney injury+/chronic kidney disease-; and 1.5 L for acute kidney injury-/chronic kidney disease-. The addition of cumulative fluid balance to the admission Sequential Organ Failure Assessment score had increased prognostic utility for hospital mortality when compared with Sequential Organ Failure Assessment alone, particularly in patients with acute kidney injury. CONCLUSIONS: Higher cumulative fluid balance at 72 hours of ICU admission was independently associated with hospital mortality regardless of acute kidney injury or chronic kidney disease presence. We characterized cumulative fluid balance cut-offs associated with hospital mortality based on acute kidney injury/chronic kidney disease status, underpinning the heterogeneity of fluid regulation in sepsis and kidney disease.

Nephrology

Singasani R, **Goggins M**, **Patel A**, and **Venkat K**. Liver transplant alone or simultaneous liver kidney transplantation? Case report illustrating dilemmas in patient selection for dual transplantation *Am J Kid Dis* 2016; 67(5):A101. PMID: Not assigned. Abstract

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The inferior outcomes of liver transplantation alone in end-stage liver disease (ESLD) associated with significant renal dysfunction can be improved by simultaneous liver kidney transplantation (SLK). However, excessively liberal dual organ transplantation decreases availability of kidneys for transplantation in end-stage renal disease (ESRD) patients. A recent patient of ours illustrates the potential decision-making dilemmas encountered in this setting. A 63-year-old man awaiting liver transplantation for ESLD secondary to Hepatitis-C developed acute kidney injury (AKI) with serum creatinine (SCr) increasing from 2.0 to 3.1 mg/dl over 1 week. Dysmorphic RBCs and RBC casts in the urine sediment, increase in urine protein/creatinine ratio from 0.13 g/g to 2.85 g/g, low C3/C4 complements, and positive rheumatoid factor and IgG/IgM cryoglobulins suggested hepatitis-C-associated cryoglobulinemic glomerulonephritis. Pre-transplant kidney biopsy was precluded by ESLD-associated coagulopathy. We suggested rituximab and/or methylprednisolone bolus therapy to see if AKI can be reversed and kidney transplantation avoided. However, the liver transplant team did not want to use pre-transplant immunosuppression in this very ill patient prone to opportunistic infections, which might delay/preclude life-saving liver transplantation. Further increase in SCr over next 10 days to 4.9 mg/dl led to acceptance for SLK, performed 3 weeks post-AKI development. Intraoperative native kidney biopsy revealed cryoglobulinemic glomerulonephritis. Three weeks post-transplantation, SCr was 0.8-1.0 mg/dl, with normal urinalysis and serum complement levels. It is possible that improvement of renal status was at least in part due to reversal of native glomerulonephritis by post-transplant immunosuppression. Although current guidelines recommend 4 weeks of severe AKI or >3 months of advanced chronic kidney disease (e-GFR < 40 ml/min/1.73m) as indications for SLK, patients such as ours do not clearly fit into either category and present major challenges in determining the need for dual organ transplantation.

Nephrology

Singasani R, **Ngansop T**, **Kumbar L**, **Li J**, **Yee J**, and **Yessayan L**. Renal sparing in levamis OLE/cocaine induced systemic vasculitis *Am J Kid Dis* 2016; 67(5):A101. PMID: Not assigned. Abstract

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Levamisole is an antihelminthic and immunomodulator medication, banned by the US FDA in 1998. But approximately 70% of illicit cocaine consumed in the United States is contaminated with levamisole. The most common manifestations include arthralgias (83%) and skin lesions (61%). Renal involvement with abnormal urinalysis like proteinuria, hematuria, or the presence of cellular/RBC casts on microscopy is uncommon (8 out of 30 patients) in ANCA positivity patients associated with cocaine ingestion. But all the reported severe acute kidney injury (AKI) patients had crescentic Glomerulonephritis on kidney biopsy. We report the first case, where the patient had severe AKI in setting of extensive vasculitis but no glomerulonephritis on kidney biopsy. A 49 year old male with a history of hypertension, CKD (baseline serum creatinine of 2.2), active tobacco and cocaine user presented with acute dyspnea and hemoptysis. On exam necrotic lesions at the tip of fingers and ears bilaterally were present. Lab testing revealed severe anemia, marked azotemia and deranged electrolytes. Immunological work up revealed positive ANA, myeloperoxidase antibody (anti-MPO), proteinase-3 antibody (anti-PR3), cardiolipin antibodies and hypocomplementemia. Presence of both anti-MPO and anti-PR3 is unique to levamisole/cocaine induced systemic vasculitis. Bronchoscopy showed diffuse hemorrhage, CT thorax revealed multiple consolidative opacities supporting diffuse alveolar hemorrhage. Skin biopsy showed epidermal necrosis with thrombotic vasculopathy consistent with those described for levamisole induced vasculopathy. He was started on high dose steroids and plasmapheresis. There was a thought to start aggressive immunosuppressive therapy like cyclophosphamide. Contrary to our working diagnosis, kidney biopsy showed only hypertensive global glomerulosclerosis without signs of glomerulonephritis or vasculitis. It is important not to attribute severe AKI in this patient population to renal vasculitis as it significantly affects clinical course and management like early and more aggressive immunosuppression.

Nephrology

Yee J. Improving transitions in CKD: failure mode *Adv Chronic Kidney Dis* 2016; 23(4):211-214. PMID: 27324671. Full Text

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Nephrology

Yessayan L, **Moore C**, **Lu M**, and **Yee J**. Bone-specific alkaline phosphatase and bone turnover in African American hemodialysis patients *Hemodial Int* 2016;PMID: 27350216. Full Text

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Introduction Noninvasive measures of bone activity include intact parathyroid hormone (iPTH) and bone-specific alkaline phosphatase (BSAP). Whether BSAP measurement alone or in combination with other biochemical data provides more reliable information about bone turnover than iPTH alone in African Americans on hemodialysis is unknown. Methods This cross-sectional study aimed to determine the optimal predictor and cutoff points for BSAP, iPTH, calcium and phosphorus in classifying bone biopsy findings. Forty-three African American hemodialysis patients were available for analysis. Biochemical data on the day of biopsy across a spectrum of qualitative histologic bone features were compared. Classification and regression tree analysis was used to determine both the optimal predictor and cutoff points for BSAP, iPTH, calcium and phosphorus in identifying bone turnover status. Findings Seven subjects had adynamic disease, 31 had mild/moderate hyperparathyroid bone features, and five had severe hyperparathyroid bone disease. BSAP was the optimal predictor of bone biopsy with a cutoff point of 22 ng/mL. Calcium and phosphorus had no predictive value. At BSAP </= 22 ng/mL, subjects had either adynamic bone disease or mild/moderate hyperparathyroid bone disease but iPTH was not useful in further classifying biopsy findings. When BSAP was >22 ng/mL, subjects had either mild/moderate or severe hyperparathyroid bone disease, and iPTH was useful in further classifying biopsy findings. With BSAP > 22 ng/mL and iPTH < 726 pg/mL, all subjects had mild/moderate bone turnover features. Discussion Compared to iPTH, BSAP was shown to be the optimal predictor of biopsy findings with an optimal cutoff at 22 ng/mL.

Neurology

Bulka H, **Croll S**, **Elias S**, and **Cerghet M**. Paroxysmal dystonia in inflammatory disorders of the central nervous system. A southeastern michigan cohort study *CMSC Annual Meeting* 2016;PMID: Not assigned. Abstract

Background: Paroxysmal Dystonia (PD) is a recurrent, neurological symptom characterized by sustained muscle contraction, frequently causing twisting and repetitive movements, or abnormal postures that persists seconds to minutes. This infrequent symptoms are less recognized in general practice although they have been described in inflammatory disorders of the central nervous system (CNS) specifically, in Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO). Objectives: To evaluate the presentation and treatment of paroxysmal dystonia (PD) in patients with inflammatory disorders of CNS.
Methods: Study setting was in a large integrated health care system serving residents of southeastern Michigan. Over the course of 5 years, 17 patients with inflammatory disorders of CNS presented with paroxysmal symptoms. Electronic medical records were reviewed retrospectively and data was collected on diagnosis, socio-demographic factors, neurological symptoms, MRI imaging, treatment regimen and treatment response. Descriptive statistics were used to characterize the PD cases. The Institutional Review Board approved this study. Results: Of the 17 patients with paroxysmal symptoms, 8 (47%) patients with MS and 3 (17%) with NMO presented with PD. The average age at presentation was 46.1 years (range 35-55) for MS and 47.6 years (range 36-60) for NMO. The female to male ratio was 1:1 in the MS group, while NMO patients were all female. Four (50%) patients had already an establish diagnosis of relapsing remitting MS at symptom presentation while in 4 (50%) PD was the first symptom of MS. Two patients in the NMO group developed paroxysmal dystonia after the initial acute phase of transverse myelitis, which had lead to a definitive diagnosis for NMO, whereas one patient developed the symptoms a few weeks following a relapse in the form of transverse myelitis. T2 FLAIR MR images showed new lesions in MS patients corresponding to symptoms in areas of midbrain (1/8), pons (1/8), medulla (1/8), posterior limb of internal capsule (1/8), thalamus (1/8), basal ganglia (1/8), cerebral peduncle (1/8) and cerebellar peduncle (1/8). Seven (87.5%) patients in MS group responded to monotherapy in less than 8 weeks from symptom onset. 5/7 received carbamazepine; 1/7 oxcarbazepine; 1/7 gabapentin. Patients with NMO required a combination of several agents and resolution of symptoms took up to 24 months. Conclusions: Recognition of paroxysmal dystonia as a neurological symptom in MS is important, especially since this can be a presenting feature of the disease. In NMO it is important to be aware that these symptoms can occur after the active stage of transverse myelitis. Unlike many other manifestations of MS, paroxysmal dystonia is frequently abolished with monotherapy, whereas this manifestation in the NMO group requires a multi-therapeutic approach and a longer duration before symptom resolution.

Neurology
Gulyani S, Salas R, Mari Z, Choi S, **Mahajan A**, and Gamaldo C. Evaluating and managing sleep disorders in the parkinson's disease clinic *Basal Ganglia* 2016; 6(3):165-172. PMID: Not assigned. Article Request Form

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Parkinson's disease is a multi-systems neurodegenerative disorder that is characterized by a combination of motor and non-motor symptoms. Non-motor symptoms of Parkinson's disease comprise a variety of cognitive, neuropsychiatric, autonomic, sensory, and sleep complaints. Although sleep disruption represents one of the most common non-motor symptom complaints among Parkinson's disease patients, recommendations regarding effective evaluation and management strategies for this specific population remain limited.

Neurology
Hampson NB, Kieburtz KD, **LeWitt PA**, Leinonen M, and Freed MI. Prospective evaluation of pulmonary function in parkinson's disease patients with motor fluctuations (12 of 25 words) *Int J Neurosci* 2016:1-20. PMID: 27345931. Article Request Form

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BACKGROUND: Spirometry patterns suggesting restrictive and obstructive pulmonary dysfunction have been reported in Parkinson's disease (PD). However, the patterns' precise relation to PD pathophysiology remains unclear. PURPOSE/AIM: To assess ON- versus OFF-state pulmonary function, the quality of its spirometric evaluation, and the quality of longitudinal spirometric findings in a large sample of PD patients with motor fluctuations. METHODS: During a placebo-controlled trial of CVT-301, an inhaled levodopa formulation, in PD patients with >/=2 hours/day of OFF time, spirometry was performed by American Thoracic Society (ATS) guidelines at screening and throughout the 4-week treatment period. RESULTS: Among 86 patients, mean motor impairment during an OFF state at screening was moderately severe. However, mean spirometry results at screening were within normal ranges, and in a mixed model for repeated measures (MMRM), the results at screening were not dependent on motor state (ON vs OFF). In the placebo group (n = 43), 76% of ON-state and 81% of OFF-state examinations throughout the study met ATS quality metrics, and in an MMRM analysis mean findings at these patients' arrivals for treatment-period visits showed no significant 4-week change. Across all 86 patients, flow-volume curves prior to any study-drug administration showed only a 3% incidence of "sawtooth" morphology. CONCLUSIONS: In PD patients with motor fluctuations, longitudinal spirometry of acceptable quality was generally obtained. Although mean findings were normal, about a quarter of spirograms did not meet ATS quality criteria. Spirogram morphology may be less indicative of various forms of respiratory dysfunction than has previously been reported in PD.

Neurology
Jiang Q, **Zhang L**, **Ding G**, **Davoodi-Bojd E**, **Li Q**, **Li L**, **Sadry N**, Nedergaard M, **Chopp M**, and **Zhang Z**. Impairment of the glymphatic system after diabetes *J Cereb Blood Flow Metab* 2016;PMID: 27306755. Full Text

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The glymphatic system has recently been shown to clear brain extracellular solutes and abnormalities in glymphatic clearance system may contribute to both initiation and progression of neurological diseases. Despite that diabetes is known as a risk factor for vascular diseases, little is known how diabetes affects the glymphatic system. The current study is the first investigation of the effect of diabetes on the glymphatic system and the link between alteration of glymphatic clearance and cognitive impairment in Type-2 diabetes mellitus rats. MRI analysis revealed that clearance of cerebrospinal fluid contrast agent Gd-DTPA from the interstitial space was slowed by a factor of three in the hippocampus of Type-2 diabetes mellitus rats compared to the non-DM rats and confirmed by florescence imaging analysis. Cognitive deficits detected by behavioral tests were highly and inversely correlated to the retention of Gd-

DTPA contrast and fluorescent tracer in the hippocampus of Type-2 diabetes mellitus rats. Type-2 diabetes mellitus suppresses clearance of interstitial fluid in the hippocampus and hypothalamus, suggesting that an impairment of the glymphatic system contributes to Type-2 diabetes mellitus-induced cognitive deficits. Whole brain MRI provides a sensitive, non-invasive tool to quantitatively evaluate cerebrospinal fluid and interstitial fluid exchange in Type-2 diabetes mellitus and possibly in other neurological disorders, with potential clinical application.

Neurology

Liu XS, **Fan BY**, **Pan WL**, **Li C**, **Levin AM**, **Wang X**, **Zhang RL**, **Zervos TM**, Hu J, Zhang XM, **Chopp M**, and **Zhang ZG**. Identification of miRNomes associated with adult neurogenesis after stroke using Argonaute 2-based RNA sequencing *RNA Biol* 2016:0. PMID: 27315491. Article Request Form

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Neurogenesis is associated with functional recovery after stroke. However, the underlying molecular mechanisms have not been fully investigated. Using an Ago2-based RNA immunoprecipitation to immunoprecipated Ago2-RNA complexes followed by RNA sequencing (Ago2 RIP-seq) approach, we profiled the miRNomes in neural progenitor cells (NPCs) harvested from the subventricular zone (SVZ) of the lateral ventricles of young adult rats. We identified more than 7 and 15 million reads in normal and ischemic NPC libraries, respectively. We found that stroke substantially changed Ago2-associated miRNA profiles in NPCs compared to those in non-ischemic NPCs. We also discovered a new complex repertoire of isomiRs and multiple miRNA-miRNA* pairs and numerous novel miRNAs in the non-ischemic and ischemic NPCs. Amongst them, pc-3p-17172 significantly regulated NPC proliferation and neuronal differentiation. Collectively, the present study reveals profiles of Ago2-associated miRNomes in non-ischemic and ischemic NPCs, which provide a molecular basis to further investigate the role of miRNAs in mediating adult neurogenesis under physiological and ischemic conditions.

Neurology

Mangalam AK, **Rattan R**, **Suhail H**, **Singh J**, Hoda MN, **Deshpande M**, Fulzele S, Denic A, Shridhar V, Kumar A, Viollet B, Rodriguez M, and **Giri S**. AMP-activated protein kinase suppresses autoimmune central nervous system disease by regulating m1-type macrophage-th17 axis *J Immunol* 2016;PMID: 27354217. Full Text

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The AMP-activated protein kinase, AMPK, is an energy-sensing, metabolic switch implicated in various metabolic disorders; however, its role in inflammation is not well defined. We have previously shown that loss of AMPK exacerbates experimental autoimmune encephalomyelitis (EAE) disease severity. In this study, we investigated the mechanism through which AMPK modulates inflammatory disease like EAE. AMPKalpha1 knockout (alpha1KO) mice with EAE showed severe demyelination and inflammation in the brain and spinal cord compared with wild-type due to higher expression of proinflammatory Th17 cytokines, including IL-17, IL-23, and IL-1beta, impaired blood-brain

barrier integrity, and increased infiltration of inflammatory cells in the CNS. Infiltrated CD4 cells in the brains and spinal cords of alpha1KO with EAE were significantly higher compared with wild-type EAE and were characterized as IL-17 (IL-17 and GM-CSF double-positive) CD4 cells. Increased inflammatory response in alpha1KO mice was due to polarization of macrophages (Mvarphi) to proinflammatory M1 type phenotype (IL-10lowIL-23/IL-1beta/IL-6high), and these M1 Mvarphi showed stronger capacity to induce allogenic as well as Ag-specific (myelin oligodendrocyte glycoprotein [MOG]35-55) T cell response. Mvarphi from alpha1KO mice also enhanced the encephalitogenic property of MOG35-55-primed CD4 T cells in B6 mice. The increased encephalitogenic MOG-restricted CD4+ T cells were due to an autocrine effect of IL-1beta/IL-23-mediated induction of IL-6 production in alpha1KO Mvarphi, which in turn induce IL-17 and GM-CSF production in CD4 cells. Collectively, our data indicate that AMPK controls the inflammatory disease by regulating the M1 phenotype-Th17 axis in an animal model of multiple sclerosis.

Neurology

Nazem-Zadeh MR, Elisevich K, **Air EL**, **Schwalb JM**, **Divine G**, **Kaur M**, **Wasade VS**, **Mahmoudi F**, **Shokri S**, **Bagher-Ebadian H**, and **Soltanian-Zadeh H**. DTI-based response-driven modeling of mTLE laterality *Neuroimage Clin* 2016; 11:694-706. PMID: 27330966. Full Text

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PURPOSE: To develop lateralization models for distinguishing between unilateral and bilateral mesial temporal lobe epilepsy (mTLE) and determining laterality in cases of unilateral mTLE. BACKGROUND: mTLE is the most common form of medically refractory focal epilepsy. Many mTLE patients fail to demonstrate an unambiguous unilateral ictal onset. Intracranial EEG (icEEG) monitoring can be performed to establish whether the ictal origin is unilateral or truly bilateral with independent bitemporal ictal origin. However, because of the expense and risk of intracranial electrode placement, much research has been done to determine if the need for icEEG can be obviated with noninvasive neuroimaging methods, such as diffusion tensor imaging (DTI). METHODS: Fractional anisotropy (FA) was used to quantify microstructural changes reflected in the diffusivity properties of the corpus callosum, cingulum, and fornix, in a retrospective cohort of 31 patients confirmed to have unilateral (n = 24) or bilateral (n = 7) mTLE. All unilateral mTLE patients underwent resection with an Engel class I outcome. Eleven were reported to have hippocampal sclerosis on pathological analysis; nine had undergone prior icEEG. The bilateral mTLE patients had undergone icEEG demonstrating independent epileptiform activity in both right and left hemispheres. Twenty-three nonepileptic subjects were included as controls. RESULTS: In cases of right mTLE, FA showed significant differences from control in all callosal subregions, in both left and right superior cingulate subregions, and in forniceal crura. Comparison of right and left mTLE cases showed significant differences in FA of callosal genu, rostral body, and splenium and the right posteroinferior and superior cingulate subregions. In cases of left mTLE, FA showed significant differences from control only in the callosal isthmus. Significant differences in FA were identified when cases of right mTLE were compared with bilateral mTLE cases in the rostral and midbody callosal subregions and isthmus. Based on 11 FA measurements in the cingulate, callosal and forniceal subregions, a response-driven lateralization model successfully differentiated all cases (n = 54) into groups of unilateral right (n = 12), unilateral left (n = 12), and bilateral mTLE (n = 7), and nonepileptic control (23). CONCLUSION: The proposed response-driven DTI biomarker is intended to lessen diagnostic ambiguity of laterality in cases of mTLE and help optimize selection of surgical candidates. Application of this model shows promise in reducing the need for invasive icEEG in prospective cases.

Neurosurgery

Ali R. Ictal cardiac ryhthym abnormalities *Open Cardiovasc Med J* 2016; 10:105-109. PMID: 27347227. Full Text

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Cardiac rhythm abnormalities in the context of epilepsy are a well-known phenomenon. However, they are under-recognized and often missed. The pathophysiology of these events is unclear. Bradycardia and asystole are preceded by seizure onset suggesting ictal propagation into the cortex impacting cardiac autonomic function, and the insula and amygdala being possible culprits. Sudden unexpected death in epilepsy (SUDEP) refers to the unanticipated death of a patient with epilepsy not related to status epilepticus, trauma, drowning, or suicide. Frequent refractory generalized tonic-clonic seizures, anti-epileptic polytherapy, and prolonged duration of epilepsy are some of the commonly identified risk factors for SUDEP. However, the most consistent risk factor out of these is an increased frequency of generalized tonic-clonic seizures (GTC). Prevention of SUDEP is extremely important in patients with chronic, generalized epilepsy. Since increased frequency of GTCS is the most consistently reported risk factor for SUDEP, effective seizure control is the most important preventive strategy.

Neurosurgery

Burgett ME, Lathia JD, Roth P, Nowacki AS, Galileo DS, Pugacheva E, Huang P, Vasanji A, Li M, Byzova T, **Mikkelsen T**, Bao S, Rich JN, Weller M, and Gladson CL. Direct contact with perivascular tumor cells enhances integrin alphavbeta3 signaling and migration of endothelial cells *Oncotarget* 2016;PMID: 27270311. Full Text

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The secretion of soluble pro-angiogenic factors by tumor cells and stromal cells in the perivascular niche promotes the aggressive angiogenesis that is typical of glioblastoma (GBM). Here, we show that angiogenesis also can be promoted by a direct interaction between brain tumor cells, including tumor cells with cancer stem-like properties (CSCs), and endothelial cells (ECs). As shown in vitro, this direct interaction is mediated by binding of integrin alphavbeta3 expressed on ECs to the RGD-peptide in L1CAM expressed on CSCs. It promotes both EC network formation and enhances directed migration toward basic fibroblast growth factor. Activation of alphavbeta3 and bone marrow tyrosine kinase on chromosome X (BMX) is required for migration stimulated by direct binding but not for migration stimulated by soluble factors. RGD-peptide treatment of mice with established intracerebral GBM xenografts significantly reduced the percentage of Sox2-positive tumor cells and CSCs in close proximity to ECs, decreased integrin alphavbeta3 and BMX activation and p130CAS phosphorylation in the ECs, and reduced the vessel surface area. These results reveal a previously unrecognized aspect of the regulation of angiogenesis in GBM that can impact therapeutic anti-angiogenic targeting.

Neurosurgery

Dewan MC, Thompson RC, **Kalkanis SN**, Barker FG, 2nd, and Hadjipanayis CG. Prophylactic antiepileptic drug administration following brain tumor resection: results of a recent AANS/CNS Section on Tumors survey *J Neurosurg* 2016:1-7. PMID: 27341048. Full Text

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OBJECTIVE Antiepileptic drugs (AEDs) are often administered prophylactically following brain tumor resection. With conflicting evidence and unestablished guidelines, however, the nature of this practice among tumor surgeons is unknown. METHODS On November 24, 2015, a REDCap (Research Electronic Database Capture) survey was sent to members of the AANS/CNS Section on Tumors to query practice patterns. RESULTS Responses were received from 144 individuals, including 18.8% of board-certified neurosurgeons surveyed (across 86 institutions, 16 countries, and 5 continents). The majority reported practicing in an academic setting (85%) as a tumor specialist (71%). Sixty-three percent reported always or almost always prescribing AED prophylaxis postoperatively in patients with a supratentorial brain tumor without a prior seizure history. Meanwhile, 9% prescribed occasionally and 28% rarely

prescribed AED prophylaxis. The most common agent was levetiracetam (85%). The duration of seizure prophylaxis varied widely: 25% of surgeons administered prophylaxis for 7 days, 16% for 2 weeks, 21% for 2 to 6 weeks, and 13% for longer than 6 weeks. Most surgeons (61%) believed that tumor pathology influences epileptogenicity, with high-grade glioma (39%), low-grade glioma (31%), and metastases (24%) carrying the greatest seizure risk. While the majority used prophylaxis, 62% did not believe or were unsure if prophylactic AEDs reduced seizures postoperatively. The vast majority (82%) stated that a well-designed randomized trial would help guide their future clinical decision making. CONCLUSIONS Wide knowledge and practice gaps exist regarding the frequency, duration, and setting of AED prophylaxis for seizure-naive patients undergoing brain tumor resection. Acceptance of universal practice guidelines on this topic is unlikely until higher-level evidence supporting or refuting the value of modern seizure prophylaxis is demonstrated.

Neurosurgery
Montalvo M, **Ali R**, Silver B, and Khan M. Long-term arrhythmia monitoring in cryptogenic stroke: Who, how, and for how long? *Open Cardiovasc Med J* 2016; 10:89-93. PMID: 27347225. Full Text

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Cryptogenic stroke and transient ischemic attack (TIA) account for approximately one-third of stroke patients [1]. Paroxys-mal atrial fibrillation (PAF) has been suggested as a major etiology of these cryptogenic strokes [2, 3]. PAF can be difficult to diagnose because it is intermittent, often brief, and asymptomatic. PAF might be more prevalent than persistent atrial fibrillation in stroke and TIA patients, especially in younger populations [4, 5]. In patients with atrial fibrillation, anticoagulation provides significant risk reduction [6]. A new generation of oral anticoagulants has been approved for non-valvular atrial fibrillation, providing a variety of therapeutic options for patients with atrial fibrillation and risk of stroke [7]. Prior practice included an admission electrocardiogram (ECG) and continuous telemetry monitoring while in hospital [8]. However, this approach can lead to under-detection of brief asymptomatic events, which can occur at variable intervals, often outside of the hospital setting. Technological advancements have led to devices that can monitor cardiac rhythms outside of the hospital for longer durations resulting in higher yield of detection of atrial fibrillation events. Moreover, recent studies show that the normal monitoring time for arrhythmias may be shorter than ideal in order to detect atrial fibrillation, and increasing this interval could significantly improve detection of atrial fibrillation in these patients [9, 10]. The aim of this study is to review the literature in order to define what subgroup of patients, with what methodologies, and for how long monitoring for atrial fibrillation should occur in patients presenting with cryptogenic stroke.

Neurosurgery
Nazem-Zadeh MR, Elisevich K, **Air EL**, **Schwalb JM**, **Divine G**, **Kaur M**, **Wasade VS**, **Mahmoudi F**, **Shokri S**, **Bagher-Ebadian H**, and **Soltanian-Zadeh H**. DTI-based response-driven modeling of mTLE laterality *Neuroimage Clin* 2016; 11:694-706. PMID: 27330966. Full Text

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form of medically refractory focal epilepsy. Many mTLE patients fail to demonstrate an unambiguous unilateral ictal onset. Intracranial EEG (icEEG) monitoring can be performed to establish whether the ictal origin is unilateral or truly bilateral with independent bitemporal ictal origin. However, because of the expense and risk of intracranial electrode placement, much research has been done to determine if the need for icEEG can be obviated with noninvasive neuroimaging methods, such as diffusion tensor imaging (DTI). METHODS: Fractional anisotropy (FA) was used to quantify microstructural changes reflected in the diffusivity properties of the corpus callosum, cingulum, and fornix, in a retrospective cohort of 31 patients confirmed to have unilateral (n = 24) or bilateral (n = 7) mTLE. All unilateral mTLE patients underwent resection with an Engel class I outcome. Eleven were reported to have hippocampal sclerosis on pathological analysis; nine had undergone prior icEEG. The bilateral mTLE patients had undergone icEEG demonstrating independent epileptiform activity in both right and left hemispheres. Twenty-three nonepileptic subjects were included as controls. RESULTS: In cases of right mTLE, FA showed significant differences from control in all callosal subregions, in both left and right superior cingulate subregions, and in forniceal crura. Comparison of right and left mTLE cases showed significant differences in FA of callosal genu, rostral body, and splenium and the right posteroinferior and superior cingulate subregions. In cases of left mTLE, FA showed significant differences from control only in the callosal isthmus. Significant differences in FA were identified when cases of right mTLE were compared with bilateral mTLE cases in the rostral and midbody callosal subregions and isthmus. Based on 11 FA measurements in the cingulate, callosal and forniceal subregions, a response-driven lateralization model successfully differentiated all cases (n = 54) into groups of unilateral right (n = 12), unilateral left (n = 12), and bilateral mTLE (n = 7), and nonepileptic control (23). CONCLUSION: The proposed response-driven DTI biomarker is intended to lessen diagnostic ambiguity of laterality in cases of mTLE and help optimize selection of surgical candidates. Application of this model shows promise in reducing the need for invasive icEEG in prospective cases.

Neurosurgery
Ramaswamy V, Hielscher T, Mack SC, Lassaletta A, Lin T, Pajtler KW, Jones DT, Luu B, Cavalli FM, Aldape K, Remke M, Mynarek M, Rutkowski S, Gururangan S, McLendon RE, Lipp ES, Dunham C, Hukin J, Eisenstat DD, Fulton D, van Landeghem FK, Santi M, van Veelen MC, Van Meir EG, Osuka S, Fan X, Muraszko KM, Tirapelli DP, Oba-Shinjo SM, Marie SK, Carlotti CG, Lee JY, Nageswara Rao AA, Giannini C, Faria CC, Nunes S, Mora J, Hamilton RL, Hauser P, Jabado N, Petrecca K, Jung S, Massimi L, Zollo M, Cinalli G, Bognar L, Klekner A, Hortobagyi T, Leary S, Ermoian RP, Olson JM, Leonard JR, Gardner C, Grajkowska WA, Chambless LB, Cain J, Eberhart CG, Ahsan S, Massimino M, Giangaspero F, Buttarelli FR, Packer RJ, Emery L, Yong WH, Soto H, Liau LM, Everson R, Grossbach A, Shalaby T, Grotzer M, Karajannis MA, Zagzag D, Wheeler H, von Hoff K, Alonso MM, Tunon T, Schuller U, Zitterbart K, Sterba J, Chan JA, Guzman M, Elbabaa SK, Colman H, Dhall G, Fisher PG, Fouladi M, Gajjar A, Goldman S, Hwang E, Kool M, Ladha H, Vera-Bolanos E, Wani K, Lieberman F, **Mikkelsen T**, Omuro AM, Pollack IF, Prados M, Robins HI, Soffietti R, Wu J, Metellus P, Tabori U, Bartels U, Bouffet E, Hawkins CE, Rutka JT, Dirks P, Pfister SM, Merchant TE, Gilbert MR, Armstrong TS, Korshunov A, Ellison DW, and Taylor MD. Therapeutic impact of cytoreductive surgery and irradiation of posterior fossa ependymoma in the molecular era: A retrospective multicohort analysis *J Clin Oncol* 2016;PMID: 27269943. Full Text

PURPOSE: Posterior fossa ependymoma comprises two distinct molecular variants termed EPN_PFA and EPN_PFB that have a distinct biology and natural history. The therapeutic value of cytoreductive surgery and radiation therapy for posterior fossa ependymoma after accounting for molecular subgroup is not known. METHODS: Four independent nonoverlapping retrospective cohorts of posterior fossa ependymomas (n = 820) were profiled using genome-wide methylation arrays. Risk stratification models were designed based on known clinical and newly described molecular biomarkers identified by multivariable Cox proportional hazards analyses. RESULTS: Molecular subgroup is a powerful independent predictor of outcome even when accounting for age or treatment regimen. Incompletely resected EPN_PFA ependymomas have a dismal prognosis, with a 5-year progression-free survival ranging from 26.1% to 56.8% across all four cohorts. Although first-line (adjuvant) radiation is clearly beneficial for completely resected EPN_PFA, a substantial proportion of patients with EPN_PFB can be cured with surgery alone, and patients with relapsed EPN_PFB can often be treated successfully with delayed external-beam irradiation. CONCLUSION: The most impactful biomarker for posterior fossa ependymoma is molecular subgroup affiliation, independent of other demographic or treatment variables. However, both EPN_PFA and EPN_PFB still benefit from increased extent of resection, with the survival rates being particularly poor for subtotally resected EPN_PFA, even with adjuvant radiation therapy. Patients with EPN_PFB who undergo gross total resection are at lower risk for relapse and should be considered for inclusion in a randomized clinical trial of observation alone with radiation reserved for those who experience recurrence.

Neurosurgery
Tahir RA, and **Pabaney AH**. Therapeutic hypothermia and ischemic stroke: A literature review *Surg Neurol Int* 2016; 7(Suppl 14):S381-386. PMID: 27313963. Full Text

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BACKGROUND: Ischemic stroke is the fifth leading cause of death in the US. Clinical techniques aimed at helping to reduce the morbidity associated with stroke have been studied extensively, including therapeutic hypothermia. In this study, the authors review the literature regarding the role of therapeutic hypothermia in ischemic stroke to appreciate the evolution of hypothermia technology over several decades and to critically analyze several early clinical studies to validate its use in ischemic stroke. METHODS: A comprehensive literature search was performed using PubMed and Google Scholar databases. Search terms included "hypothermia and ischemic stroke" and "therapeutic hypothermia." A comprehensive search of the current clinical trials using clinicaltrials.gov was conducted using the keywords "stroke and hypothermia" to evaluate early and ongoing clinical trials utilizing hypothermia in ischemic stroke. RESULTS: A comprehensive review of the evolution of hypothermia in stroke and the current status of this treatment was performed. Clinical studies were critically analyzed to appreciate their strengths and pitfalls. Ongoing and future registered clinical studies were highlighted and analyzed compared to the reported results of previous trials. CONCLUSION: Although hypothermia has been used for various purposes over several decades, its efficacy in the treatment of ischemic stroke is debatable. Several trials have proven its safety and feasibility; however, more robust, randomized clinical trials with large volumes of patients are needed to fully establish its utility in the clinical setting.

Obstetrics, Gynecology and Women's Health Services

Hijaz M, **Chhina J**, Mert I, Taylor M, **Dar S**, Al-Wahab Z, Ali-Fehmi R, **Buekers T**, **Munkarah AR**, and **Rattan R**. Preclinical evaluation of olaparib and metformin combination in BRCA1 wildtype ovarian cancer *Gynecol Oncol* 2016;PMID: 27282964. Full Text

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OBJECTIVES: BRCA mutated ovarian cancers show increased responsiveness to PARP inhibitors. PARP inhibitors target DNA repair and provide a second hit to BRCA mutated tumors, resulting in "synthetic lethality". We investigated a combination of metformin and olaparib to provide "synthetic lethality" in BRCA intact ovarian cancer cells. METHODS: Ovarian cancer cell lines (UWB1.289, UWB1.289.BRCA, SKOV3, OVCAR5, A2780 and C200) were treated with a combination of metformin and olaparib. Cell viability was assessed by MTT and colony formation assays. Flow cytometry was used to detect cell cycle events. In vivo studies were performed in SKOV3 or A2780 xenografts in nude mice. Animals were treated with single agent, metformin or olaparib or combination. Molecular downstream effects were examined by immunohistochemistry. RESULTS: Compared to single drug treatment, combination of olaparib and metformin resulted in significant reduction of cell proliferation and colony formation ($p<0.001$) in ovarian cancer cells. This treatment was associated with a significant S-phase cell cycle arrest ($p<0.05$). Combination of olaparib and metformin significantly inhibited SKOV3 and A2780 ovarian tumor xenografts which were accompanied with decreased Ki-index ($p<0.001$). Metformin did not affect DNA damage signaling, while olaparib induced adenosine monophosphate activated kinase activation; that was further potentiated with metformin combination in vivo. CONCLUSION: Combining PARP inhibitors with metformin enhances its anti-proliferative activity in BRCA mutant ovarian cancer cells. Furthermore, the combination showed significant activity in BRCA intact cancer cells in vitro and in vivo. This is a promising treatment regimen for women with epithelial ovarian cancer irrespective of BRCA status.

Obstetrics, Gynecology and Women's Health Services
Jaffee KD, **Shires DA**, and **Stroumsa D**. Discrimination and delayed health care among transgender women and men: Implications for improving medical education and health care delivery *Med Care* 2016;PMID: 27314263. Full Text

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BACKGROUND: The transgender community experiences health care discrimination and approximately 1 in 4 transgender people were denied equal treatment in health care settings. Discrimination is one of the many factors significantly associated with health care utilization and delayed care. OBJECTIVES: We assessed factors associated with delayed medical care due to discrimination among transgender patients, and evaluated the relationship between perceived provider knowledge and delayed care using Anderson's behavioral model of health services utilization. RESEARCH DESIGN: Multivariable logistic regression analysis was used to test whether predisposing, enabling, and health system factors were associated with delaying needed care for transgender women and transgender men. SUBJECTS: A sample of 3486 transgender participants who took part in the National Transgender Discrimination Survey in 2008 and 2009. MEASURES: Predisposing, enabling, and health system environment factors, and delayed needed health care. RESULTS: Overall, 30.8% of transgender participants delayed or did not seek needed health care due to discrimination. Respondents who had to teach health care providers about transgender people were 4 times more likely to delay needed health care due to discrimination. CONCLUSIONS: Transgender patients who need to teach their providers about transgender people are significantly more likely to postpone or not seek needed care. Systemic changes in provider education and training, along with health care system adaptations to ensure appropriate, safe, and respectful care, are necessary to close the knowledge and treatment gaps and prevent delayed care with its ensuing long-term health implications.

Obstetrics, Gynecology and Women's Health Services
Mangalam AK, **Rattan R**, **Suhail H**, **Singh J**, Hoda MN, **Deshpande M**, Fulzele S, Denic A, Shridhar V, Kumar A, Viollet B, Rodriguez M, and **Giri S**. AMP-activated protein kinase suppresses autoimmune central nervous system disease by regulating m1-type macrophage-th17 axis *J Immunol* 2016;PMID: 27354217. Full Text

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The AMP-activated protein kinase, AMPK, is an energy-sensing, metabolic switch implicated in various metabolic disorders; however, its role in inflammation is not well defined. We have previously shown that loss of AMPK exacerbates experimental autoimmune encephalomyelitis (EAE) disease severity. In this study, we investigated the mechanism through which AMPK modulates inflammatory disease like EAE. AMPKalpha1 knockout (alpha1KO) mice with EAE showed severe demyelination and inflammation in the brain and spinal cord compared with wild-type due to higher expression of proinflammatory Th17 cytokines, including IL-17, IL-23, and IL-1beta, impaired blood-brain barrier integrity, and increased infiltration of inflammatory cells in the CNS. Infiltrated CD4 cells in the brains and spinal cords of alpha1KO with EAE were significantly higher compared with wild-type EAE and were characterized as IL-17 (IL-17 and GM-CSF double-positive) CD4 cells. Increased inflammatory response in alpha1KO mice was due to polarization of macrophages (Mvarphi) to proinflammatory M1 type phenotype (IL-10lowIL-23/IL-1beta/IL-6high), and these M1 Mvarphi showed stronger capacity to induce allogenic as well as Ag-specific (myelin oligodendrocyte glycoprotein [MOG]35-55) T cell response. Mvarphi from alpha1KO mice also enhanced the encephalitogenic property of MOG35-55-primed CD4 T cells in B6 mice. The increased encephalitogenic MOG-restricted CD4+ T cells were due to an autocrine effect of IL-1beta/IL-23-mediated induction of IL-6 production in alpha1KO Mvarphi, which in

turn induce IL-17 and GM-CSF production in CD4 cells. Collectively, our data indicate that AMPK controls the inflammatory disease by regulating the M1 phenotype-Th17 axis in an animal model of multiple sclerosis.

Obstetrics, Gynecology and Women's Health Services

Mazloomdoost D, Kanter G, Chan RC, Deveaneau N, Wyman AM, Von Bargen EC, Chaudhry Z, **Elshatanoufy S**, Miranne JM, Chu CM, Pauls RN, Arya LA, and Antosh DD. Social networking and Internet use among pelvic floor patients: a multicenter survey *Am J Obstet Gynecol* 2016;PMID: 27319368. Full Text

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BACKGROUND: Internet resources are becoming increasingly important for patients seeking medical knowledge. It is imperative to understand patient use and preferences for using the Internet and social networking web sites to optimize patient education. OBJECTIVES: The purpose of this study was to evaluate social networking and Internet use among women with pelvic floor complaints to seek information for their conditions as well as describe the likelihood, preferences, and predictors of web site usage. STUDY DESIGN: This was a cross-sectional, multicenter study of women presenting to clinical practices of 10 female pelvic medicine and reconstructive surgery fellowship programs across the United States, affiliated with the Fellows' Pelvic Research Network. New female patients presenting with pelvic floor complaints, including urinary incontinence, pelvic organ prolapse, and fecal incontinence were eligible. Participants completed a 24 item questionnaire designed by the authors to assess demographic information, general Internet use, preferences regarding social networking web sites, referral patterns, and resources utilized to learn about their pelvic floor complaints. Internet use was quantified as high (>/=4 times/wk), moderate (2-3 times/wk), or minimal (</=1 time/wk). Means were used for normally distributed data and medians for data not meeting this assumption. Fisher exact and chi2 tests were used to evaluate the associations between variables and Internet use. RESULTS: A total of 282 surveys were analyzed. The majority of participants, 83.3%, were white. The mean age was 55.8 years. Referrals to urogynecology practices were most frequently from obstetrician/gynecologists (39.9%) and primary care providers (27.8%). Subjects were well distributed geographically, with the largest representation from the South (38.0%). Almost one third (29.9%) were most bothered by prolapse complaints, 22.0% by urgency urinary incontinence, 20.9% by stress urinary incontinence, 14.9% by urgency/frequency symptoms, and 4.1% by fecal incontinence. The majority, 75.0%, described high Internet use, whereas 8.5% moderately and 4.8% minimally used the Internet. Women most often used the Internet for personal motivations including medical research (76.4%), and 42.6% reported Google to be their primary search engine. Despite this, only 4.9% primarily used the Internet to learn about their pelvic floor condition, more commonly consulting an obstetrician-gynecologist for this information (39.4%). The majority (74.1%) held a social networking account, and 45.9% visited these daily. Nearly half, 41.7%, expressed the desire to use social networking web sites to learn about their condition. Women <65 years old were significantly more likely to have high Internet use (83.4% vs 68.8%, P = .018) and to desire using social networking web sites to learn about their pelvic floor complaint (P = .008). The presenting complaint was not associated with Internet use (P = .905) or the desire to use social networking web sites to learn about pelvic floor disorders (P = .201). CONCLUSION: Women presenting to urogynecology practices have high Internet use and a desire to learn about their conditions via social networking web sites. Despite this, obstetrician-gynecologists remain a common resource for information. Nonetheless, urogynecology practices and national organizations would likely

benefit from increasing their Internet resources for patient education in pelvic floor disorders, although patients should be made aware of available resources.

Obstetrics, Gynecology and Women's Health Services

Wahid M, Mandal RK, **Dar SA**, Jawed A, Lohani M, Areeshi MY, Akhter N, and Haque S. Therapeutic potential and critical analysis of trastuzumab and bevacizumab in combination with different chemotherapeutic agents against metastatic breast/colorectal cancer affecting various endpoints *Crit Rev Oncol Hematol* 2016;PMID: 27357488. Full Text

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Researchers are working day and night across the globe to eradicate or at least lessen the menace of cancer faced by the mankind. The two very frequently occurring cancers faced by the human beings are metastatic breast cancer and metastatic colorectal cancer. The various chemotherapeutic agents like anthracycline, cyclophosphamide, paclitaxel, irinotecan, fluorouracil and leucovorin etc., have been used impressively for long. But the obstinate character of metastatic breast cancer and metastatic colorectal cancer needs more to tackle the threat. So, the scientists found the use of monoclonal antibodies trastuzumab (Herceptin(R)) and bevacizumab (Avastin(R)) for the same. The current study critically investigates the therapeutic potential of trastuzumab and bevacizumab in combination with various chemotherapeutic agents against metastatic breast cancer and metastatic colorectal cancer. To the best of our knowledge, this is the very first critical analysis showing percent wise increase in various positive endpoints like median time to disease progression, median survival, and progression free survival etc. for the treatment of metastatic breast/colorectal cancer using trastuzumab and bevacizumab in combination with different chemotherapeutic agents and provides the rational for the success and failure of the selected monoclonal antibodies.

Orthopaedics

Makhni EC, **Weber AE**, **Ball B**, and **Thomas A**. Principles of Postoperative Shoulder Rehabilitation in Throwing Athletes *Oper Tech Sports Med* 2016;PMID: Not assigned. Full Text

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The rehabilitation of the overhead throwing athlete is a complex and often lengthy process. After completion of the intial phases of rehab involving strength and motion recovery, sports specific throwing rehabilitation and graduated return to throwing are required. Safe and timely return to throwing following shoulder surgery in baseball players requires sophisticated coordination and communication between clinicians, coaches, and players. Strict adherence to underlying principles of an interval throwing program would afford players the best chance of successfully returning to his or her preinjury level of performance. Open and constant communication between players, trainers, and coaches would ensure that any soreness or pain experienced by the player would be reported and assessed in a timely manner. Such reporting would minimize the chance of delaying progress through the interval throwing program.

Orthopaedics

Mehran N, Williams PN, **Keller RA**, Khalil LS, Lombardo SJ, and Kharrazi FD. Athletic performance at the national basketball association combine after anterior cruciate ligament reconstruction *Orthop J Sports Med* 2016; 4(5):2325967116648083. PMID: 27294169. Full Text

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BACKGROUND: Anterior cruciate ligament (ACL) injuries are significant injuries in elite-level basketball players. In-game statistical performance after ACL reconstruction has been demonstrated; however, few studies have reviewed functional performance in National Basketball Association (NBA)-caliber athletes after ACL reconstruction. PURPOSE: To compare NBA Combine performance of athletes after ACL reconstruction with an age-, size-, and position-matched control group of players with no previous reported knee injury requiring surgery. We hypothesized that there is no difference between the 2 groups in functional performance. STUDY DESIGN: Cross-sectional study; Level of evidence, 3. METHODS: A total of 1092 NBA-caliber players who participated in the NBA Combine between 2000 and 2015 were reviewed. Twenty-one athletes were identified as having primary ACL reconstruction prior to participation in the combine. This study group was compared with an age-, size-, and position-matched control group in objective functional performance testing, including the shuttle run test, lane agility test, three-quarter court sprint, vertical jump (no step), and maximum vertical jump (running start). RESULTS: With regard to quickness and agility, both ACL-reconstructed athletes and controls scored an average of 11.5 seconds in the lane agility test and 3.1 seconds in the shuttle run test (P = .745 and .346, respectively). Speed and acceleration was measured by the three-quarter court sprint, in which both the study group and the control group averaged 3.3 seconds (P = .516). In the maximum vertical jump, which demonstrates an athlete's jumping ability with a running start, the ACL reconstruction group had an average height of 33.6 inches while the controls averaged 33.9 inches (P = .548). In the standing vertical jump, the ACL reconstruction group averaged 28.2 inches while the control group averaged 29.2 inches (P = .067). CONCLUSION: In athletes who are able to return to sport and compete at a high level such as the NBA Combine, there is no significant difference in any combine performance test between players who have had primary ACL reconstruction compared with an age-, size-, and position-matched control group. CLINICAL RELEVANCE: Athletes with previous ACL reconstruction who are able to return to high-level professional basketball have equivalent performance measures with regard to speed, quickness, and jumping ability as those athletes who have not undergone knee surgery.

Orthopaedics

Okoroha KR, **Keller RA**, **Marshall NE**, **Jung EK**, **Mehran N**, **Owashi E**, and **Moutzouros V**. Liposomal bupivacaine versus femoral nerve block for pain control after anterior cruciate ligament reconstruction: A prospective randomized trial *Arthroscopy* 2016;PMID: 27349715. Full Text

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PURPOSE: To compare femoral nerve block (FNB) versus local liposomal bupivacaine (LB) for pain control in patients undergoing anterior cruciate ligament (ACL) reconstruction. METHODS: Eighty-five patients undergoing primary ACL reconstruction were assessed for participation. We performed a prospective randomized trial in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement. The study arms included either intraoperative local infiltration of LB (20 mL of bupivacaine/10 mL of saline solution) or preoperative FNB with a primary outcome of postoperative pain levels (visual analog scale) for 4 days. Secondary outcomes assessed included opioid consumption (intravenous morphine equivalents), hours slept, patient satisfaction, and calls to the physician. Randomization was by a computerized algorithm. The observer was blinded and the patient was not blinded to the intervention. RESULTS: One patient declined participation; 2 patients were excluded after randomization. A total of 82 patients were analyzed. Outcomes showed a significant increase in pain in the LB group between 5 and 8 hours postoperatively (mean +/- standard deviation, 6.3 +/- 2.0 versus 4.8 +/- 2.6; P = .01). There were no significant differences between the groups in mean daily pain levels, morphine equivalents, or patient satisfaction when we controlled for graft type, age, body mass index, and sex. Patients receiving an FNB had a nonsignificant increase in number of sleep disturbances on the day of surgery (mean +/- standard deviation, 4.4 +/- 3.7 v 3.1 +/- 2.1; P = .09) and were more likely to call their doctor the following day because of pain (29% v 8%, P = .04). Six patients in the FNB group had either prolonged quadriceps inhibition or sensory disturbance. One patient in the LB group required reoperation for a flexion contracture. CONCLUSIONS: An increase in acute postoperative pain

was found with LB compared with FNB for post-ACL reconstruction pain control. After the acute postoperative period, there were no significant differences in opioid consumption or pain control. The occurrence of nerve irritation postoperatively was found to be higher in the FNB group. LEVEL OF EVIDENCE: Level I, prospective randomized trial.

Orthopaedics
Shehab R. 679 Clinical Case Slide Discussant - Upper Extremity - Shoulder *Med Sci Sports Exerc* 2016; 48(5 Suppl 1):179. PMID: 27359822. Abstract

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Orthopaedics
Zhang L, **Yang M**, **Mayer T**, Johnstone B, **Les C**, **Frisch N**, **Parsons T**, **Mi QS**, and **Gibson G**. Use of MicroRNA biomarkers to distinguish enchondroma from low-grade chondrosarcoma *Connect Tissue Res* 2016:1-7. PMID: 27267924. Article Request Form

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Establishing a definitive diagnosis between benign enchondroma versus low-grade chondrosarcoma presents a potential challenge to both clinicians and pathologists. microRNAs (small non-coding RNAs) have proven to be effective biomarkers for the identification of tumors and tumor progression. We present analysis, both array and quantitative PCR, that shows consistently and substantially increased expression of two microRNAs, miRs-181a and -138, in low-grade chondrosarcomas compared with enchondromas. The data suggest these microRNAs would provide an analytical distinction between the chondrosarcoma and benign neoplasms that can be performed in formalin-fixed paraffin-embedded specimens. Together with recent publications, these data indicate that miRs-181a and -138 also play a role in tumor development and homeostasis and may provide new targets for the development of much needed therapeutic intervention.

Otolaryngology – Head and Neck Surgery
Chen KM, **Datta I**, **Stephen JK**, **Chitale D**, **Divine G**, and **Worsham MJ**. ER negative-specific differentially methylated genes identify master regulators to expose potential epigenetic drivers of aggressive disease *Eur J Cancer* 2016; 54:S48. PMID: Not assigned. Abstract

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The majority of published studies investigating driver genes have focused primarily on genomic mutations which have led to novel study designs (basket trials) where patients with a rare mutation, regardless of tumor histology, are matched to a drug expected to work through the mutated pathway. This dominant focus on genomic mutations has yet to configure in epigenetics. There has been relatively little advancement in changing the management of women with ER negative BC, mainly due to a dearth of actionable therapeutic targets. Our drill-down approach identified an ER negative-specific 16 gene methylation signature (AHNAK, ALPL, ANXA2R, CCND1, CIRBP, CPQ, DST, EGFR, ESR1, GPRC5B, HERC5, IL22RA2, MITF, OBSL1, POU3F3, RB1CC1) starting from a discovery approach (Illumina Infinium HumanMethylation 450 BeadChip, 40 ER negative vs. 40 ER positive BC) followed by expression verification, significant rankings in biologicalpathways (Ingenuity Pathway Analysis), and confirmation by targeted sequencing using Illumina MiSeq. Causal Networks are small hierarchical networks of regulators that control the expression/methylation of dataset targets. They can enhance understanding of the effect of master regulators on disease or function. The objective of this study was to identify regulatory networks utilizing IPA's Causal Network Analysis (CNA) in order to illuminate possible causes and mechanisms underlying the biological activities of the 16 candidate gene signature differentiating ER negative from ER positive BC. To reflect expected gene expression direction implied by methylation changes for the 16 candidate genes, the inverse of the methylation ratio from ER negative vs. ER positive tissue was used for CNA. CNA software identified 4 hierarchical networks and their corresponding master regulatory molecules, diethylstilbestrol, MSH2, 15-ketoprotaglandin E2, and transcription regulator SP1. Diethylstilbestrol and SP1 had direct regulatory influence (depth level 1) to the candidate molecules ALPL, CCND1, EGFR, ESR1 and CCND1, CIRBP, EGFR, ESR1, respectively. CNA raised the profile of ALPL,

CCND1, CIRBP, EGFR, ESR1 (5/16 candidate genes) for further consideration as potential epigenetic drivers of ER negative BC.

Otolaryngology – Head and Neck Surgery
Garcia-Rodriguez L, **Dharia R**, Heilbronn C, and **Ghanem T**. Unconventional fix for an orocutaneous fistula *Ear Nose Throat J* 2016; 95(6):212-215. PMID: 27304437. Full Text

Department of Otolaryngology-Head and Neck Surgery, Henry Ford Health System, Detroit, MI, USA.

Otolaryngology – Head and Neck Surgery
Turfe Z, Pettinga J, Leduc O, Leduc A, and Komorowska-Timek E. Chemotherapy port related lymphedema after axillary lymph node dissection *Breast* 2016; 28:145-147. PMID: 27318169. Full Text

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The Mascagni lymphatic pathway comprises superficial channels along the clavicle that drain upper extremity lymph. A 65 year-old woman with recurrent left breast cancer presented with a non-functioning chemotherapy port in the right deltopectoral groove. She had undergone right mastectomy with axillary lymph node dissection (ALND). After port removal and wound closure she developed right upper extremity lymphedema. Patients who have undergone ALND may depend solely on this pathway for upper extremity lymphatic drainage. LEVEL OF EVIDENCE: level V.

Otolaryngology – Head and Neck Surgery
Witsell DL, Khoury T, Schulz KA, **Stachler R**, Tucci DL, and Wojdyla D. Evaluation of compliance for treatment of sudden hearing loss: A CHEER network study *Otolaryngol Head Neck Surg* 2016; 155(1):48-55. PMID: 27371626. Full Text

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OBJECTIVE: The objective of this study is to describe the presentation and management of sudden sensorineural hearing loss for patients seen in academic and community-based practices within the context of the American Academy of Otolaryngology-Head and Neck Surgery Foundation's "Clinical Practice Guideline: Sudden Hearing Loss." The intention is to use these findings to guide implementation strategies and quality improvement initiatives and as pilot data for the development of clinical research initiatives. STUDY DESIGN: A cross-sectional study of patients with sudden hearing loss. SETTING: Patients were recruited from practices within the Creating Healthcare Excellence through Education and Research (CHEER) network. The CHEER network is an National Institutes of Health-funded network of 30 otolaryngology sites across the country, half of which are community based and half of which are academic practices. SUBJECTS AND METHODS: A total of 173 patients were recruited. Data were gathered via custom questionnaires collected by study site coordinators and entered into a secure online platform. Descriptive analyses and correlation statistics were run with SAS 9.3.1. RESULTS: Of the 13 guideline statements in the American Academy of Otolaryngology-Head and Neck Surgery Foundation's clinical practice guideline on sudden hearing loss, 11 statements were evaluable through this study. Compliance for otolaryngologists was >95% for key action statements (KASs) 1, 3, and 6; 90% to 95% for KASs 5 and 10; and <90% for KASs 7 and 13. Compliance was <45% for nonotolaryngologists for KASs 3 and 5-7. CONCLUSIONS: There is opportunity for nonotolaryngologists to improve for statements 3 and 5-7. Otolaryngologists are compliant with many of the KASs overall, but there is significant room for improvement.

Otolaryngology – Head and Neck Surgery

Worsham MJ, **Chen KM**, **Stephen JK**, **Datta I**, and **Divine G**. Integrating epigenetics into personalized medicine *Eur J Cancer* 2016; 54:S44. PMID: Not assigned. Abstract

M.J. Worsham, Henry Ford Health System, Detroit, United States

The majority of published studies investigating driver genes have focused primarily on genomic mutations which have led to novel study designs (basket trials) where patients with a rare mutation, regardless of tumor histology, are matched to a drug expected to work through the mutated pathway. This dominant focus on genomic mutations has yet to configure in epigenetics. It is well known that epigenetic silencing of driver genes leads to various genomic alterations, including mismatch repair deficiency, altered DNA repair and loss of chromosomal stability. In human papilloma virus (HPV) positive head and neck squamous cell carcinoma (HNSCC), recent studies are beginning to establish a mechanistic role for promoter methylation with potential to impact improved survival outcomes. The purpose of this study was to assess the 'driver' potential of 11 genes identified by Lechner et al 2013 as significantly differentially methylated between HPV positive and HPV negative HNSCC tumor samples using the Illumina 450 K platform in two independent sample sets. Our independent Illumina 450 K cohort comprised of 4 HPV positive and 4 HPV negative freshly frozen primary HNSCC. For methylation confirmation, the targeted sequencing (Illumina MiSeq) cohort (n = 18) consisted of an additional sample set of 10 HNSCC, 7 HPV positive and 3 HPV negative cases. HPV was measured using realtime quantitative PCR (qPCR). Assessment for biologic significance was performed using Ingenuity Pathway Analysis (IPA). Methylation status of all 11 genes as either hypo- or hypermethylated was in agreement with the results of the Lechner et al., study. IPA's enriched networks analysis produced one network with MSX2 as a central node. Locally dense interactions between genes in networks tend to reflect significant biology throwing the spotlight on to the MSX2 gene. Our study further supports MSX2 together with PCDHB11, C14orf162, and MEI1 as potential epigenetic drivers in HPV-associated HNSCC.

Pathology

Alikhan M, Song JY, Sohani AR, Moroch J, Plonquet A, Duffield AS, Borowitz MJ, Jiang L, Bueso-Ramos C, **Inamdar K**, **Menon MP**, Gurbuxani S, Chan E, Smith SM, Nicolae A, Jaffe ES, Gaulard P, and Venkataraman G. Peripheral T-cell lymphomas of follicular helper T-cell type frequently display an aberrant CD3-/dimCD4+ population by flow cytometry: an important clue to the diagnosis of a Hodgkin lymphoma mimic *Mod Pathol* 2016;PMID: 27312067. Full Text

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Department of Pathology, City of Hope Medical Center, Duarte, CA, USA.
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National Cancer Institute, Section of Hematopathology, National Institutes of Health, Bethesda, MD, USA.

Nodal follicular helper T-cell-derived lymphoproliferations (specifically the less common peripheral T-cell lymphomas of follicular type) exhibit a spectrum of histologic features that may mimic reactive hyperplasia or Hodgkin lymphoma. Even though angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma of follicular type share a common biologic origin from follicular helper T-cells and their morphology has been well characterized, flow cytometry of peripheral T-cell lymphomas of follicular type has not been widely discussed as a tool for identifying this reactive hyperplasia/Hodgkin lymphoma mimic. We identified 10 peripheral T-cell lymphomas of follicular type with available flow cytometry data from five different institutions, including two cases with peripheral blood evaluation. For comparison, we examined flow cytometry data for 8 classical Hodgkin lymphomas (including 1 lymphocyte-rich classical Hodgkin lymphoma), 15 nodular lymphocyte predominant Hodgkin lymphomas, 15 angioimmunoblastic T-cell lymphomas, and 26 reactive nodes. Lymph node histology and flow cytometry data were reviewed, specifically for the presence of a CD3-/dimCD4+ aberrant T-cell population (described in angioimmunoblastic T-cell lymphomas), besides other T-cell aberrancies. Nine of 10 (90%) peripheral T-cell lymphomas of follicular type showed a CD3-/dimCD4+ T-cell population constituting 29.3% (range 7.9-62%) of all lymphocytes. Five of 10 (50%) had nodular lymphocyte predominant Hodgkin lymphoma or lymphocyte-rich classical Hodgkin lymphoma-like morphology with scattered Hodgkin-like cells that expressed CD20, CD30, CD15, and MUM1. Three cases had a nodular growth pattern and three others exhibited a perifollicular growth pattern without Hodgkin-like cells. Epstein-Barr virus was positive in 1 of 10 cases (10%). PCR analysis showed clonal T-cell receptor gamma gene rearrangement in all 10

peripheral T-cell lymphomas of follicular type. By flow cytometry, 11 of 15 (73.3%) angioimmunoblastic T-cell lymphomas showed the CD3-/dimCD4+ population (mean: 19.5%, range: 3-71.8%). Using a threshold of 3% for CD3-/dimCD4+ T cells, all 15 nodular lymphocyte predominant Hodgkin lymphoma controls and 8 classical Hodgkin lymphomas were negative (Mann-Whitney P=0.01, F-PTCL vs Hodgkin lymphomas), as were 25 of 26 reactive lymph nodes. The high frequency of CD3-/dimCD4+ aberrant T cells is similar in angioimmunoblastic T-cell lymphomas and peripheral T-cell lymphomas of follicular type, and is a useful feature in distinguishing peripheral T-cell lymphomas of follicular type from morphologic mimics such as reactive hyperplasia or Hodgkin lymphoma.Modern Pathology advance online publication, 17 June 2016; doi:10.1038/modpathol.2016.113.

Pathology
Williamson SR. What is the malignant potential of clear cell papillary renal cell carcinoma? *Urol Oncol* 2016;PMID: 27364705. Full Text

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

Pathology
Zhang L, **Yang M**, **Mayer T**, Johnstone B, **Les C**, **Frisch N**, **Parsons T**, **Mi QS**, and **Gibson G**. Use of MicroRNA biomarkers to distinguish enchondroma from low-grade chondrosarcoma *Connect Tissue Res* 2016:1-7. PMID: 27267924. Article Request Form

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Establishing a definitive diagnosis between benign enchondroma versus low-grade chondrosarcoma presents a potential challenge to both clinicians and pathologists. microRNAs (small non-coding RNAs) have proven to be effective biomarkers for the identification of tumors and tumor progression. We present analysis, both array and quantitative PCR, that shows consistently and substantially increased expression of two microRNAs, miRs-181a and -138, in low-grade chondrosarcomas compared with enchondromas. The data suggest these microRNAs would provide an analytical distinction between the chondrosarcoma and benign neoplasms that can be performed in formalin-fixed paraffin-embedded specimens. Together with recent publications, these data indicate that miRs-181a and -138 also play a role in tumor development and homeostasis and may provide new targets for the development of much needed therapeutic intervention.

Pharmacy
Horng M, **Mohammad I**, **Smith ZR**, **Awdish RL**, and **Cajigas HR**. Inhaled iloprost for chronic thromboembolic pulmonary hypertension (CTEPH) during pregnancy: a case report *Pharmacotherapy* 2016;PMID: 27341074. Full Text

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Department of Pulmonary Medicine, Henry Ford Hospital, Detroit, MI.
Department of Pulmonary Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subset of pulmonary hypertension caused by acute and recurrent pulmonary emboli. Pulmonary thromboendarterectomy is the treatment of choice, but 10-50% of patients are ineligible for this procedure. We describe the case of a 25-year-old, morbidly obese (228-kg, body mass index 83.5 kg/m2) pregnant woman (G3 P2) who presented at 24 weeks' gestation; bilateral pulmonary angiography revealed filling defects and confirmed the diagnosis of CTEPH. The patient was evaluated and deemed to present too high of a risk for pulmonary thromboendarterectomy, so a multidisciplinary team initiated medical therapy. Sildenafil 20 mg orally 3 times daily was started at week 24 of gestation, and inhaled iloprost was added at 26 weeks and titrated to 5 mcg inhaled every 2 hours in order to optimize hemodynamic status prior to a cesarean section delivery scheduled to be performed 6 weeks later. At 32 weeks of gestation, the patient's pulmonary arterial systolic pressure was 77 mm Hg, right atrial pressure was 15 mm Hg, and pulmonary capillary wedge pressure of 16 mm Hg, and a healthy 1741-g male infant was delivered by cesarean section. The patient was transferred back to the medical intensive care unit in stable condition and discharged home 9 days following the procedure. Pharmacotherapeutic

strategies for patients with CTEPH who become pregnant are limited to phosphodiesterase type 5 inhibitors and prostacyclin analog therapies due to the teratogenicity of the other drug classes used to treat the disorder (endothelin receptor antagonists and soluble guanylate cyclase stimulators). To our knowledge, this is the first case report of inhaled iloprost use in addition to oral sildenafil to improve patient symptomatology and hemodynamics during the peripartum period of a young pregnant patient with inoperable CTEPH. This drug therapy was used safely, with no noted adverse effects to the newborn or to the patient. This article is protected by copyright. All rights reserved.

Pharmacy

Smith ZR, **Makowski CT**, and **Awdish RL**. Treatment of patients with chronic thrombo embolic pulmonary hypertension: focus on riociguat *Ther Clin Risk Manag* 2016; 12:957-964. PMID: 27354811. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, MI, USA.
Pulmonary and Critical Care Medicine Division, Henry Ford Hospital, Detroit, MI, USA.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease of the pulmonary vascular bed that is characterized by elevations in the mean pulmonary artery pressure in the setting of perfusion defects on ventilation-perfusion scan, and subsequently confirmed by pulmonary angiography. CTEPH, or World Health Organization (WHO) group 4 pulmonary hypertension, is a result of unresolved thromboembolic obstruction in the pulmonary arteries. Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH as it is a potentially curative therapy. However, up to one-third of patients are not candidates for the surgery, either due to distal and inaccessible nature of the lesions or comorbid conditions. Due to remodeling that occurs in nonobstructed pulmonary vessels, a portion of patients who have undergone PEA have residual CTEPH after the procedure, attributable to high shear stress prior to PEA. This phenomenon has led to the understanding of a so-called "two-compartment model" of CTEPH, opening the door to pharmacologic treatment strategies. In 2013, riociguat, a soluble guanylate cyclase stimulator, was approved in the US and Europe for the treatment of inoperable or persistent/recurrent CTEPH. This article reviews the current management of CTEPH with a focus on riociguat.

Public Health Sciences

Baptist AP, **Islam N**, and **Joseph CL**. Technology-based interventions for asthma-can they help decrease health disparities? *J Allergy Clin Immunol Pract* 2016;PMID: 27286777. Full Text

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Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich.

Asthma is a condition that has consistently demonstrated significant health outcome inequalities for minority populations. One approach used for care of patients with asthma is the incorporation of technology for behavioral modification, symptom monitoring, education, and/or treatment decision making. Whether such technological interventions can improve the care of black and inner-city patients is unknown. We reviewed all randomized controlled trial technological interventions from 2000 to 2015 performed in minority populations. A total of 16 articles met inclusion and exclusion criteria; all but 1 was performed in a childhood or adolescent age group. The interventions used MPEG audio layer-3 players, text messaging, computer/Web-based systems, video games, and interactive voice response. Many used tailored content and/or a specific behavior theory. Although the interventions were based on technology, most required additional special staffing. Subject user satisfaction was positive, and improvements were noted in asthma knowledge, medication adherence, asthma symptoms, and quality of life. Unfortunately, health care utilization (emergency department visits and/or hospitalizations) was typically not improved by the interventions. Although no single intervention modality was vastly superior, the computer-based interventions appeared to have the most positive results. In summary, technology-based interventions have a high level of user satisfaction among minority and urban/low-income individuals with asthma, and can improve asthma outcomes. Further large-scale studies are needed to assess whether such interventions can decrease health disparities in asthma.

Public Health Sciences

Chen KM, **Datta I**, **Stephen JK**, **Chitale D**, **Divine G**, and **Worsham MJ**. ER negative-specific differentially methylated genes identify master regulators to expose potential epigenetic drivers of aggressive disease *Eur J Cancer* 2016; 54:S48. PMID: Not assigned. Abstract

K.M. Chen, Henry Ford Health System, Detroit, United States

The majority of published studies investigating driver genes have focused primarily on genomic mutations which have led to novel study designs (basket trials) where patients with a rare mutation, regardless of tumor histology, are matched to a drug expected to work through the mutated pathway. This dominant focus on genomic mutations has yet to configure in epigenetics. There has been relatively little advancement in changing the management of women with ER negative BC, mainly due to a dearth of actionable therapeutic targets. Our drill-down approach identified an ER negative-specific 16 gene methylation signature (AHNAK, ALPL, ANXA2R, CCND1, CIRBP, CPQ, DST, EGFR, ESR1, GPRC5B, HERC5, IL22RA2, MITF, OBSL1, POU3F3, RB1CC1) starting from a discovery approach (Illumina Infinium HumanMethylation 450 BeadChip, 40 ER negative vs. 40 ER positive BC) followed by expression verification, significant rankings in biologicalpathways (Ingenuity Pathway Analysis), and confirmation by targeted sequencing using Illumina MiSeq. Causal Networks are small hierarchical networks of regulators that control the expression/methylation of dataset targets. They can enhance understanding of the effect of master regulators on disease or function. The objective of this study was to identify regulatory networks utilizing IPA's Causal Network Analysis (CNA) in order to illuminate possible causes and mechanisms underlying the biological activities of the 16 candidate gene signature differentiating ER negative from ER positive BC. To reflect expected gene expression direction implied by methylation changes for the 16 candidate genes, the inverse of the methylation ratio from ER negative vs. ER positive tissue was used for CNA. CNA software identified 4 hierarchical networks and their corresponding master regulatory molecules, diethylstilbestrol, MSH2, 15-ketoprotaglandin E2, and transcription regulator SP1. Diethylstilbestrol and SP1 had direct regulatory influence (depth level 1) to the candidate molecules ALPL, CCND1, EGFR, ESR1 and CCND1, CIRBP, EGFR, ESR1, respectively. CNA raised the profile of ALPL, CCND1, CIRBP, EGFR, ESR1 (5/16 candidate genes) for further consideration as potential epigenetic drivers of ER negative BC.

Public Health Sciences

Joseph CLM, Ownby DR, **Zoratti E**, **Johnson D**, Considine S, **Bourgeois R**, **Melkonian C**, **Miree C**, **Cole Johnson C**, and **Lu M**. Recruitment experience for a pragmatic randomized controlled trial: Using EMR initiatives and minimizing research infrastructure *Clin Res Regul Aff* 2016:1-8. PMID: Not assigned. Article Request Form

C.L.M. Joseph, Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA

Modernized approaches to multi-site randomized controlled trials (RCT) include the use of electronic medical records (EMR) for recruitment, remote data capture (RDC) for multisite data collection, and strategies to reduce the need for research infrastructure. These features facilitate the conduct of pragmatic trials, or trials conducted in 'real life' settings. This study describes the recruitment experience of an RCT to evaluate a clinic-based intervention targeting urban youth with asthma. Using encounter and prescription databases, a list of potentially-eligible patients was linked to the Epic appointment scheduling system. Patients were enrolled during a scheduled visit and then electronically randomized to a tailored vs generic online intervention. In total, 1146 appointments for 580 eligible patients visiting five clinics were identified, of which 45.9% (266/580) were randomized to reach targeted enrollment (n = 250). RDC facilitated multisite enrollment. Intervention content was further personalized through real-time entry of asthma medications prescribed at the clinic visit. EMR monitoring helped with recruitment trouble-shooting. Systemic challenges included a system-wide EMR transition and a system-wide reorganization of clinic staffing. In conclusion, modernized RCTs can accelerate translation of research findings. Electronic initiatives facilitated implementation of this RCT; however, adaptations to recruitment strategies resulted in a more 'explanatory' framework.

Public Health Sciences

Kumar N, **Nakagawa P**, **Janic B**, **Romero CA**, **Worou ME**, **Peterson EL**, Ongeri EE, Niyitegeka JMV, **Rhaleb NE**, and **Carretero OA**. The anti-inflammatory peptide AC-SDKP is released from thymosin β4 by meprin α and prolyl oligopeptidase *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

N. Kumar, Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, United States

N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a natural tetrapeptide with anti-inflammatory and anti-fibrotic properties. We have previously shown that prolyl oligopeptidase (POP) is involved in the Ac-SDKP release from thymosin β4 (Tβ4). However, POP can only hydrolyze peptides shorter than 30 amino acids and Tβ4 is 43 amino acids long. This suggests that Tβ4 must be hydrolyzed by another peptidase that releases N-terminal intermediate peptide(s) <30 amino acids before POP hydrolysis takes place. Our search in peptidase database for potential candidate(s) gave high score for meprin α metalloprotease. Therefore, we hypothesize that Tβ4 is hydrolyzed by meprin α prior to POP hydrolysis. To test this, in vitro and in vivo studies were performed. In vitro, we found that the incubation of Tβ4 with both, meprin α and POP releases Ac-SDKP, whereas it failed when Tβ4 is incubated with either meprin α or POP alone. Incubation of Tβ4 with rat kidney homogenate increases Ac-SDKP, which is blocked

by actinonin (meprin α inhibitor). In addition, kidney from meprin α knockout mice showed a significantly lower Ac-SDKP as compared to its wild type control. In vivo, we observed that rat treated with captopril (ACE inhibitor) increased plasma concentrations of Ac-SDKP, which is inhibited by the co-administration of actinonin (vehicle 3.1±0.22 nmol/L; captopril 15.1±0.7 nmol/L; captopril + actinonin 6.1±0.3 nmol/L; vehicle versus captopril, P<0.002; captopril versus captopril + actinonin, P<0.002). Similar results were obtained with urinary Ac-SDKP excretion. We conclude that Ac-SDKP is released from Tβ4 by the successive action of meprin α and POP.

Public Health Sciences

Li J, **Gordon S**, **Rupp L**, **Zhang T**, Boscarino J, Trinacty C, Schmidt M, Moorman A, Holmberg S, and **Lu M**. Long-term fibrosis and viral level progression among treated and untreated patients with chronic hepatitis B *J Hepatol* 2016; 64(2):S371. PMID: Not assigned. Abstract

J. Li, Department of Public Health Sciences, Detroit, United States

Background and Aims: The temporal relationship between HBV DNA viral load and liver fibrosis progression remains controversial. Using data from in the Chronic Hepatitis Cohort Study (CHeCS), a longitudinal study of patients from four large US health systems, we investigated long-term trajectories of viral load and FIB4 among HBV patients with and without antiviral therapy. Methods: Observation for each patient commenced at the “index date,” either the date of first treatment initiation (treated) or the earliest date of viral load measurement (untreated). Median FIB4 scores and viral load levels derived from routine testing were summarized in 30-day intervals for up to 5 years after index. Propensity scores for inverse probability of treatment weighting (IPTW) were used to control for bias in treatment selection. The propensity scores were derived using multiple logistic regression with a large selection of baseline covariates. Changes in FIB4 and viral load over time were modeled using a bivariate piecewise linear spline mixed effects model. Results: 1,126 untreated and 928 treated patients were included. The five-year dynamics of viral load and FIB4 exhibited a bi-phasic pattern. Viral load declined 31% ($p < 0.001$) per month for the first 5 months after treatment initiation, then slowed to a 2.3% ($p < 0.001$) decline per month thereafter. A non-significant viral load decline was observed for untreated patients. FIB4 began to decline 0.4% per month ($p < 0.001$) at 5 months post-treatment initiation and stabilized at 28 months. Starting at approximately 28 months after index, FIB4 significantly increased by 0.6% per month ($p < 0.001$) among untreated patients. FIB4 trajectories were consistent across baseline FIB4 levels. Conclusions: Antiviral therapy results in a rapid HBV DNA viral load decline followed by a delayed decline in FIB4. In untreated patients, viral load remains stable and significantly higher than in treated patients, and FIB4 gradually increases over time, suggesting fibrosis progression. (Figure presented).

Public Health Sciences

Liu XS, **Fan BY**, **Pan WL**, **Li C**, **Levin AM**, **Wang X**, **Zhang RL**, **Zervos TM**, Hu J, Zhang XM, **Chopp M**, and **Zhang ZG**. Identification of miRNomes associated with adult neurogenesis after stroke using Argonaute 2-based RNA sequencing *RNA Biol* 2016:0. PMID: 27315491. Article Request Form

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Neurogenesis is associated with functional recovery after stroke. However, the underlying molecular mechanisms have not been fully investigated. Using an Ago2-based RNA immunoprecipitation to immunoprecipated Ago2-RNA complexes followed by RNA sequencing (Ago2 RIP-seq) approach, we profiled the miRNomes in neural progenitor cells (NPCs) harvested from the subventricular zone (SVZ) of the lateral ventricles of young adult rats. We identified more than 7 and 15 million reads in normal and ischemic NPC libraries, respectively. We found that stroke substantially changed Ago2-associated miRNA profiles in NPCs compared to those in non-ischemic NPCs. We also discovered a new complex repertoire of isomiRs and multiple miRNA-miRNA* pairs and numerous novel miRNAs in the non-ischemic and ischemic NPCs. Amongst them, pc-3p-17172 significantly regulated NPC proliferation and neuronal differentiation. Collectively, the present study reveals profiles of Ago2-associated miRNomes in non-ischemic and ischemic NPCs, which provide a molecular basis to further investigate the role of miRNAs in mediating adult neurogenesis under physiological and ischemic conditions.

Public Health Sciences

Neugut AI, Hillyer GC, Kushi LH, **Lamerato L**, Buono DL, **Nathanson SD**, Bovbjerg DH, Mandelblatt JS, Tsai WY, Jacobson JS, and Hershman DL. A prospective cohort study of early discontinuation of adjuvant chemotherapy in women with breast cancer: the breast cancer quality of care study (BQUAL) *Breast Cancer Res Treat* 2016;PMID: 27287779. Full Text

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For many women with non-metastatic breast cancer, adjuvant chemotherapy prevents recurrence and extends survival. Women who discontinue chemotherapy early may reduce those benefits, but little is known about what predicts early discontinuation. We sought to determine prospectively the rate and reasons for early discontinuation of adjuvant chemotherapy in women with breast cancer. We conducted a prospective cohort study among three U.S. health care organizations. Of 1158 women with newly diagnosed non-metastatic breast cancer, 2006-2010, we analyzed 445 (38.4 %) patients who initiated standard adjuvant chemotherapy as defined by accepted guidelines. We interviewed patients at baseline and twice during treatment regarding sociodemographic/psychosocial factors and treatment decision-making and collected clinical data. They were categorized according to the number of cycles required by the chemotherapy regimen they had initiated. The outcome was early discontinuation (<80 % of planned cycles). Of patients analyzed, 392 (88.1 %) completed the prescribed therapy. The strongest predictor was receipt of a regimen entailing >4 cycles of therapy (18.1 % for longer regimens, 7.4 % for 4 cycles) (odds ratio [OR] 2.59, 95 % CI 1.32-5.08), controlling for race, age, stage, hormone receptor status, social support, optimism, spirituality, stress, and physical symptoms. Higher levels of psychological symptoms on the Memorial symptom assessment scale also increased the odds of early discontinuation (OR 1.92, 95 % CI 0.998-3.68). The large majority of patients who initiated adjuvant chemotherapy for breast cancer completed their prescribed regimens, but early discontinuation was associated with lengthier regimens and, with borderline statistical significance, for those with psychological side effects.

Public Health Sciences

Petrie JG, Ohmit SE, Cheng CK, Martin ET, Malosh RE, Lauring AS, **Lamerato LE**, **Reyes KC**, Flannery B, Ferdinands JM, and Monto AS. Influenza vaccine effectiveness against antigenically drifted influenza higher than expected in hospitalized adults: 2014-2015 *Clin Infect Dis* 2016;PMID: 27369320. Full Text

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BACKGROUND: The 2014-2015 influenza season was severe, with widespread circulation of influenza A (H3N2) viruses that were antigenically drifted from the vaccine virus. Reported vaccine effectiveness (VE) estimates from ambulatory care settings were markedly decreased. METHODS: Adults, hospitalized at two hospitals in southeast Michigan for acute respiratory illnesses, defined by admission diagnoses, of </=10 days duration were prospectively

enrolled. Throat and nasal swab specimens were collected, combined, and tested for influenza by RT-PCR. VE was estimated by comparing the vaccination status of those who tested positive for influenza with those who tested negative in logistic regression models adjusted for age, sex, hospital, calendar time, time from illness onset to specimen collection, frailty score, and Charlson Comorbidity Index (CCI). RESULTS: Among 624 patients included in the analysis, 421 (68%) were considered vaccinated, 337 (54%) were female, 220 (35%) were age >/=65 years, and 92% had CCI >0 indicating >/=1 comorbid conditions. 98 (16%) patients tested positive for influenza A (H3N2); among 60 (61%) A (H3N2) viruses tested by pyrosequencing, 53 (88%) belonged to the drifted 3C.2a genetic group. Adjusted VE was 43% (95% CI: 4 to 67) against influenza A (H3N2); 40% (95% CI: -13 to 68) for those <65 years of age and 48% (95% CI: -33 to 80) for those >/=65. Sensitivity analyses largely supported these estimates. CONCLUSIONS: VE estimates appeared higher than reports from similar studies in ambulatory care settings, suggesting that the 2014-15 vaccine may have been more effective in preventing severe illness requiring hospitalization.

Public Health Sciences

Valerio MA, **Peterson EL**, Wittich AR, and **Joseph CL**. Examining health literacy among urban African-American adolescents with asthma *J Asthma* 2016:0. PMID: 27359106. Full Text

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OBJECTIVE: This exploratory study assessed health literacy among urban African-American high school students to improve understanding of the association between adolescent health literacy and asthma. METHODS: We conducted a secondary data analysis of the control group (n = 181) of the Puff City randomized controlled trial (2006-2010), a web-based intervention to promote asthma management among students, grades 9 through 12. A validated self-report 3-item health literacy screening instrument was completed at final online follow-up survey. Logistic regression was used to explore the association between health literacy, demographic characteristics, quality of life, asthma management, and health care utilization. RESULTS: Multivariate analysis revealed that an overall inadequate health literacy score was associated with students who were more likely to be younger (OR 0.61; 95% CI 0.44-0.84), not on Medicaid (OR 0.36; 95% CI 0.17-0.76), have at least one hospitalization (OR 1.29; 95% CI 1.07-1.56); and a lower overall quality of life (OR 0.75; 95% CI 0.59-0.95). Those lacking confidence in filling out medical forms, needing help reading hospital materials, and having difficulty understanding written information were more likely to not have a rescue inhaler (OR 0.49; 95% CI 0.25-0.94), have one or more emergency visits (OR 1.21 95% CI 1.02-1.43), and one or more hospitalizations (OR 1.19; 95% CI 1.01-1.41), respectively. CONCLUSIONS: The findings indicate a significant association between inadequate health literary and suboptimal asthma management. It is important to advance understanding of adolescent health literacy, especially those at-risk, as they assume asthma self-management tasks and move toward independent adult self-care.

Public Health Sciences

Worsham MJ, **Chen KM**, **Stephen JK**, **Datta I**, and **Divine G**. Integrating epigenetics into personalized medicine *Eur J Cancer* 2016; 54:S44. PMID: Not assigned. Abstract

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The majority of published studies investigating driver genes have focused primarily on genomic mutations which have led to novel study designs (basket trials) where patients with a rare mutation, regardless of tumor histology, are matched to a drug expected to work through the mutated pathway. This dominant focus on genomic mutations has yet to configure in epigenetics. It is well known that epigenetic silencing of driver genes leads to various genomic alterations, including mismatch repair deficiency, altered DNA repair and loss of chromosomal stability. In human papilloma virus (HPV) positive head and neck squamous cell carcinoma (HNSCC), recent studies are beginning to establish a mechanistic role for promoter methylation with potential to impact improved survival outcomes. The purpose of this study was to assess the 'driver' potential of 11 genes identified by Lechner et al 2013 as significantly differentially methylated between HPV positive and HPV negative HNSCC tumor samples using the Illumina 450 K platform in two independent sample sets. Our independent Illumina 450 K cohort comprised of 4 HPV positive and 4 HPV negative freshly frozen primary HNSCC. For methylation confirmation, the targeted sequencing (Illumina MiSeq) cohort (n = 18) consisted of an additional sample set of 10 HNSCC, 7 HPV positive and 3 HPV negative cases. HPV

was measured using realtime quantitative PCR (qPCR). Assessment for biologic significance was performed using Ingenuity Pathway Analysis (IPA). Methylation status of all 11 genes as either hypo- or hypermethylated was in agreement with the results of the Lechner et al., study. IPA's enriched networks analysis produced one network with MSX2 as a central node. Locally dense interactions between genes in networks tend to reflect significant biology throwing the spotlight on to the MSX2 gene. Our study further supports MSX2 together with PCDHB11, C14orf162, and MEI1 as potential epigenetic drivers in HPV-associated HNSCC.

Public Health Sciences
Yessayan L, **Moore C**, **Lu M**, and **Yee J**. Bone-specific alkaline phosphatase and bone turnover in African American hemodialysis patients *Hemodial Int* 2016;PMID: 27350216. Full Text

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Introduction Noninvasive measures of bone activity include intact parathyroid hormone (iPTH) and bone-specific alkaline phosphatase (BSAP). Whether BSAP measurement alone or in combination with other biochemical data provides more reliable information about bone turnover than iPTH alone in African Americans on hemodialysis is unknown. Methods This cross-sectional study aimed to determine the optimal predictor and cutoff points for BSAP, iPTH, calcium and phosphorus in classifying bone biopsy findings. Forty-three African American hemodialysis patients were available for analysis. Biochemical data on the day of biopsy across a spectrum of qualitative histologic bone features were compared. Classification and regression tree analysis was used to determine both the optimal predictor and cutoff points for BSAP, iPTH, calcium and phosphorus in identifying bone turnover status. Findings Seven subjects had adynamic disease, 31 had mild/moderate hyperparathyroid bone features, and five had severe hyperparathyroid bone disease. BSAP was the optimal predictor of bone biopsy with a cutoff point of 22 ng/mL. Calcium and phosphorus had no predictive value. At BSAP </= 22 ng/mL, subjects had either adynamic bone disease or mild/moderate hyperparathyroid bone disease but iPTH was not useful in further classifying biopsy findings. When BSAP was >22 ng/mL, subjects had either mild/moderate or severe hyperparathyroid bone disease, and iPTH was useful in further classifying biopsy findings. With BSAP > 22 ng/mL and iPTH < 726 pg/mL, all subjects had mild/moderate bone turnover features. Discussion Compared to iPTH, BSAP was shown to be the optimal predictor of biopsy findings with an optimal cutoff at 22 ng/mL.

Public Health Sciences
Yin C, **Weiland M**, **Li J**, **She R**, **Zhou L**, and **Mi Q**. Serum miRNAs as potential biomarkers for early prediction of type 1 diabetes *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

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Background The incidence of type 1 diabetes (T1D), a T cell-mediated beta cell destructive autoimmune disease, has been increasing about 3-4% annually for several decades. Individuals at risk for T1D are diagnosed at a late stage when the possibility for disease prevention is absent. Autoantibodies (AA) to islet antigens such as islet antigen (IA)-2, IA-2b, and glutamate decarboxylase (GAD65) appear earlier before T1D onset and are used for early T1D prediction. However, the appearance of islet AA marks a relatively late stage of the autoimmune process and therefore is not suitable for early disease intervention. More importantly AA lack causal relationship with the pathogenesis of T1D. Therefore, there is an urgent need for better (increased specificity/sensitivity) and earlier (predating autoantibodies) markers for the prediction of AA development. MicroRNAs (miRNAs) have emerged as an important regulatory factors in pancreatic β-cell development, homeostasis, function, and in a variety of immune cell development, differentiation and function. Our recent study showed that miRNAs regulate T1D development and serum miRNAs are potential biomarkers for T1D progression in mouse models. Our objective here is to identify specific serum miRNA biomarkers for earlier and better prediction of individuals at risk for T1D in human. Method We performed serum miRNA expressions profiles in 35 AA positive (IAA and ICA) non-T1D subjects and 40 AA negative relative subjects from the Diabetes Prevention Trial-Type 1 (DPT-1) cohort, using the TaqMan low-density arrays. miRNAs with changed expression level were further confirmed by a single TaqMan RT-PCR. Result 9 miRNAs (miR-146a, miR-561 and miR-548a-3p, miR-184 and miR-200a) were down-regulated and 2 miRNAs (miR-30c and miR-487a) are up-regulated in the serum of AA+ non-T1D subjects compared to that from AA- subjects (two-sample t-test P<0.05). In addition, a cluster of five miRNAs (miR-146a, miR-197, miR-193b, miR-574-3p, and miR-561) was identified to clearly separate AA+ subjects from AA- subjects with higher sensitivity and specificity (LASSO logistic regression). miRNA target and pathway prediction analyses revealed that some of these miRNAs are related to

immune function and beta-cell homeostasis and potentially involved in autoimmune processes. Conclusion We have identified distinct serum miRNA expressions profiles in AA+ subjects compared to AA- subjects. These serum miRNAs could serve as potential biomarkers for early prediction of autoimmune processes in individuals at risk for T1D, which need to be further confirmed in the future studies.

Public Health Sciences
Zhu L, **Xu J**, **Harding P**, and **Yang XP**. Role of ACE2 in the cardioprotective effects of angiotensin II type 2 receptors *FASEB Journal* 2016; 30PMID: Not assigned. Abstract

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Blockade of angiotensin II (Ang II) type 1 receptors with angiotensin receptor blockers (ARBs) activates the Ang II type 2 receptors (AT2) and also increases angiotensin-converting enzyme 2 (ACE2) expression and Ang 1-7 levels. However, it is not known whether activation of AT2 and ACE2 are synergistically associated to exert cardioprotection. We hypothesize that activation of AT2 increases the expression and activity of ACE2, leading to cardioprotection. Transgenic mice with cardiac overexpression of AT2 (Tg-AT2) were subjected to myocardial infarction (MI) for 12 weeks. We found that Tg-AT2 mice had cardiac ACE2 protein expression 2.36±0.07-fold higher than the wild-type (WT) controls, associated with better preserved cardiac function compared with WT controls (ejection fraction: 41.6±2.3% vs 27.6±1.8%). In AT2-stimulated coronary artery endothelial cells, ACE2 protein expression was increased by 1.79±0.04-fold and ACE2 activity was enhanced from 0.61± 0.05 (basal) to 0.95±0.03 pg/μl/h/μg protein. These effects were blunted by AT2 antagonist. Furthermore, activation of AT2 increased cGMP by 1.71±0.12-fold, which was diminished by Mas receptors antagonist. AT2 activation also increased Ang 1-7 from 0.1±0.05 (basal) to 15.6±0.5 (pg/ml/μg protein) and this effect was diminished by the AT2 antagonist. Our data suggest that the cardioprotective effects of AT2 is in part mediated via activation of ACE2, enhancing the release of Ang 1-7 and leading to cardioprotection.

Pulmonary
Abrencillo RA, Khemasuwan D, and **Diaz-Mendoza JI**. A Young Man with Acute Progressive Respiratory Distress and a Right Inguinal Mass *Ann Am Thorac Soc* 2016; 13(6):970-975. PMID: 27295158. Full Text

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Pulmonary
Cheng P, **Tran M**, Tallent G, **Pillai V**, **Cuamatzi A**, **Bazan L**, **Moss K**, and **Drake CL**. Circadian misalignment and cognitive flexibility in night shift workers *Sleep* 2016; 39:A173. PMID: Not assigned. Abstract

P. Cheng, Henry Ford Health System, Detroit, United States

Introduction: Circadian misalignment can impact health and performance, and is of particular concern for shift workers, whose work schedules may be at odds with their endogenous sleep-wake rhythms. Impairments in cognitive performance have been observed as a result of circadian misalignment; however, these observations have been limited generally to vigilance and reaction time. Less is known regarding on-task cognitive performance. The task-switching paradigm is often used to measure executive control of cognition, particularly in attentional flexibility. In this paradigm, trials involving varying task-rules are completed in quick succession. Some trials employ the same taskrule as the previous trials (“repeat” trials), whereas others employ a different task-rule (“switch” trials). Switch trials require the individual to cognitively switch task-rules, and therefore should result in longer reaction times compared to repeat trials (i.e., “switch cost”). Larger switch costs are indicative of increased effort in set switching, and therefore reduced cognitive flexibility. Successful task-switching performance also requires adequate inhibition of prior task rules, which can be measured by reaction time on trials returning to the same taskrule after a switch trial, compared to performance following successive switch trials (i.e., “set inhibition”). Methods: Twenty-one permanent night shift workers (13 female) participated in a larger study examining the consequences of circadian misalignment on health. Circadian phase was evaluated using dimlight salivary melatonin onset (DLMO). DLMO at or after 6am was considered full circadian alignment. Cognitive flexibility was evaluated using a computerized task-switching paradigm. Results: A multiple linear regression indicated that switch-costs increased linearly with increasing circadian misalignment due to earlier DLMOs ($\beta = .54$, $p < .01$), controlling for sex and age as covariates. No significant effect was detected with set-inhibition. Conclusion: Results indicate that cognitive flexibility is related to circadian alignment,

with better alignment associated with increased flexibility. This offers further insight into the cognitive vulnerabilities related to circadian misalignment that may impact risk for errors, accidents, and injuries, particularly for shift workers.

Pulmonary

Durrence H, **Drake CL**, **Tran KM**, **Bazan L**, **Cheng P**, **Pillai V**, and **Roth T**. Double-blind, placebo-controlled, 4-way crossover study comparing the effects of doxepin 6 MG and zolpidem 10 MG on gait, balance, and cognitive performance in healthy volunteers *Sleep* 2016; 39:A206. PMID: Not assigned. Abstract

H. Durrence, Pernix Therapeutics, Del Mar, United States

Introduction: Falls are the leading cause of injury in older adults, accounting for millions of injuries. Frequency of nocturnal awakenings, sleep medication use, insomnia, and nocturia are independent risk factors for falls and hip fractures. To examine the effect of sleep medicine on gait and balance, we evaluated doxepin (DXP; Silenor®) 6mg (DXP6) and zolpidem 10mg (Z10), the highest doses indicated for insomnia. Additionally, the effects on memory were examined. Methods: This 4-way crossover study assessed the effects of a single dose of DXP6 compared with matching placebo and a single dose of Z10 compared with matching placebo at the respective Tmax in adult male volunteers (n = 39). Gait, balance, and memory were assessed 4 hou rs postdose for DX P6 and placebo and at 1.5 hours postdose for Z10 and placebo. After awakening, subjects performed the Tandem Walk (TW), the Berg Balance Scale (BBS) followed by immediate free recall while delayed recall was a ssessed 15 minutes after morning awakening. Results: Z10, but not DXP6, showed significantly poorer performance relative to placebo on all outcome measures. Also, in a direct comparison, performance on Z10 was impaired relative to DX P6. Measures that were significantly impaired (all p-values < 0.0001) for Z10 included TW #step-offs (500% more than DXP6), TW time to complete, BBS score, words recalled immediately and delayed (340% fewer words than DXP6). Conclusion: These data indicate that doxepin at the highest hypnotic dose (DXP6) did not cause impairment in gait, balance, or memory. In contrast, zolpidem at the highest hypnotic dose had broad CNS depressant effects. Functions as diverse as memory and balance were negatively impacted by Z10 directly or indirectly through its sedative activity. Further research is needed to determine if impairment is generalizable to other medications binding at the benzodiazepine receptor but not to drugs working on transmitters mediating wakefulness such histamine.

Pulmonary

Durrence H, **Roth T**, **Tran KM**, **Singh M**, **Cheng P**, **Pillai V**, and **Drake C**. Arousability of insomnia patients and healthy volunteers is not impacted by the sleep-specific doses of doxepin (3 MG and 6 MG), but is impacted in healthy volunteers using zolpidem 10 MG *Sleep* 2016; 39:A201. PMID: Not assigned. Abstract

H. Durrence, Pernix Therapeutics, Del Mar, United States

Introduction: Ability to awaken to external or internal stimuli (arousability) is important. However, arousability is rarely assessed in evaluating hypnotics. An indirect approach to assessing arousability is examining sleep maintenance (SM) and relating wake-after-sleeponset (WASO) to number-of-awakenings (NAW). Decreased NAW reflects a drug's potential for blunting arousal response. Decreased WASO coupled with no decrease in NAW reflects ability to hasten return to sleep. To explore arousability, we evaluated the effects of doxepin (DXP; Silenor®) 3mg and 6mg (i.e. indicated for insomnia). Further, we directly evaluated Auditory Awakening Threshold (AAT) with DXP and zolpidem. Methods: Two placebo-controlled efficacy trials and an AAT trial are reported. Study A was a 12-week trial in elderly insomniacs (DXP 3mg); Study B was a 5-week trial in adult insomniacs (DXP 3mg and 6mg). Study C was a 4-way crossover trial assessing a single dose of DXP 6mg (DXP6), zolpidem 10mg (Z10) and placebo (2 placebo conditions). AAT was evaluated at the Tmax of each active medication and its corresponding placebo. Results: DXP 3mg (Study A and B; p < 0.0001) and 6 mg (Study B; p < 0.0001) significantly decreased WASO across the trials. Importantly, NAW were not decreased at any dose or time point in either study. In Study C, the AAT (expressed as dB) for Z10, was significantly higher (p < 0.0001) than both PBO groups and DXP6, with a mean dB level of 102 (DXP6 83dB, average placebo 81dB). Further, 24 Z10 subjects did not awaken at max AAT (110dB; 4 subjects in all 3 other groups). Conclusion: DXP (3mg, 6mg) improved WASO without altering NAW. Further, DXP6 did not impact AAT; in contrast Z10 increased arousal threshold. These data demonstrate that DXP improved SM without impacting arousability. Further research to determine if this more broadly reflects differences between drugs that work via the sleep (agonist) versus wake (antagonist) system.

Pulmonary

Horng M, **Mohammad I**, **Smith ZR**, **Awdish RL**, and **Cajigas HR**. Inhaled iloprost for chronic thromboembolic pulmonary hypertension (CTEPH) during pregnancy: a case report *Pharmacotherapy* 2016;PMID: 27341074.
Full Text

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a subset of pulmonary hypertension caused by acute and recurrent pulmonary emboli. Pulmonary thromboendarterectomy is the treatment of choice, but 10-50% of patients are ineligible for this procedure. We describe the case of a 25-year-old, morbidly obese (228-kg, body mass index 83.5 kg/m2) pregnant woman (G3 P2) who presented at 24 weeks' gestation; bilateral pulmonary angiography revealed filling defects and confirmed the diagnosis of CTEPH. The patient was evaluated and deemed to present too high of a risk for pulmonary thromboendarterectomy, so a multidisciplinary team initiated medical therapy. Sildenafil 20 mg orally 3 times daily was started at week 24 of gestation, and inhaled iloprost was added at 26 weeks and titrated to 5 mcg inhaled every 2 hours in order to optimize hemodynamic status prior to a cesarean section delivery scheduled to be performed 6 weeks later. At 32 weeks of gestation, the patient's pulmonary arterial systolic pressure was 77 mm Hg, right atrial pressure was 15 mm Hg, and pulmonary capillary wedge pressure of 16 mm Hg, and a healthy 1741-g male infant was delivered by cesarean section. The patient was transferred back to the medical intensive care unit in stable condition and discharged home 9 days following the procedure. Pharmacotherapeutic strategies for patients with CTEPH who become pregnant are limited to phosphodiesterase type 5 inhibitors and prostacyclin analog therapies due to the teratogenicity of the other drug classes used to treat the disorder (endothelin receptor antagonists and soluble guanylate cyclase stimulators). To our knowledge, this is the first case report of inhaled iloprost use in addition to oral sildenafil to improve patient symptomatology and hemodynamics during the peripartum period of a young pregnant patient with inoperable CTEPH. This drug therapy was used safely, with no noted adverse effects to the newborn or to the patient.

Pulmonary

Nguyen HB, **Jaehne AK**, Jayaprakash N, Semler MW, **Hegab S**, Yataco AC, **Tatem G**, Salem D, **Moore S**, Boka K, **Gill JK**, **Gardner-Gray J**, **Pflaum J**, **Domecq JP**, **Hurst G**, Belsky JB, **Fowkes R**, Elkin RB, Simpson SQ, Falk JL, Singer DJ, and **Rivers EP**. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE *Crit Care* 2016; 20(1):160. PMID: 27364620. Full Text

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Prior to 2001 there was no standard for early management of severe sepsis and septic shock in the emergency department. In the presence of standard or usual care, the prevailing mortality was over 40-50 %. In response, a systems-based approach, similar to that in acute myocardial infarction, stroke and trauma, called early goal-directed therapy was compared to standard care and this clinical trial resulted in a significant mortality reduction. Since the

publication of that trial, similar outcome benefits have been reported in over 70 observational and randomized controlled studies comprising over 70,000 patients. As a result, early goal-directed therapy was largely incorporated into the first 6 hours of sepsis management (resuscitation bundle) adopted by the Surviving Sepsis Campaign and disseminated internationally as the standard of care for early sepsis management. Recently a trio of trials (ProCESS, ARISE, and ProMISe), while reporting an all-time low sepsis mortality, question the continued need for all of the elements of early goal-directed therapy or the need for protocolized care for patients with severe and septic shock. A review of the early hemodynamic pathogenesis, historical development, and definition of early goal-directed therapy, comparing trial conduction methodology and the changing landscape of sepsis mortality, are essential for an appropriate interpretation of these trials and their conclusions.

Pulmonary

Smith ZR, **Makowski CT**, and **Awdish RL**. Treatment of patients with chronic thrombo embolic pulmonary hypertension: focus on riociguat *Ther Clin Risk Manag* 2016; 12:957-964. PMID: 27354811. Full Text

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease of the pulmonary vascular bed that is characterized by elevations in the mean pulmonary artery pressure in the setting of perfusion defects on ventilation-perfusion scan, and subsequently confirmed by pulmonary angiography. CTEPH, or World Health Organization (WHO) group 4 pulmonary hypertension, is a result of unresolved thromboembolic obstruction in the pulmonary arteries. Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH as it is a potentially curative therapy. However, up to one-third of patients are not candidates for the surgery, either due to distal and inaccessible nature of the lesions or comorbid conditions. Due to remodeling that occurs in nonobstructed pulmonary vessels, a portion of patients who have undergone PEA have residual CTEPH after the procedure, attributable to high shear stress prior to PEA. This phenomenon has led to the understanding of a so-called "two-compartment model" of CTEPH, opening the door to pharmacologic treatment strategies. In 2013, riociguat, a soluble guanylate cyclase stimulator, was approved in the US and Europe for the treatment of inoperable or persistent/recurrent CTEPH. This article reviews the current management of CTEPH with a focus on riociguat.

Radiation Oncology

Beitler JJ, Quon H, Jones CU, Salama JK, Busse PM, Cooper JS, Koyfman SA, Ridge JA, Saba NF, **Siddiqui F**, Smith RV, Worden F, Yao M, and Yom SS. ACR Appropriateness Criteria(R) Locoregional therapy for resectable oropharyngeal squamous cell carcinomas *Head Neck* 2016;PMID: 27330003. Full Text

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Henry Ford Hospital, Detroit, Michigan.
Montefiore Medical Center, Bronx, New York, American College of Surgeons.
University of Michigan, Ann Arbor, Michigan, American Society of Clinical Oncology.
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BACKGROUND: There are no level I studies to guide treatment for resectable oropharyngeal squamous cell carcinoma (SCC). Treatment toxicities influence management recommendations. Ongoing investigations are examining deintensified treatments for human papillomavirus (HPV)-associated oropharyngeal SCC. METHODS: The Appropriateness Criteria panel, using modified Delphi methodology, produced a literature summary, an assessment of treatment recommendations, and cases to illustrate their use. RESULTS: A multidisciplinary team produces optimum results. Based on HPV status, smoking history, and staging, patients are divided into groups at low, intermediate, and high-risk of death. In the future, treatment recommendations may be influenced by HPV status, which has changed the epidemiology of oropharyngeal SCC. CONCLUSION: T1 to T2N0M0 resectable oropharyngeal SCC can be treated with surgery or radiation without chemotherapy. Patients with T1-2N1-2aM0 disease can receive radiation, chemoradiation, or transoral surgery with neck dissection and appropriate adjuvant

therapy. Patients with T1-2N2b-3M0 disease should receive chemoradiation or transoral surgery with neck dissection and appropriate adjuvant therapy. Concurrent chemoradiation is preferred for T3 to T4 disease. (c) 2016 American College of Radiology. Head Neck, 2016.

Radiation Oncology

Burmeister J, Chen Z, **Chetty IJ**, Dieterich S, **Doemer A**, Dominello MM, Howell RM, McDermott P, Nalichowski A, Prisciandaro J, Ritter T, **Smith C**, Schreiber E, Shafman T, **Sutlief S**, and Xiao Y. The american society for radiation oncology's 2015 core physics curriculum for radiation oncology residents *Int J Radiat Oncol Biol Phys* 2016; 95(4):1298-1303. PMID: 27354135. Full Text

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PURPOSE: The American Society for Radiation Oncology (ASTRO) Physics Core Curriculum Subcommittee (PCCSC) has updated the recommended physics curriculum for radiation oncology resident education to improve consistency in teaching, intensity, and subject matter. METHODS AND MATERIALS: The ASTRO PCCSC is composed of physicists and physicians involved in radiation oncology residency education. The PCCSC updated existing sections within the curriculum, created new sections, and attempted to provide additional clinical context to the curricular material through creation of practical clinical experiences. Finally, we reviewed the American Board of Radiology (ABR) blueprint of examination topics for correlation with this curriculum. RESULTS: The new curriculum represents 56 hours of resident physics didactic education, including a 4-hour initial orientation. The committee recommends completion of this curriculum at least twice to assure both timely presentation of material and re-emphasis after clinical experience. In addition, practical clinical physics and treatment planning modules were created as a supplement to the didactic training. Major changes to the curriculum include addition of Fundamental Physics, Stereotactic Radiosurgery/Stereotactic Body Radiation Therapy, and Safety and Incidents sections, and elimination of the Radiopharmaceutical Physics and Dosimetry and Hyperthermia sections. Simulation and Treatment Verification and optional Research and Development in Radiation Oncology sections were also added. A feedback loop was established with the ABR to help assure that the physics component of the ABR radiation oncology initial certification examination remains consistent with this curriculum. CONCLUSIONS: The ASTRO physics core curriculum for radiation oncology residents has been updated in an effort to identify the most important physics topics for preparing residents for careers in radiation oncology, to reflect changes in technology and practice since the publication of previous recommended curricula, and to provide practical training modules in clinical radiation oncology physics and treatment planning. The PCCSC is committed to keeping the curriculum current and consistent with the ABR examination blueprint.

Radiation Oncology

Movsas TZ, Yechieli R, **Movsas B**, and Darwish-Yassine M. Partner's perspective on long-term sexual dysfunction after prostate cancer treatment *Am J Clin Oncol* 2016; 39(3):276-279. PMID: 24685887. Full Text

*Midland County Department of Public Health, Midland daggerHenry Ford Hospital, Detroit double daggerMichigan Public Health Institute, Okemos, MI.

OBJECTIVE: Prostate cancer is the most common type of male cancer in the United States and the negative effect of prostate cancer treatment on sexual function has been well documented. The objective of this study was to examine the long-term impact of sexual dysfunction on spouses or partners of prostate cancer survivors. METHODS: A total of 742 spouses of prostate cancer survivors was mailed surveys by the Michigan Public Health Institute, of which 379 were returned (51%). Nine surveys were excluded owing to study ineligibility. Spouses responding to the survey

completed a combination of modified items from the Sexual Adjustment Questionnaire and researcher-developed items. RESULTS: Over 75% of spouses reported a decline in sex life quality after treatment. Communication about sexual issues between survivors and their health care providers was rated as good to excellent by 54.7% of partners, whereas 35.1% reported it as fair to poor. Approximately 60% of physicians initially recommended some form of sexual treatment. However, despite the persistence of sexual dysfunction, only 7% of the prostate cancer survivors were currently receiving treatment. Only 4.1% of health care providers referred the survivor to a sex therapist. CONCLUSIONS: Physicians need to understand the importance of the open, ongoing communication with prostate cancer survivors about sexual issues because sexual dysfunction seems to continue indefinitely after completion of treatment. Research on the effectiveness of behavioral interventions in restoring sexual health is critically needed for this population, especially as first-line sexual aids and medications are often not satisfactory solutions.

Radiation Oncology

Xu H, Vile DJ, Sharma M, **Gordon JJ**, and Siebers JV. Erratum: "Coverage-based treatment planning to accommodate deformable organ variations in prostate cancer treatment" [Med. Phys. 41(10), 101705 (14pp.) (2014)] *Med Phys* 2016; 43(6):3206. PMID: 27277064. Full Text

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Radiology

Badano A, Wang J, Boynton P, Le Callet P, Cheng WC, Deroo D, **Flynn MJ**, Matsui T, Penczek J, Revie C, Samei E, Steven PM, Swiderski S, Van Hoey G, Yamaguchi M, Hasegawa M, and Nagy BV. Technical note: Gray tracking in medical color displays-a report of task group 196 *Med Phys* 2016; 43(7):4017. PMID: 27370120.
Article Request Form

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PURPOSE: The authors discuss measurement methods and instrumentation useful for the characterization of the gray tracking performance of medical color monitors for diagnostic applications. The authors define gray tracking as the variability in the chromaticity of the gray levels in a color monitor. METHODS: The authors present data regarding the capability of color measurement instruments with respect to their abilities to measure a target white point corresponding to the CIE Standard Illuminant D65 at different luminance values within the grayscale palette of a medical display. The authors then discuss evidence of significant differences in performance among color measurement instruments currently available for medical physicists to perform calibrations and image quality checks for the consistent representation of color in medical displays. In addition, the authors introduce two metrics for quantifying grayscale chromaticity consistency of gray tracking. RESULTS: The authors' findings show that there is an order of magnitude difference in the accuracy of field and reference instruments. The gray tracking metrics quantify how close the grayscale chromaticity is to the chromaticity of the full white point (equal amounts of red, green, and blue at maximum level) or to consecutive levels (equal values for red, green, and blue), with a lower value representing an improved grayscale tracking performance. An illustrative example of how to calculate and report the gray tracking performance according to the Task Group definitions is provided. CONCLUSIONS: The authors' proposed methodology for characterizing the grayscale degradation in chromaticity for color monitors that can be

used to establish standards and procedures aiding in the quality control testing of color displays and color measurement instrumentation.

Radiology

Nazem-Zadeh MR, Elisevich K, **Air EL**, **Schwalb JM**, **Divine G**, **Kaur M**, **Wasade VS**, **Mahmoudi F**, **Shokri S**, **Bagher-Ebadian H**, and **Soltanian-Zadeh H**. DTI-based response-driven modeling of mTLE laterality *Neuroimage Clin* 2016; 11:694-706. PMID: 27330966. Full Text

Radiology and Research Administration Department, Henry Ford Health System, Detroit, MI 48202, USA.
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PURPOSE: To develop lateralization models for distinguishing between unilateral and bilateral mesial temporal lobe epilepsy (mTLE) and determining laterality in cases of unilateral mTLE. BACKGROUND: mTLE is the most common form of medically refractory focal epilepsy. Many mTLE patients fail to demonstrate an unambiguous unilateral ictal onset. Intracranial EEG (icEEG) monitoring can be performed to establish whether the ictal origin is unilateral or truly bilateral with independent bitemporal ictal origin. However, because of the expense and risk of intracranial electrode placement, much research has been done to determine if the need for icEEG can be obviated with noninvasive neuroimaging methods, such as diffusion tensor imaging (DTI). METHODS: Fractional anisotropy (FA) was used to quantify microstructural changes reflected in the diffusivity properties of the corpus callosum, cingulum, and fornix, in a retrospective cohort of 31 patients confirmed to have unilateral (n = 24) or bilateral (n = 7) mTLE. All unilateral mTLE patients underwent resection with an Engel class I outcome. Eleven were reported to have hippocampal sclerosis on pathological analysis; nine had undergone prior icEEG. The bilateral mTLE patients had undergone icEEG demonstrating independent epileptiform activity in both right and left hemispheres. Twenty-three nonepileptic subjects were included as controls. RESULTS: In cases of right mTLE, FA showed significant differences from control in all callosal subregions, in both left and right superior cingulate subregions, and in forniceal crura. Comparison of right and left mTLE cases showed significant differences in FA of callosal genu, rostral body, and splenium and the right posteroinferior and superior cingulate subregions. In cases of left mTLE, FA showed significant differences from control only in the callosal isthmus. Significant differences in FA were identified when cases of right mTLE were compared with bilateral mTLE cases in the rostral and midbody callosal subregions and isthmus. Based on 11 FA measurements in the cingulate, callosal and forniceal subregions, a response-driven lateralization model successfully differentiated all cases (n = 54) into groups of unilateral right (n = 12), unilateral left (n = 12), and bilateral mTLE (n = 7), and nonepileptic control (23). CONCLUSION: The proposed response-driven DTI biomarker is intended to lessen diagnostic ambiguity of laterality in cases of mTLE and help optimize selection of surgical candidates. Application of this model shows promise in reducing the need for invasive icEEG in prospective cases.

Radiology

Shaaban S, Alsulami M, Arbab SA, Ara R, Shankar A, Iskander A, Angara K, Jain M, **Bagher-Ebadian H**, Achyut BR, and Arbab AS. Targeting bone marrow to potentiate the anti-tumor effect of tyrosine kinase inhibitor in preclinical rat model of human glioblastoma *Int J Cancer Res* 2016; 12(2):69-81. PMID: Not assigned. Article Request Form

A.S. Arbab, Laboratory of Tumor Angiogenesis, Cancer Center, Georgia Regents University, Augusta, United States

Background and Objective: Antiangiogenic agents caused paradoxical increase in pro-growth and pro-angiogenic factors and caused tumor growth in glioblastoma (GBM). It is hypothesized that paradoxical increase in pro-angiogenic factors would mobilize Bone Marrow Derived Cells (BMDCs) to the treated tumor and cause refractory tumor growth. The purposes of the studies were to determine whether whole body irradiation (WBIR) or a CXCR4 antagonist (AMD3100) will potentiate the effect of vatalanib (a VEGFR2 tyrosine kinase inhibitor) and prevent the

refractory growth of GBM. Methodology: Human GBM were grown orthotopically in three groups of rats (control, pretreated with WBIR and AMD3100) and randomly selected for vehicle or vatalanib treatments for 2 weeks. Then all animals underwent Magnetic Resonance Imaging (MRI) followed by euthanasia and histochemical analysis. Results: Tumor volume and different vascular parameters (plasma volume (vp), forward transfer constant (Ktrans), back flow constant (kep), extravascular extracellular space volume (ve) were determined from MRI. In control group, vatalanib treatment increased the tumor growth significantly compared to that of vehicle treatment but by preventing the mobilization of BMDCs and interaction of CXCR4-SDF-1 using WBIR and ADM3100, respectively, paradoxical growth of tumor was controlled. Pretreatment with WBIR or AMD3100 also decreased tumor cell migration, despite the fact that ADM3100 increased the accumulation of M1 and M2 macrophages in the tumors. Vatalanib also increased Ktans and ve in control animals but both of the vascular parameters were decreased when the animals were pretreated with WBIR and AMD3100. Conclusion: In conclusion, depleting bone marrow cells or CXCR4 interaction can potentiate the effect of vatalanib.

Research Administration

Nazem-Zadeh MR, Elisevich K, **Air EL**, **Schwalb JM**, **Divine G**, **Kaur M**, **Wasade VS**, **Mahmoudi F**, **Shokri S**, **Bagher-Ebadian H**, and **Soltanian-Zadeh H**. DTI-based response-driven modeling of mTLE laterality *Neuroimage Clin* 2016; 11:694-706. PMID: 27330966. Full Text

Radiology and Research Administration Department, Henry Ford Health System, Detroit, MI 48202, USA.
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PURPOSE: To develop lateralization models for distinguishing between unilateral and bilateral mesial temporal lobe epilepsy (mTLE) and determining laterality in cases of unilateral mTLE. BACKGROUND: mTLE is the most common form of medically refractory focal epilepsy. Many mTLE patients fail to demonstrate an unambiguous unilateral ictal onset. Intracranial EEG (icEEG) monitoring can be performed to establish whether the ictal origin is unilateral or truly bilateral with independent bitemporal ictal origin. However, because of the expense and risk of intracranial electrode placement, much research has been done to determine if the need for icEEG can be obviated with noninvasive neuroimaging methods, such as diffusion tensor imaging (DTI). METHODS: Fractional anisotropy (FA) was used to quantify microstructural changes reflected in the diffusivity properties of the corpus callosum, cingulum, and fornix, in a retrospective cohort of 31 patients confirmed to have unilateral (n = 24) or bilateral (n = 7) mTLE. All unilateral mTLE patients underwent resection with an Engel class I outcome. Eleven were reported to have hippocampal sclerosis on pathological analysis; nine had undergone prior icEEG. The bilateral mTLE patients had undergone icEEG demonstrating independent epileptiform activity in both right and left hemispheres. Twenty-three nonepileptic subjects were included as controls. RESULTS: In cases of right mTLE, FA showed significant differences from control in all callosal subregions, in both left and right superior cingulate subregions, and in forniceal crura. Comparison of right and left mTLE cases showed significant differences in FA of callosal genu, rostral body, and splenium and the right posteroinferior and superior cingulate subregions. In cases of left mTLE, FA showed significant differences from control only in the callosal isthmus. Significant differences in FA were identified when cases of right mTLE were compared with bilateral mTLE cases in the rostral and midbody callosal subregions and isthmus. Based on 11 FA measurements in the cingulate, callosal and forniceal subregions, a response-driven lateralization model successfully differentiated all cases (n = 54) into groups of unilateral right (n = 12), unilateral left (n = 12), and bilateral mTLE (n = 7), and nonepileptic control (23). CONCLUSION: The proposed response-driven DTI biomarker is intended to lessen diagnostic ambiguity of laterality in cases of mTLE and help optimize selection of surgical candidates. Application of this model shows promise in reducing the need for invasive icEEG in prospective cases.

Sleep Medicine

Carr AN, Ramsey DL, Brum JM, Thomas P, Kappler G, Chan K, **Koshorek G**, and **Roth T**. Diphenhydramine HCL improves both objective and subjective sleep parameters in an occasional sleeplessness population *Sleep* 2016; 39:A212. PMID: Not assigned. Abstract

A.N. Carr, Procter and Gamble, Cincinnati, United States

Introduction: Diphenhydramine HCl (DPH) is an antihistamine of the ethanolamine class with well documented sedating properties. Little is known about its sleep inducing properties in otherwise healthy populations experiencing episodes of “sleeplessness”. Methods: This was a 4-week, randomized, crossover, double-blind, placebo-controlled, 9-day treatment period, in-home study to assess the efficacy of diphenhydramine hydrochloride (30 mL, ZzzQuil, 50 mg) in 33 subjects with occasional sleeplessness. Sleep parameters were assessed using the ZEO Sleep Manager (ZSM), Actiwatch 2, and subjects sleep questionnaires. Occasional sleeplessness was verified with a 7 day baseline period sleep diary. Subjects self-administered medication, as needed, for the first 7 nights of treatment followed by 2 mandatory nights. A washout period (no treatment) of at least 5 days occurred between treatments. Results: Twenty-two subjects completed the study and were evaluable. DPH improved several sleep parameters assessed by the ZSM device relative to placebo (change from baseline) including latency to persistent sleep ($p = 0.0312$; primary efficacy variable), sleep efficiency ($p = 0.0488$) and minutes in “light sleep” ($p = 0.0219$). Importantly, DPH also positively impacted subject assessments of sleep including total sleep time ($p = 0.0023$), sleep onset latency ($p = 0.0209$), sleep efficiency ($p = 0.0037$), sleep quality ($p = 0.0017$), time awake after sleep onset ($p = 0.0148$), ease of falling asleep ($p = 0.0162$) and depth of sleep ($p = 0.0014$). Adverse events (AEs) were similar between treatments. Conclusion: Diphenhydramine (50 mg) administered in an in-home setting provides rapid onset of sleep and improves several sleep parameters in subjects experiencing occasional sleeplessness on both objective and subjective measurements.

Sleep Medicine

Cheng P, **Tran M**, Tallent G, **Pillai V**, **Cuamatzi A**, **Bazan L**, **Moss K**, and **Drake CL**. Circadian misalignment and cognitive flexibility in night shift workers *Sleep* 2016; 39:A173. PMID: Not assigned. Abstract

P. Cheng, Henry Ford Health System, Detroit, United States

Introduction: Circadian misalignment can impact health and performance, and is of particular concern for shift workers, whose work schedules may be at odds with their endogenous sleep-wake rhythms. Impairments in cognitive performance have been observed as a result of circadian misalignment; however, these observations have been limited generally to vigilance and reaction time. Less is known regarding on-task cognitive performance. The task-switching paradigm is often used to measure executive control of cognition, particularly in attentional flexibility. In this paradigm, trials involving varying task-rules are completed in quick succession. Some trials employ the same taskrule as the previous trials (“repeat” trials), whereas others employ a different task-rule (“switch” trials). Switch trials require the individual to cognitively switch task-rules, and therefore should result in longer reaction times compared to repeat trials (i.e., “switch cost”). Larger switch costs are indicative of increased effort in set switching, and therefore reduced cognitive flexibility. Successful task-switching performance also requires adequate inhibition of prior task rules, which can be measured by reaction time on trials returning to the same taskrule after a switch trial, compared to performance following successive switch trials (i.e., “set inhibition”). Methods: Twenty-one permanent night shift workers (13 female) participated in a larger study examining the consequences of circadian misalignment on health. Circadian phase was evaluated using dimlight salivary melatonin onset (DLMO). DLMO at or after 6am was considered full circadian alignment. Cognitive flexibility was evaluated using a computerized task-switching paradigm. Results: A multiple linear regression indicated that switch-costs increased linearly with increasing circadian misalignment due to earlier DLMOs ($\beta = .54$, $p < .01$), controlling for sex and age as covariates. No significant effect was detected with set-inhibition. Conclusion: Results indicate that cognitive flexibility is related to circadian alignment, with better alignment associated with increased flexibility. This offers further insight into the cognitive vulnerabilities related to circadian misalignment that may impact risk for errors, accidents, and injuries, particularly for shift workers.

Sleep Medicine

Durrence H, **Drake CL**, **Tran KM**, **Bazan L**, **Cheng P**, **Pillai V**, and **Roth T**. Double-blind, placebo-controlled, 4-way crossover study comparing the effects of doxepin 6 MG and zolpidem 10 MG on gait, balance, and cognitive performance in healthy volunteers *Sleep* 2016; 39:A206. PMID: Not assigned. Abstract

H. Durrence, Pernix Therapeutics, Del Mar, United States

Introduction: Falls are the leading cause of injury in older adults, accounting for millions of injuries. Frequency of nocturnal awakenings, sleep medication use, insomnia, and nocturia are independent risk factors for falls and hip fractures. To examine the effect of sleep medicine on gait and balance, we evaluated doxepin (DXP; Silenor®) 6mg (DXP6) and zolpidem 10mg (Z10), the highest doses indicated for insomnia. Additionally, the effects on memory were examined. Methods: This 4-way crossover study assessed the effects of a single dose of DXP6 compared with matching placebo and a single dose of Z10 compared with matching placebo at the respective Tmax in adult male volunteers (n = 39). Gait, balance, and memory were assessed 4 hou rs postdose for DX P6 and placebo and at 1.5 hours postdose for Z10 and placebo. After awakening, subjects performed the Tandem Walk (TW), the Berg Balance Scale (BBS) followed by immediate free recall while delayed recall was a ssessed 15 minutes after morning awakening. Results: Z10, but not DXP6, showed significantly poorer performance relative to placebo on all outcome measures. Also, in a direct comparison, performance on Z10 was impaired relative to DX P6. Measures that were significantly impaired (all p-values < 0.0001) for Z10 included TW #step-offs (500% more than DXP6), TW time to complete, BBS score, words recalled immediately and delayed (340% fewer words than DXP6). Conclusion: These data indicate that doxepin at the highest hypnotic dose (DXP6) did not cause impairment in gait, balance, or memory. In contrast, zolpidem at the highest hypnotic dose had broad CNS depressant effects. Functions as diverse as memory and balance were negatively impacted by Z10 directly or indirectly through its sedative activity. Further research is needed to determine if impairment is generalizable to other medications binding at the benzodiazepine receptor but not to drugs working on transmitters mediating wakefulness such histamine.

Sleep Medicine

Durrence H, **Roth T**, **Tran KM**, **Singh M**, **Cheng P**, **Pillai V**, and **Drake C**. Arousability of insomnia patients and healthy volunteers is not impacted by the sleep-specific doses of doxepin (3 MG and 6 MG), but is impacted in healthy volunteers using zolpidem 10 MG *Sleep* 2016; 39:A201. PMID: Not assigned. Abstract

H. Durrence, Pernix Therapeutics, Del Mar, United States

Introduction: Ability to awaken to external or internal stimuli (arousability) is important. However, arousability is rarely assessed in evaluating hypnotics. An indirect approach to assessing arousability is examining sleep maintenance (SM) and relating wake-after-sleeponset (WASO) to number-of-awakenings (NAW). Decreased NAW reflects a drug's potential for blunting arousal response. Decreased WASO coupled with no decrease in NAW reflects ability to hasten return to sleep. To explore arousability, we evaluated the effects of doxepin (DXP; Silenor®) 3mg and 6mg (i.e. indicated for insomnia). Further, we directly evaluated Auditory Awakening Threshold (AAT) with DXP and zolpidem. Methods: Two placebo-controlled efficacy trials and an AAT trial are reported. Study A was a 12-week trial in elderly insomniacs (DXP 3mg); Study B was a 5-week trial in adult insomniacs (DXP 3mg and 6mg). Study C was a 4-way crossover trial assessing a single dose of DXP 6mg (DXP6), zolpidem 10mg (Z10) and placebo (2 placebo conditions). AAT was evaluated at the Tmax of each active medication and its corresponding placebo. Results: DXP 3mg (Study A and B; p < 0.0001) and 6 mg (Study B; p < 0.0001) significantly decreased WASO across the trials. Importantly, NAW were not decreased at any dose or time point in either study. In Study C, the AAT (expressed as dB) for Z10, was significantly higher (p < 0.0001) than both PBO groups and DXP6, with a mean dB level of 102 (DXP6 83dB, average placebo 81dB). Further, 24 Z10 subjects did not awaken at max AAT (110dB; 4 subjects in all 3 other groups). Conclusion: DXP (3mg, 6mg) improved WASO without altering NAW. Further, DXP6 did not impact AAT; in contrast Z10 increased arousal threshold. These data demonstrate that DXP improved SM without impacting arousability. Further research to determine if this more broadly reflects differences between drugs that work via the sleep (agonist) versus wake (antagonist) system.

Sleep Medicine

Fellman-Couture C, **Pillai V**, Arnedt J, Anderson J, **Moss K**, **Roth T**, and **Drake C**. Long-term efficacy of cognitive behavior therapy for menopausal insomnia *Sleep* 2016; 39:A198-A199. PMID: Not assigned. Abstract

C. Fellman-Couture, Henry Ford Health System, Detroit, United States

Introduction: Insomnia is highly prevalent among post-menopausal women. We examined the efficacy of nurse-administered Cognitive Behavioral Therapy for Insomnia (CBT-I) in comparison to Sleep Restriction Therapy (SRT) and an Information-only control (IC) condition. Methods: Post-menopausal females (n = 88) suffering from insomnia concurrent with menopause were recruited. Participants were screened for contraindicative psychopathology and sleep disorders via Structured Clinical Interview for DSM-IV Disorders and polysomnography (PSG). All participants showed an average wake after sleep onset > 45 minutes as evidenced by two nights of PSG. They were then randomized to a 6-week CBT-I (n = 35), 2-week SRT (n = 28), or a 6-week IC condition (n = 25). Participants completed the Insom nia Severity Index (ISI) and the Fatigue Severity Scale (FSS) scales at baseline (Time-1), 1 week post-treatment (Time-2), and at a 6-month follow-up (Time-3). Results: There were no significant between-

group differences in Time1 ISI (CBTI: 14.54 ± 3.84; SRT: 14.75 ± 3.52; IC: 15.8 ± 4.59) or FSS scores (CBTI: 32.46 ± 10.28; SRT: 33.11 ± 9.81; IC: 31.56 ± 10.40). At Time-2, the CBTI (-8.33 ± 0.96) and SRT groups (-6.54 ± 0.71) showed a significantly greater reduction in ISI scores ($F = 15.93$; $p < .01$) than did the IC group (-1.80 ± 0.64). These reductions were maintained in the CBTI group at Time-3 (-8.13 ± 1.16), and were significantly larger than corresponding changes in the IC group ($F = 5.90$; $p < .05$). With respect to FSS scores, both the CBTI (-5.39 ± 1.46) and SRT groups (-4.57 ± 1.48) showed a significantly greater reduction ($F = 4.34$; $p < .05$) at Time-2 than did the IC group (0.37 ± 1.29). There were no between-group differences in FSS change scores at Time-3. Conclusion: These results suggest that CBT-I and SRT are both associated with a post-treatment reduction in insomnia symptoms and fatigue in women with menopausal-insomnia. However, unlike SRT, CBTI-related improvements in insomnia symptoms are robust even at 6-months post-treatment.

Sleep Medicine
Gelaye B, Zhong QY, Barrios YV, Redline S, **Drake CL**, and Williams MA. Psychometric evaluation of the ford insomnia response to stress test (FIRST) in early pregnancy *J Clin Sleep Med* 2016; 12(4):579-587. PMID: 26857055. Full Text

Department of Epidemiology, Harvard School of Public Health, Boston, MA.
Department of Medicine, Brigham and Women's Hospital, Boston, MA.
Harvard Medical School, Boston, MA.
Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI.

STUDY OBJECTIVES: To evaluate the construct validity and factor structure of the Spanish-language version of the Ford Insomnia Response to Stress Test questionnaire (FIRST-S) when used in early pregnancy. METHODS: A cohort of 647 women were interviewed at </= 16 weeks of gestation to collect information regarding lifestyle, demographic, and sleep characteristics. The factorial structure of the FIRST-S was tested through exploratory and confirmatory factor analyses (EFA and CFA). Internal consistency and construct validity were also assessed by evaluating the association between the FIRST-S with symptoms of depression, anxiety, and sleep quality. Item response theory (IRT) analyses were conducted to complement classical test theory (CTT) analytic approaches. RESULTS: The mean score of the FIRST-S was 13.8 (range: 9-33). The results of the EFA showed that the FIRST-S contained a one-factor solution that accounted for 69.8% of the variance. The FIRST-S items showed good internal consistency (Cronbach alpha = 0.81). CFA results corroborated the one-factor structure finding from the EFA; and yielded measures indicating goodness of fit (comparative fit index of 0.902) and accuracy (root mean square error of approximation of 0.057). The FIRST-S had good construct validity as demonstrated by statistically significant associations of FIRST-S scores with sleep quality, antepartum depression and anxiety symptoms. Finally, results from IRT analyses suggested excellent item infit and outfit measures. CONCLUSIONS: The FIRST-S was found to have good construct validity and internal consistency for assessing vulnerability to insomnia during early pregnancy.

Sleep Medicine
Goldschmied JR, **Cheng P**, Armitage R, and Deldin P. Accumulation and dissipation of slow-wave activity and the effect on mood disturbance *Sleep* 2016; 39:A304. PMID: Not assigned. Abstract

J.R. Goldschmied, University of Michigan, Ann Arbor, United States

Introduction: Very recent research has demonstrated that manipulations to slow-wave activity in those with Major Depressive Disorder (MDD) can predict changes in mood. Previous work has also shown that slow-wave activity can be increased with a mild homeostatic challenge, a three-hour sleep delay. The aim of the current study was to determine if a sleep delay challenge (SDC) would likewise predict mood disturbance in a sample of depressed and healthy adults (HC). Methods: Participants spent three consecutive nights in the sleep laboratory. On night three, participants bedtimes were delayed by three hours. The Profile of Mood States (POMS) questionnaire was administered to assess mood disturbance. In order to explore if the SDC had a significant effect on the amount of slow-wave activity (SWA), SWA across the night and during each NREM period were examined at baseline and following SDC. Subsequently, regression analyses were conducted with SWA at each of the four NREM periods, individually, as the predictor variable, and the POMS measure of total mood disturbance at post as the outcome variable. Amount of Stage 1 sleep, Stage 2 Sleep, REM, and Awake & Movement were entered as covariates to control for the non-slow wave components of sleep. Results: As expected, the HC group exhibited significantly more SWA across the night following the sleep delay, and during the first and fourth NREM periods, specifically. In contrast, the SDC did not result in increased SWA across the night in the MDD group. Results from multiple regression revealed that following a 3-hour sleep delay, increased SWA, specifically in the 2nd NREM period, was predictive of increased mood disturbance in those with MDD. Healthy control participants did not show this relationship. Conclusion: The present study demonstrated that an increase in the amount of SWA from the 2nd

NREM period following a sleep delay paradigm predicted an increase in total mood disturbance in individuals with MDD. Following homeostatic sleep challenges, studies have shown that SWA increases during the first NREM period as an indicator of the increased homeostatic drive for sleep followed by a prompt decrease, indicative of the healthy dissipation and regulation of SWA. The results found presently may suggest that prompt accumulation and dissipation of SWA following a mild homeostatic sleep challenge may be essential for healthy emotional functioning.

Sleep Medicine

Gordon VH, Dhand R, Dudney T, Shamiyeh J, Heidel R, and **Roehrs T**. Total sleep time strongly correlates with self-reported hospital admissions; an inpatient COPD cohort survey *Sleep* 2016; 39:A269. PMID: Not assigned. Abstract

V.H. Gordon, University of Tennessee, Knoxville, United States

Introduction: 36% of American adults suffer from sleep loss. An estimated 15 million Americans have been told they have COPD by a medical professional. Di rect costs of COPD care a re an estimated $29.5 billion annually. Sleeping less than 7 hours per night on a regular basis is associated with adverse health outcomes. Therefore, we conducted a self-report survey, on an inpatient cohort, to evaluate total sleep time (TST) and Pittsburgh Sleep Quality Index (PSQI) scores in patients with COPD exacerbation. Methods: Using a real time, inpatient, screening process, we identified COPD patients in the hospital setting and surveyed 55 patients from July 2015 to December 2015 at a University Hospital. Inclusion criteria were ≥ 18 years old, screened for COPD as cause for hospitalization, and could comprehend English. Patients were only excluded if they could not comprehend English, or if they refused for any reason. 5 patients declined to take the survey. A seven question survey was developed after focus group sessions, with physicians in the fields of pulmonary, critical care, and sleep medicine contributing. Permission was obtained, and a Pittsburgh Sleep Quality Index (PSQI) form was also attached. No identifying patient information was collected and therefore an implied consent waiver was added to the survey form. A total of 50 surveys were collected for a pilot study. Not all surveys were filled out as instructed, however this data was still included. Skewness and kurtosis statistics yielded normal distribution. Pearson r correlations were run between responses to survery items to test for potential associations. In order to adjust for testing multiple hypotheses concurrently, a Bonferroni correction was employed for alpha value (.05/3 tests = Bonferroni corrected alpha value of 0.17) Results: A significant negative correlation between Average Hours of Sleep reported and Total Hospital Admissions reported was found ($r = -0.34$, $p = .01$). A probable Type II error was found between Average Hours of Sleep reported and Last 12 months Hospital Admissions ($r = -0.3$, $p = .04$). PSQI did not correlate significantly with hospitalizations. Conclusion: Total sleep time correlated significantly with reported hospitalizations. Patients with COPD that get < 6 hours of sleep on average, reported more hospitalizations.

Sleep Medicine

Jarrin DC, Chen IY, Ivers H, Lamy M, **Drake CL**, and Morin CM. Temporal stability of the ford insomnia response to stress test (FIRST) *Sleep* 2016; 39:A195. PMID: Not assigned. Abstract

D.C. Jarrin, Université Laval, Québec City, Canada

Introduction: The Ford Insomnia Response to Stress Test (FIRST) is a self-report tool that measures and identifies individuals with sleep reactivity (i.e., one's vulnerability to experience situational insomnia under stressful conditions). While the use of the FIRST has grown in the field, evidence of its long-term stability is lacking. The present psychometric study investigated the temporal stability of the FIRST in a population-based sample of adults with and without insomnia. Methods: Pa r ticipa nt s included 1,122 adult s (M = 49.9 years, SD = 14.8; 38.8% male) presenting an insomnia syndrome (n = 159), insomnia symptoms (n = 152), or good sleep (n = 811). Participants completed the FIRST on three different occasions: baseline and at follow-up 6and 12-months later. Intraclass correlation coefficients (ICC) using the FIRST total score were computed for baseline to 6-month and for baseline to 12-month intervals. Results: Among those with an insomnia syndrome, the FIRST yielded high temporal stability for baseline to 6-month (ICC = .80) and baseline to 12-month intervals (ICC = .77). Among those with insomnia symptoms, the FIRST also yielded high and equivalent stability for both intervals (ICC = .78). Among good sleepers, stability estimates were high for baseline to 6-month (ICC = .81) and for baseline to 12-month intervals (ICC = .82). Conclusion: Overall, sleep reactivity, as measured by the FIRST, demonstrates moderate to high temporal stability over time. These findings support the use of the FIRST as a relatively stable marker of sleep reactivity.

Sleep Medicine
Muzet A, Werner S, Fuchs G, **Roth T**, Saoud JB, Viola AU, Schaffhauser JY, and Luthringer R. Assessing sleep architecture and continuity measures through the analysis of heart rate and wrist movement recordings in healthy subjects: Comparison with results based on polysomnography *Sleep Medicine* 2016; 21:47-56. PMID: Not assigned. Full Text

S. Werner, PPRS, Paris, France

Objective: The objective of the study was to evaluate the reliability of a new methodology for assessing sleep architecture descriptors based on heart rate and body movement recordings. Methods: Twelve healthy male and female subjects between 18 and 40 years of age, without sleep disorders and not taking any drug or medication that could affect sleep, were recorded continuously during five consecutive nights. Together with the standard polysomnography, heart rate was recorded with a Holter and wrist movements by actimetry.Of the 60 recorded nights, 48 artifact-free nights were analyzed by two independent and well-trained visual scorers according to the rules of the American Academy of Sleep Medicine. Sleep stages were assigned to every 30-s epoch. In parallel, the same nights were analyzed by the new methodology using only heart rate and actimetry data, allowing a 1-s epoch sleep stage classification. Sleep architecture was measured for 48 nights, independently for the two manual scorings and the automatic analysis. Results: Over 42 nights, the intra-class correlation coefficient, used to assess the consistency or reproducibility of quantitative measurements made by different observers, was classified as excellent when all 12 descriptors were combined. Analyses of the individual descriptors showed excellent interclass correlation for eight and good for four of the 12. Conclusion: The automatic analysis of heart rate and body movement during sleep allows for the evaluation of sleep architecture and continuity that is equivalent to those obtained by manual scoring of polysomnography. The technique used here is simple and robust to allow for home sleep monitoring.

Sleep Medicine
Palagini L, Mazzei I, Cipollone G, Mauri M, and **Drake CL**. The role of attachment style in stress perception and reactivity in Insomnia Disorder *Sleep* 2016; 39:A186. PMID: Not assigned. Abstract

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

Introduction: According to cognitive theories, unhelpful cognitions may contribute to the development and maintenance of insomnia. Interpersonal theories in insomnia have been studied less. Attachment theory is one of the integrative theories that can be used as a cognitiveinterpersonal framework for understanding the development and maintenance of insomnia. Attachment insecurity (vs. security) is associated with a vulnerability in response to stress. Because stress perception and reactivity are crucial for insomnia, according to the stres sdiathesis model, the aim was to study their possible association with attachment style. Methods: The study consisted of 45 subjects who met the diagnostic criteria for Insomnia Disorder (ID) (DSM-5) and 35 healthy controls (H). Insomnia Severity Index (ISI), Attachment Style Questionnaire (ASQ), Perceived Stress Scale (PSS), Ford Insomnia Response to Stress Test (FIRST) were administered while controlling for psychiatric symptoms. Differences in means between ID and H groups were assessed using t-test or Mann-Whitney U/Wilcoxon test. Univariate and multivariate regression analyses were then performed. Results: Subjects with ID (F 23, mean age 45+1.3) presented higher ISI, PPS, and FIRST scores than H subjects (F 20, mean age 46+1.2) (respectively ISI:16.4+5 vs 4.2+1.7 $p < .01$, PPS: 17.1+8.7 vs 10.1+2.3 $p < .05$, FIRST: 23.6+6.9 vs 15.2+2.3). They also showed higher scores in ASQ fearful (27.5+1.5 vs 16.5+0.6, $p < .05$) and preoccupied styles (26.5+0.6 vs 13.5+0.7, $p < .05$). Considering all the variables, PPS was best determined by ASQ preoccupied (coeff. = .39, $p = .003$), and FIRST by ASQ fearful (coeff. = .61, $p = .004$). Conclusion: Attachment dynamics are theorized to shape the schemas and expectations an individual has of others. Subjects with insomnia show insecure attachment style, they seem uncomfortable with relationships or they depend on them. Insecure attachment in insomnia seems to negatively influence stress perception and reactivity and may contribute to the development and maintenance of insomnia. An interpersonal approach should be considered as part of the psychological treatment for insomnia.

Sleep Medicine
Pillai V, Kalmbach D, Arnedt J, and **Drake CL**. Sleep system sensitization: Evidence for changing roles of etiological factors in insomnia *Sleep* 2016; 39:A186. PMID: Not assigned. Abstract

V. Pillai, Henry Ford Health System, Detroit, United States

Introduction: Prior literature on insomnia risk factors has largely focused on premorbid vulnerabilities, with less attention given to the evolution of such vulnerabilities in response to insomnia onset. This study evaluated whether the sleep system becomes sensitized as a consequence of insomnia development. Further, we also tested the impact

of sleep system sensitization on depression and anxiety. Methods: The study involved three annual waves of data collection from a large cohort. Participants were adults with no lifetime history of insomnia or depression at baseline, who developed insomnia at the 1-year follow-up (N = 262). Sleep reactivity was measured using the the Ford Insomnia Response to Stress Test (FIRST), whereas as depression and anxiety were assessed using the QIDS and BAI respectively. The sample was split into two groups based on baseline FIRST scores using a ≥ 16 cut-point representing low and high sleep reactivity. Results: Insomniacs with low premorbid sleep reactivity reported large increases in sleep reactivity from baseline to 1-y follow-up (t = 7.26, p < .001, Cohen's d = 1.25). Overall, 68.3% of insomniacs with low pre-morbid sleep reactivity were re-classified as having high sleep reactivity at the time of insomnia onset. Notably, results showed that sleep reactivity at 2-y follow-up was significantly higher than baseline, even after insomnia remission (t = 3.10, p < .01, Cohen's d = .70). Finally, analyses revealed that increases in FIRST scores predicted greater depression (partial r = .24, p < .001) and anxiety (par tial r = .26, p < .001) at insomnia onset. Notably, the impact of sleep system sensitization on depression was stable at 2-y follow-up (par tial r = .19, p = .01). Conclusion: Data suppor ted sleep system sensitization as a consequence of insomnia development in individuals with low premorbid sleep reactivity. Harmful effects of sleep system sensitization may extend beyond risk for future insomnia, and may result in increased vulnerability to depression and anxiety.

Sleep Medicine
Pillai V, **Roth T**, and **Drake CL**. Towards quantitative cutoffs for insomnia: how current diagnostic criteria mischaracterize remission *Sleep Med* 2016;PMID: 27288048. Full Text

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OBJECTIVE: Although sleep symptoms of insomnia can be quantified, none of the current diagnostic systems stipulate quantitative cutoffs for sleep-onset latency (SOL) or wake time after sleep onset (WASO). Diagnoses are based instead on idiographic patient reports of "difficulty" falling/staying asleep. Therefore, we examined whether remission of insomnia as per the diagnostic criteria results from a normalization of quantitative sleep disturbance, or if it is simply reflective of tolerance to sleep symptoms. METHODS: This study involved a yearlong prospective investigation of 649 adults (48.1 +/- 11.6 years; 69.3% female) with DSM-5-based insomnia. Participants completed measures of sleep disturbance, perceived sleep-related distress, daytime sleepiness, functional impairment, and workplace productivity at baseline and follow-up one year later. RESULTS: A total of 271 participants no longer met the DSM-5-based insomnia criteria at follow-up. However, 66% of these remitters reported >/=31 min of SOL and/or WASO. Daytime impairment in this subgroup of remitters was no different from that among individuals who met the diagnostic criteria at both baseline and follow-up (ie, chronic insomniacs). By contrast, follow-up impairment was significantly lower (F = 12.3; P < 0.01) among remitters whose sleep disturbance returned below empirically derived quantitative cutoffs (both SOL and WASO <31 min) than in chronic insomniacs. CONCLUSION: This is the first study on the long-term course of insomnia based on the newly established DSM-5 criteria. A troubling implication of findings is that a majority of insomniacs stop meeting the diagnostic criteria despite continued sleep disturbance and impairment. "Remission" in these cases is attributable instead to tolerance of sleep symptoms. Incorporating quantitative criteria into current diagnoses may offer a more sensitive assay of treatment needs.

Sleep Medicine
Pillai V, **Tran KM**, **Roth T**, and **Drake CL**. Limitations of current diagnostic criteria for insomnia: A case for quantitative cut-offs *Sleep* 2016; 39:A198. PMID: Not assigned. Abstract

V. Pillai, Henry Ford Health System, Detroit, United States

Introduction: Though the nocturnal symptoms of insomnia can be quantified, current diagnostic systems do not stipulate quantitative cut-offs for sleep-onset-latency (SOL) or wake-time-after-sleep-onset (WASO). Diagnoses are based instead on idiographic patient reports of 'difficulty' falling/staying asleep. Therefore, we examined whether remission of insomnia per diagnostic criteria results from a normalization of quantitative sleep disturbance, or if it is simply reflective of tolerance to sleep symptoms. Methods: This study involved a year-long prospective investigation of 649 adults (48.1 ± 11.6 y; 69.3% female) with DSM-5 insomnia. Participants completed measures of sleep disturbance, perceived sleep-related distress, daytime sleepiness, functional impairment, and workplace productivity at baseline and at follow-up one year later. Results: 271 participants no longer met diagnostic criteria for insomnia at follow-up. However, 67% of these 'remitters' reported averaging < 7 hours of nightly sleep time, and 66% reported ≥ 31 minutes of SOL and/or WASO. Importantly, daytime impairment in this subgroup of remitters was no different than among individuals who met diagnostic criteria at both baseline and follow-up (i.e., chronic insomniacs). By contrast, follow-up impairment was significantly lower (F = 12.3; p < .01) among remitters whose sleep disturbance returned below empirically-derived quantitative cut-offs (both SOL & WASO < 31 minutes) than in chronic insomniacs.

Conclusion: This is the first study on the long-term course of insomnia based on the newly established DSM-5 criteria. At roubling implication of findings is that a majority of insomniacs stop meeting diagnostic criteria despite continued sleep disturbance and impairment. 'Remission' in these cases is attributable instead to tolerance of sleep symptoms. Our findings are therefore largely supportive of recent efforts to derive quantitative thresholds for the severity of nocturnal sleep symptoms, and to incorporate these into future diagnostic systems.

Sleep Medicine

Roehrs T, **Koshorek G**, **Withrow D**, and **Roth T**. Cortisol and hyperarousal in insomnia *Sleep* 2016; 39:A201. PMID: Not assigned. Abstract

T. Roehrs, Henry Ford Health System, Detroit, United States

Introduction: Insomnia is a disorder of hyperarousal shown by elevated sleep latency on the Multiple Sleep Latency Test (MSLT) and other arousal measures. We have reported elevated NE in insomnia as a function of MSLT. Others have reported pre sleep cortisol elevations in insomnia vs controls. We sought to determine whether cortisol levels, both diurnal and presleep, would also vary as a function of MSLT. Methods: DSM-IVR diagnosed insomniacs (N = 110), aged 32-65 yrs, having a PSG sleep efficiency of 85% or less, no other sleep disorder, unstable medial or psychiatric diseases or drug dependency were recruited. On a screening MSLT 26 had MSLTs of 10 or less (Lo) and 44 of 15 min or more (Hi). Participants took 10mg zolpidem or placebo (30 min before bedtime), double-blind, nightly for 12 months. In months 1, 4, 8 and 12, urine was collected over 24 hrs in 8 hraliquots and assayed for cor tisol (Ward Laboratories, Ann Arbor, MI). Saliva samples were collected 35 min before bedtime and the drug administration in month 1 and 8, analyzed for cortisol levels (Salimetrics, State College, PA), and compared to a control group (N = 41). Results: Presleep salivary cortisol was higher in insomniacs than controls (2.23+/-2.12 vs 1.49+/-0.91 ug/L, $p < .01$), but did not differ as a function of MSLT. Nightly zolpidem reduced pre-sleep cortisol relative to placebo on both months (Zol - M1:1.51+/0.87; M8:1.52+/0.80 vs Pbo - M1:1.79+/1.44; M8:1.94+/1.48 ug/L, $p < .02$) with no months effects. Daytime (0700-1500 hrs) urinary cortisol was higher overall in the Hi vs Lo MSLT insomniacs (Hi: 18.6+/-10.9 vs Lo: 12.9+/-7.1 ug/L, $p < .04$), did not change across months, and was not reduced with zolpidem vs placebo. Conclusion: Hyperarousal in insomnia is associated with higher daytime urinary cortisol levels, but is not affected by zolpidem. In contrast, pre-sleep salivary cortisol does not vary as a function of MSLT, but is reduced by zolpidem. These data suggest cortisol elevations have both a state and trait etiology.

Sleep Medicine

Roehrs T, **Koshorek G**, **Withrow D**, Tancer M, and **Roth T**. How representative are insomnia clinical trials? *Sleep* 2016; 39:A198. PMID: Not assigned. Abstract

T. Roehrs, Henry Ford Health System, Detroit, United States

Introduction: Clinical trials of pharmacological treatments for insomnia have specific inclusion and exclusion criteria, including polysomnographic (PSG) criteria for sleep onset, sleep maintenance and sleep efficiency. The question arises as to how representative these subjects are of the broader insomnia population. We systematically counted reasons for exclusion during recruitment to a five-year NIH-funded zolpidem efficacy trial in chronic insomnia. Methods: Persons (N = 116), aged 32-65 yrs, meeting DSM-IVR criteria for insomnia and a PSG sleep efficiency of < 85%, no other primary sleep disorders, no psychiatric diseases or drug dependency and in good health were recruited to participate in a 12 month clinical trial of nightly use of zolpidem 10 mg or placebo. Advertisements in newspapers, hospital intranet news, and hospital clinics solicited individuals with chronic difficulty falling asleep, staying asleep, or awakening too early. Screening was conducted through an initial telephone interview followed by a clinic visit that included a brief physical, medical and drug use history, laboratory blood/urine testing, psychiatric screen (SCID), and clinical PSG. All subjects screened beyond the phone screen signed an informed consent. Results: For 116 participants 2886 telephone interviews were conducted with 25% declining after hearing study specifics. Of those with continued interest 25% reported present (within past year) mental health problems, 18% chronic unstable health problems, 14% past or present drug/alcohol abuse, and 14% did not meet DSM-IVR criteria for insomnia. Of the remaining 410, 294 (72%) were excluded. Among those excluded 30% did not report for PSG, 22% failed the PSG (i.e. AHI > 10, PLMAI > 10, or SE > 85%), 17% failed the SCID, 14% failed the health screen, and 11% a drug screen Conclusion: These data suggest persons entering an insomnia clinical trial are a highly selected sample. They show, while insomnia is comorbid with other conditions, clinical trials are carried out in primary insomnia, which is not representative of the broader insomnia population.

Sleep Medicine

Verster JC, Peters LV, Van De Loo AJ, Bouwmeester NH, Tiplady B, Alford C, and **Roth T**. Meta-analysis on the next-morning effects of hypnotic drugs on short- and long-term memory functioning in healthy adults and elderly *Sleep* 2016; 39:A210-A211. PMID: Not assigned. Abstract

J.C. Verster, Utrecht University, Utrecht, Netherlands

Introduction: Sleep medication taken at bedtime may negatively affect next-morning cognitive performance. The aim of these metaanalyses was to determine the effect of hypnotic drugs on next-day short- and long term memory functioning. Methods: A literature search (Pubmed, Embase, PsycInfo, Scopus, Web of Science, and Cochrane) yielded N = 33.969 potentially relevant articles. Studies were included if they assessed next-morning shortor long-term memory after bedtime administration of recommended dosages of hypnotic drugs, were double-blind, placebo-controlled, conducted in healthy volunteers, and sufficient data was reported, they were included in the meta-analyses. Separate analyses were performed for adults (18-65 years old) and elderly healthy volunteers (≥ 65 years old). Results: In adults, eight studies assessing next-morning short-term memory (after bedtime administration of nitrazepam, triazolam, temazepam, flurazepam, melatonin, zaleplon, lormetazepam, zolpidem), and five studies assessing long-term memory (after bedtime administration of triazolam, nitrazepam, zopiclone, flurazepam, zolpidem) were included in the meta-analyses. The analyses revealed that both next-morning short-term memory (ES = 0.427, p = 0.0001; 95%CI: 0.212 to 0.641) and long-term memory (ES = 0.536, p = 0.0001; 95%CI: 0.247 to 0.824) were significantly impaired. In elderly, three studies assessing next-morning short-term memory (after bedtime administration of flurazepam, zolpidem, temazepam), and three studies assessing long-term memory (after bedtime administration of flurazepam, zolpidem, temazepam) were included in the meta-analyses. The analyses revealed that in elderly next-morning short-term memory (ES = 0.412, p = 0.019; 95%CI: 0.068 to 0.757) was significantly impaired. No significant impairment was found for long-term memory (ES = -0.038, p = 0.825; 95%CI: -0.380 to 0.303). Conclusion: The meta-analysis results suggest that sleep medication, when administered in recommended dosages at bedtime, significantly impair next-morning short- and long term memory.

Stroke Program – Neuroscience

Holm AL, **Rowe Gorosh M**, **Brady M**, and **White-Perkins D**. Recognizing privilege and bias: An interactive exercise to expand health care providers' personal awareness *Acad Med* 2016;PMID: 27355785. Full Text

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PROBLEM: Despite increasing awareness of the social determinants of health, health care disparities among sociocultural groups persist. Health care providers' unconscious bias resulting from unrecognized social privilege is one contributor to these disparities. APPROACH: In 2009, Henry Ford Health System initiated the Healthcare Equity Campaign both to raise employees' awareness of inequalities related to the social determinants of health and to increase their motivation to reduce them. After conducting awareness-raising activities to increase employees' understanding of the social determinants of health, a curriculum team developed the interactive Privilege and Responsibility Curricular Exercise (PRCE) and incorporated it into a series of trainings. The team designed the exercise to enhance participants' awareness of privilege in their lives and work, to improve their understanding of the impact of privilege on their own and others' lived experiences as a step beyond cultural competence toward cultural humility, and to encourage them to leverage their advantages to reduce health care inequities. OUTCOMES: About 300 participants of diverse professional and personal backgrounds from across the health system completed the training between the spring of 2009 and the spring of 2012, and many provided qualitative feedback about the exercise. Evaluations showed the exercise's potential as a powerful learning experience that might enhance a variety of equity- or diversity-related trainings, and also showed that participants considered the PRCE a highlight of the training. NEXT STEPS: The PRCE is worthy of additional study and could prove valuable to other organizations.

Surgery

Mohammad F, **Kabbani L**, **Lin J**, **Karamanos E**, **Esmael F**, and **Shepard A**. Post-procedural pseudoaneurysms: Single-center experience *Vascular* 2016;PMID: 27370682. Full Text

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OBJECTIVES: Pseudoaneurysms are a well-recognized complication of percutaneous angiographic procedures. Ultrasound-guided thrombin injection is currently the preferred treatment modality. This study was undertaken to evaluate our experience with the management of post-procedure pseudoaneurysms. METHODS: A retrospective study was undertaken of all patients who developed a post-procedure pseudoaneurysm between March 2004 and January 2013. Data were obtained from our prospectively maintained non-invasive vascular laboratory data base. RESULTS: Overall, 167 patients (80 men) with post-procedure pseudoaneurysms were identified. The mean age was 66 years. Post-procedure pseudoaneurysms developed following diagnostic coronary angiography (38%), coronary angioplasty (37%), peripheral vascular interventions (14.7%), or other access procedures (7.6%). Mean post-procedure pseudoaneurysm diameter was 2.8 +/- 1.8 cm. One hundred forty-two post-procedure pseudoaneurysms were injected with thrombin under ultrasound guidance. Primary success rate was 93.5%. There were 12 (8.5%) procedural failures of which seven (58%) responded to reinjection, three (25%) required operative management, one was treated with ultrasound-guided compression, and one (8.3%) was simply observed. On multivariate analysis, failures were associated with increased aneurysm diameter (p = 0.006; odds ratio 2.23, 95% CI 1.25 to 3.96), end-stage renal disease (p = 0.013; odds ratio 1.15, 95% CI 1.09 to 1.78) and superficial femoral artery aneurysm origin (p = 0.031; odds ratio 0.20, 95% CI 0.04 to 0.86). There were two episodes of thrombus formation in the femoral artery; one resolved with anticoagulation alone, and the other required thrombectomy. CONCLUSIONS: Percutaneous ultrasound-guided thrombin injection is an effective and safe method for managing post-procedure pseudoaneurysms. Failure rates are low and associated with large aneurysm size, superficial femoral artery origin and end-stage renal disease.

Surgery

Neugut AI, Hillyer GC, Kushi LH, **Lamerato L**, Buono DL, **Nathanson SD**, Bovbjerg DH, Mandelblatt JS, Tsai WY, Jacobson JS, and Hershman DL. A prospective cohort study of early discontinuation of adjuvant chemotherapy in women with breast cancer: the breast cancer quality of care study (BQUAL) *Breast Cancer Res Treat* 2016;PMID: 27287779. Full Text

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For many women with non-metastatic breast cancer, adjuvant chemotherapy prevents recurrence and extends survival. Women who discontinue chemotherapy early may reduce those benefits, but little is known about what predicts early discontinuation. We sought to determine prospectively the rate and reasons for early discontinuation of adjuvant chemotherapy in women with breast cancer. We conducted a prospective cohort study among three U.S. health care organizations. Of 1158 women with newly diagnosed non-metastatic breast cancer, 2006-2010, we analyzed 445 (38.4 %) patients who initiated standard adjuvant chemotherapy as defined by accepted guidelines. We interviewed patients at baseline and twice during treatment regarding sociodemographic/psychosocial factors and treatment decision-making and collected clinical data. They were categorized according to the number of cycles

required by the chemotherapy regimen they had initiated. The outcome was early discontinuation (<80 % of planned cycles). Of patients analyzed, 392 (88.1 %) completed the prescribed therapy. The strongest predictor was receipt of a regimen entailing >4 cycles of therapy (18.1 % for longer regimens, 7.4 % for 4 cycles) (odds ratio [OR] 2.59, 95 % CI 1.32-5.08), controlling for race, age, stage, hormone receptor status, social support, optimism, spirituality, stress, and physical symptoms. Higher levels of psychological symptoms on the Memorial symptom assessment scale also increased the odds of early discontinuation (OR 1.92, 95 % CI 0.998-3.68). The large majority of patients who initiated adjuvant chemotherapy for breast cancer completed their prescribed regimens, but early discontinuation was associated with lengthier regimens and, with borderline statistical significance, for those with psychological side effects.

Surgery

Nguyen HB, **Jaehne AK**, Jayaprakash N, Semler MW, **Hegab S**, Yataco AC, **Tatem G**, Salem D, **Moore S**, Boka K, **Gill JK**, **Gardner-Gray J**, **Pflaum J**, **Domecq JP**, **Hurst G**, Belsky JB, **Fowkes R**, Elkin RB, Simpson SQ, Falk JL, Singer DJ, and **Rivers EP**. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE *Crit Care* 2016; 20(1):160. PMID: 27364620. Full Text

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Prior to 2001 there was no standard for early management of severe sepsis and septic shock in the emergency department. In the presence of standard or usual care, the prevailing mortality was over 40-50 %. In response, a systems-based approach, similar to that in acute myocardial infarction, stroke and trauma, called early goal-directed therapy was compared to standard care and this clinical trial resulted in a significant mortality reduction. Since the publication of that trial, similar outcome benefits have been reported in over 70 observational and randomized controlled studies comprising over 70,000 patients. As a result, early goal-directed therapy was largely incorporated into the first 6 hours of sepsis management (resuscitation bundle) adopted by the Surviving Sepsis Campaign and disseminated internationally as the standard of care for early sepsis management. Recently a trio of trials (ProCESS, ARISE, and ProMISe), while reporting an all-time low sepsis mortality, question the continued need for all of the elements of early goal-directed therapy or the need for protocolized care for patients with severe and septic shock. A review of the early hemodynamic pathogenesis, historical development, and definition of early goal-directed therapy, comparing trial conduction methodology and the changing landscape of sepsis mortality, are essential for an appropriate interpretation of these trials and their conclusions.

Surgery

Varban OA, Greenberg CC, Schram J, Ghaferi AA, Thumma JR, **Carlin AM**, and Dimick JB. Surgical skill in bariatric surgery: Does skill in one procedure predict outcomes for another? *Surgery* 2016;PMID: 27324569. Full Text

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BACKGROUND: Recent data establish a strong link between peer video ratings of surgical skill and clinical outcomes with laparoscopic gastric bypass. Whether skill for one bariatric procedure can predict outcomes for another related procedure is unknown. METHODS: Twenty surgeons voluntarily submitted videos of a standard laparoscopic gastric bypass procedure, which was blindly rated by 10 or more peers using a modified version of the Objective Structured Assessment of Technical Skills. Surgeons were divided into quartiles for skill in performing gastric bypass, and within 30 days of sleeve gastrectomy, their outcomes were compared. Multivariate logistic regression analysis was utilized to adjust for patient risk factors. RESULTS: Surgeons with skill ratings in the top (n = 5), middle (n = 10, middle 2 combined), and bottom (n = 5) quartiles for laparoscopic gastric bypass saw similar rates of surgical and medical complications after laparoscopic sleeve gastrectomy (top 5.7%, middle 6.4%, bottom 5.5%, P = .13). Furthermore, surgeons' skill ratings did not correlate with rates of reoperation, readmission, and emergency department visits. Top-rated surgeons had significantly faster operating room times for sleeve gastrectomy (top 76 minutes, middle 90 minutes, bottom 88 minutes; P < .001) and a higher annual volume of bariatric cases per year (top 240, middle 147, bottom 105; P = .001). CONCLUSION: Video ratings of surgical skill with laparoscopic gastric bypass do not predict outcomes of laparoscopic sleeve gastrectomy. Evaluation of surgical skill with one procedure may not apply to other related procedures and may require independent assessment of surgical technical proficiency.

Urology

Abdullah N, **Rahbar H**, **Barod R**, **Dalela D**, Larson J, Johnson M, Mass A, Zargar H, Kaouk J, Allaf M, Bhayani S, Stifelman M, and **Rogers C**. Use of the Satinsky clamp for hilar clamping during robotic partial nephrectomy: indications, technique, and multi-center outcomes *J Robot Surg* 2016;PMID: 27329237. Full Text

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A Satinsky clamp may be a backup option for hilar clamping during robotic partial nephrectomy (RPN) if there are challenges with application of bulldog clamps, but there are potential safety concerns. We evaluate outcomes of RPN using Satinsky vs. bulldog clamps, and provide tips for safe use of the Satinsky as a backup option. Using a multi-center database, we identified 1073 patients who underwent RPN between 2006 and 2013, and had information available about method of hilar clamping (bulldog clamp vs. Satinsky clamp). Patient baseline characteristics, tumor features, and perioperative outcomes were compared between the Satinsky and bulldog clamp groups. A Satinsky clamp was used for hilar clamping in 94 (8.8 %) RPN cases, and bulldog clamps were used in 979 (91.2 %) cases. The use of a Satinsky clamp was associated with greater operative time (198 vs. 175 min, p < 0.001), estimated blood loss (EBL, 200 vs. 100 ml, p < 0.001), warm ischemia time (WIT, 20 vs. 19 min, p = 0.036), transfusion rate (12.8 vs. 4.8 %, p = 0.001), and hospital stay (3 vs. 2 days, p < 0.001). Tumor characteristics and number of renal vessels were similar between groups. There were six intraoperative complications in the Satinsky clamp group, but none were directly related to the Satinsky clamp. On multivariable analysis, the use of the Satinsky clamp was not associated with increase in intraoperative or Clavien >/=3 postoperative complications, positive surgical margin rate or percentage change in estimated glomerular filtration rate. A Satinsky clamp can be a backup option for hilar clamping during challenging RPN cases, but requires careful technique, and was rarely necessary.

Urology

Concodora CW, Maizels M, Dean GE, Weiss DA, Alpert SA, Edmondson JD, **Elder JS**, Herndon A, Elmore JM, and Rychlik K. Checklist assessment tool to evaluate suitability and success of neonatal clamp circumcision: A prospective study *J Pediatr Urol* 2016;PMID: 27363331. Full Text

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BACKGROUND: The American Academy of Pediatrics (AAP) Task Force on Circumcision has called for the development of standards of trainee proficiency in regards to evaluation and technique for neonatal clamp circumcision (NCC). At the present time, there is no standardized or general consensus on patient selection for NCC. An improved method to evaluate newborns for NCC is an important first step in this process. Therefore, the authors collaborated to identify criteria useful in the evaluation of newborns for suitability for NCC, and for assessment of success after NCC and have named it "Checklist Assessment for Neonatal Clamp Circumcision Suitability (Figure)." METHODS: A national multi-institutional collaboration was created to obtain consensus on objective criteria for use in determining patient suitability for NCC, and for assessing post-circumcision success outcomes. Criteria included elements from detailed medical history, bedside physical examination, and post-circumcision follow-up. Patients desiring NCC were enrolled consecutively and prospectively. The Checklist was followed to determine which newborns were suited to NCC, and NCC was done in those cases. The patients' caretakers were given post-circumcision care instructions and a follow-up appointment. Post circumcision, the Checklist was followed to determine if the procedure resulted in a successful circumcision or if there were complications. RESULTS: A total of 193 cases were enrolled prospectively and consecutively from January 2014 through October 2014. The mean age was 15 days (1-30 days). Of those 193 patients, 129 (67%) were deemed suitable for circumcision and underwent NCC. Post-circumcision assessment showed a 100% success rate with no complications. A total of 64 (23%) cases were deemed unsuitable for NCC because at least one checklist criterion was not satisfied, most commonly: penile torsion (n = 25), chordee (n = 19), and penoscrotal webbing (n = 19). DISCUSSION: Use of the Checklist in the present study has demonstrated a method of patient screening resulting in a 100% success rate with no complications. A high proportion of patients (33%) was identified as unsuited for NCC; however, the patient population consisted of newborn males referred to pediatric urology, and thus does not represent the general population, which is expected to have a lower proportion of unsuited patients. Regardless, the Checklist has the potential to enhance the decision-making process for both urologic and non-urologic care providers. CONCLUSIONS: The use of the "Checklist Assessment for Neonatal Clamp Circumcision Suitability" assessment tool improves identification of patients unsuited for NCC and thereby potentially decreases the likelihood of circumcision-related complications.

Urology

Sood A, **Li H**, Suson KD, Majumder K, **Sedki M**, **Abdollah F**, **Sammon JD**, **Friedman A**, Loppenberg B, Lakshmanan Y, Trinh QD, and **Elder JS**. Treatment patterns, testicular loss, and disparities in inpatient surgical management of testicular torsion in boys: a population based study 1998-2010 *BJU Int* 2016;PMID: 27322784. Full Text

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OBJECTIVES: To examine temporal trends in inpatient testicular torsion (TT) treatment and testicular loss (TL), and identify risk-factors for TL utilizing a large nationally representative pediatric cohort, stratified to established high prevalence TT cohorts (neonatal TT [NTT, <1 year-old] and adolescent TT [ATT, 12-17 year-olds]). METHODS: Boys (</=17 years, n=17,478) undergoing surgical exploration for TT were identified within the Nationwide Inpatient Sample (1998-2010). Temporal trends in inpatient TT management (salvage surgery vs. orchiectomy) and TL were examined using estimated annual percent change (EAPC) methodology. Multivariable logistic regression models

identified risk-factors for TL. RESULTS: Teaching hospitals treated 90% of boys with NTT, compared to 55% with ATT (p<0.001). Of boys with NTT, 85% lost their testis, compared to 35% with ATT (p<0.001). Inpatient management of NTT declined during the study period, from 7.5/100,000 children in 1998 to 3/100,000 in 2010 (EAPC -4.95%; p<0.001). Decrease was similar but less dramatic in ATT. TL patterns did not improve. In adjusted analyses, for NTT, orchiectomy was more likely at teaching hospitals. For ATT, orchiectomy was more likely in children with comorbidities (OR=5.42; p=0.045), Medicaid coverage or self-pay (p<0.05), and weekday presentation (p=0.001). Regional or racial disposition was not associated with TL. CONCLUSIONS: There has been a gradual decrease in inpatient surgical treatment for both NTT and ATT, presumably due to increased outpatient and/or non-operative management of these children. Concerningly, TL patterns have not improved; targeted interventions such as parental and adolescent male health education may lead to timely recognition/intervention in children at-risk for ATT. We noted no regional/racial disparities in contrast to earlier studies.

Urology

Trinh QD, **Li H**, Meyer CP, Hanske J, Choueiri TK, Reznor G, Lipsitz SR, Kibel AS, Han PK, Nguyen PL, **Menon M**, and **Sammon JD**. Determinants of cancer screening in Asian-Americans *Cancer Causes Control* 2016;PMID: 27372292. Full Text

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PURPOSE: Recent data suggest that Asian-Americans (AsAs) are more likely to present with advanced disease when diagnosed with cancer. We sought to determine whether AsAs are under-utilizing recommended cancer screening. METHODS: Cross-sectional analysis of the 2012 Behavioral Risk Factor Surveillance System comprising of AsAs and non-Hispanic White (NHW) community-dwelling individuals (English and Spanish speaking) eligible for colorectal, breast, cervical, or prostate cancer screening according to the United States Preventive Services Task Force recommendations. Age, education and income level, residence location, marital status, health insurance, regular access to healthcare provider, and screening were extracted. Complex samples logistic regression models quantified the effect of race on odds of undergoing appropriate screening. Data were analyzed in 2015. RESULTS: Weighted samples of 63.3, 33.3, 47.9, and 30.3 million individuals eligible for colorectal, breast, cervical, and prostate cancer screening identified, respectively. In general, AsAs were more educated, more often married, had higher levels of income, and lived in urban/suburban residencies as compared to NHWs (all $p < 0.05$). In multivariable analyses, AsAs had lower odds of undergoing colorectal (odds ratio [OR] 0.78, 95 % confidence interval [CI] 0.63-0.96), cervical (OR 0.45, 95 % CI 0.36-0.55), and prostate cancer (OR 0.55, 95 % CI 0.39-0.78) screening and similar odds of undergoing breast cancer (OR 1.29, 95 % CI 0.92-1.82) screening as compared to NHWs. CONCLUSIONS: AsAs are less likely to undergo appropriate screening for colorectal, cervical, and prostate cancer. Contributing reasons include limitations in healthcare access, differing cultural beliefs on cancer screening and treatment, and potential physician biases. Interventions such as increasing healthcare access and literacy may improve screening rates.

Urology

Wang L, **Diaz M**, **Stricker H**, **Peabody JO**, **Menon M**, and **Rogers CG**. Adding a newly trained surgeon into a high-volume robotic prostatectomy group: are outcomes ? *J Robot Surg* 2016;PMID: 27350553. Full Text

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This study evaluates whether a new staff surgeon early in the learning curve can be integrated into a high-volume robotic practice with an established robotic team and mentorship without compromising robot-assisted radical prostatectomy (RARP) outcomes of the practice. We analyzed outcomes of 3064 patients who underwent RARP from 2007 to 2012 at a high-volume tertiary center by a robotic practice comprising three experienced robotic surgeons (2846 patients) and a newly hired surgeon (218 patients) immediately out of training (residency and oncology

fellowship with 2 years of RARP exposure). The new surgeon performed RARP with intraoperative mentorship by the senior surgeons during the first year. Complications, biochemical recurrence (BCR), positive surgical margins rate (PSM), operating time (OR time), estimated blood loss (EBL) for the new and senior surgeons were compared. Multivariable linear, logistic and exact logistic regression adjusting for disease and patient characteristics were performed. On regression analyses, case number was the most significant predictor of decrease in probability of major complications ($p = 0.025$) and BCR ($p = 0.004$) for the new surgeon. Increasing case number was not associated with decrease in minor complications, PSM, OR time, or EBL ($p > 0.05$). Inclusion of the new surgeon's outcomes did not adversely impact outcomes of the practice. In conclusion, a new surgeon joining a high-volume robotic prostatectomy program with an established robotic team and mentorship can progress through the learning curve without compromising overall outcomes of the practice. Our results may be relevant for programs hiring newly trained staff to join an established robotic practice.