
Objective: Medications for treatment of substance use disorders are underutilized in treatment programs in the United States. Little is known about how insurance enrollment within states affects treatment program decisions about whether to offer medications. The primary objective of the study was to examine the impact of health insurance enrollment on availability of substance use disorder medications among treatment programs. Methods: Data from the 2012 National Survey of Substance Abuse Treatment Services, National Survey on Drug Use and Health, American Community Survey, Area Health Resource File, and the Substance Abuse and Mental Health Services Administration were combined to examine the impact of state insurance enrollment on availability of substance use disorder medications in treatment programs (N=9,888). A two-level, random-intercept logistic regression model was estimated to account for potential unobserved heterogeneity among treatment programs nested in states. Results: The percentage of state residents with employer-based insurance and Medicaid was associated with greater odds of offering at least one medication among treatment programs. A 5% increase in the rate of private insurance enrollment was associated with a 7.7% increase in the probability of offering at least one medication, and a 5% increase in the rate of state Medicaid enrollment was associated with a 9.3% increase in the probability of offering at least one medication. Conclusions: Results point to the potential significance of health insurance enrollment in shaping the availability of substance use disorder medications. Significant expansions in health insurance enrollment spurred by the Affordable Care Act have the potential to increase access to medications for many Americans.


The Stand Up 2 Cancer/Prostate Cancer Foundation-funded West Coast Dream Team project is a prospective multi-institutional study focused on acquiring metastatic castration-resistant prostate cancer (mCRPC) biopsy tissue at the time of resistance to abiraterone or enzalutamide. It is the first large-scale study designed to analyze mCRPC tissue specifically in this patient population. Study accrual is on target, with 261 out of a planned 300 metastatic tumor biopsies performed by August 2016. Paired biopsies have been completed in 42 patients, with paired genomic data before and after therapy obtained in 26 cases. Accrual is expected to be complete by December 2016. The Stand Up 2 Cancer/Prostate Cancer Foundation-funded West Coast Dream Team project is a prospective multi-institutional study focused on acquiring metastatic castration-resistant prostate cancer (mCRPC) biopsy tissue at the time of resistance to abiraterone or enzalutamide. It is the first large-scale study designed to analyze mCRPC tissue specifically in this patient population. Study accrual is on target, with 261 out of a planned 300 metastatic tumor biopsies performed by August 2016. Paired biopsies have been completed in 42 patients, with paired genomic data before and after therapy obtained in 26 cases. Accrual is expected to be complete by December 2016. © 2016 European Association of Urology.


BACKGROUND: Early and repeated patient-provider conversations about advance care planning (ACP) are now widely recommended. We sought to characterize barriers and strategies for realizing an iterative model of ACP patient-provider communication. METHODS: A total of 2 multidisciplinary focus groups and 3 semistructured interviews with 20 providers at a large Veterans Affairs medical center. Thematic analysis was employed to identify salient themes. RESULTS: Barriers included variation among providers in approaches to ACP, lack of useful information about patient values to guide decision making, and ineffective communication between providers across settings. Strategies included eliciting patient values rather than
specific treatment choices and an increased role for primary care in the ACP process. CONCLUSIONS: Greater attention to connecting providers across the continuum, maximizing the potential of the electronic health record, and linking patient experiences to their values may help to connect ACP communication across the continuum.


OBJECTIVE: To examine the association between the presence of individual principal investigators' financial ties to the manufacturer of the study drug and the trial's outcomes after accounting for source of research funding. DESIGN: Cross sectional study of randomized controlled trials (RCTs). SETTING: Studies published in "core clinical" journals, as identified by Medline, between 1 January 2013 and 31 December 2013. PARTICIPANTS: Random sample of RCTs focused on drug efficacy. MAIN OUTCOME MEASURE: Association between financial ties of principal investigators and study outcome. RESULTS: A total of 190 papers describing 195 studies met inclusion criteria. Financial ties between principal investigators and the pharmaceutical industry were present in 132 (67.7%) studies. Of 397 principal investigators, 231 (58%) had financial ties and 166 (42%) did not. Of all principal investigators, 156 (39%) reported advisor/consultancy payments, 81 (20%) reported speakers’ fees, 81 (20%) reported unspecified financial ties, 52 (13%) reported honorariums, 52 (13%) reported employee relationships, 52 (13%) reported travel fees, 41 (10%) reported stock ownership, and 20 (5%) reported having a patent related to the study drug. The prevalence of financial ties of principal investigators was 76% (103/136) among positive studies and 49% (29/59) among negative studies. In unadjusted analyses, the presence of a financial tie was associated with a positive study outcome (odds ratio 3.23, 95% confidence interval 1.7 to 6.1). In the primary multivariate analysis, a financial tie was significantly associated with positive RCT outcome after adjustment for the study funding source (odds ratio 3.57 (1.7 to 7.7). The secondary analysis controlled for additional RCT characteristics such as study phase, sample size, country of first authors, specialty, trial registration, study design, type of analysis, comparator, and outcome measure. These characteristics did not appreciably affect the relation between financial ties and study outcomes (odds ratio 3.37, 1.4 to 7.9). CONCLUSIONS: Financial ties of principal investigators were independently associated with positive clinical trial results. These findings may be suggestive of bias in the evidence base.


Critical limb ischemia (CLI) is a diagnosis plagued by significant comorbidity and high mortality rates. Overall survival remains poor in this population regardless of the procedure-related success as demonstrated by freedom from amputation, intervention, and patency. The literature has traditionally focused on physician-centered and lesion-centered outcomes with regards to limb salvage procedures, but there remains a relative paucity of studies of CLI patients describing patient-centered outcomes such as quality of life (QoL), independent living, and ambulation status. Review of the available literature indicates patients do not always experience significant gains in their QoL after limb salvage interventions, despite reasonable graft patency, amputation-free survival, and limb salvage rates. Further research is required using QoL tools in a measurable and clinically relevant fashion to guide optimal quality care that maximizes patient-centered outcomes. © 2016 Society for Vascular Surgery


The incidence of radiocephalic arteriovenous fistulae complicated by ischemic steal syndrome is low; however, its sequelae can be quite devastating. Traditional management includes open ligation of the distal radial artery. This series details 4 cases of successful embolization of the distal radial artery for flow interruption to treat ischemic steal syndrome and salvage functional dialysis access. For radiocephalic
arteriovenous fistulae complicated by steal syndrome, distal radial artery endovascular coil embolization is a valuable treatment strategy.


**OBJECTIVES:** Elevated body mass index (BMI) is associated with deficits in working memory, reduced gray matter volume in frontal and parietal lobes, as well as changes in white matter (WM) microstructure. The current study examined whether BMI was related to working memory performance and blood oxygen level dependent (BOLD) activity, as well as WM microstructure during adolescence. **METHODS:** Linear regressions with BMI and (1) verbal working memory BOLD signal, (2) spatial working memory BOLD signal, and (3) fractional anisotropy (FA), a measure of WM microstructure, were conducted in a sample of 152 healthy adolescents ranging in BMI. **RESULTS:** BMI was inversely related to IQ and verbal and spatial working memory accuracy; however, there was no significant relationship between BMI and BOLD response for either verbal or spatial working memory. Furthermore, BMI was negatively correlated with FA in the left superior longitudinal fasciculus (SLF) and left inferior longitudinal fasciculus (ILF). ILF FA and IQ significantly mediated the relationship between BMI and verbal working memory performance, whereas SLF FA, but not IQ, significantly mediated the relationship between BMI and accuracy of both verbal and spatial working memory. **CONCLUSIONS:** These findings indicate that higher BMI is associated with decreased FA in WM fibers connecting brain regions that support working memory, and that WM microstructural deficits may underlie inferior working memory performance in youth with higher BMI. Of interest, BMI did not show the same relationship with working memory BOLD activity, which may indicate that changes in brain structure precede changes in function.


Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialized topics. At IFPA meeting 2016 there were twelve themed workshops, four of which are summarized in this report. These workshops covered innovative technologies applied to new and traditional areas of placental research: 1) genomic communication; 2) bioinformatics; 3) trophoblast biology and pathology; 4) placental transport systems.


**OBJECTIVE:** To assess the feasibility of a mindfulness-based stress reduction (MBSR) program for adolescents with widespread chronic pain and other functional somatic symptoms and to make preliminary assessments of its clinical utility. **STUDY DESIGN:** Three cohorts of subjects completed an 8-week MBSR program. Child- and parent-completed measures were collected at baseline and 8 and 12 weeks later. Measures included the Functional Disability Inventory (FDI), the Fibromyalgia/Symptom Impact Questionnaire-Revised (FIQR/SIQR), the Pediatric Quality of Life Inventory, the Multidimensional Anxiety Scale (MASC2), and the Perceived Stress Scale. Subjects and parents were interviewed following the program to assess feasibility. **RESULTS:** Fifteen of 18 subjects (83%) completed the 8-week program. No adverse events occurred. Compared with baseline scores, significant changes were found in mean scores on the FDI (33% improvement, P = .026), FIQR/SIQR (26% improvement, P = .03), and MASC2 (child: 12% improvement, P = .02; parent report: 17% improvement, P = .03) at 8 weeks. MASC2 scores (child and parent) and Perceived Stress Scale scores were significantly improved at 12 weeks. More time spent doing home practice was associated with better outcomes in the FDI and FIQR/SIQR (44% and 26% improvement, respectively). Qualitative interviews indicated that subjects and parents reported social support as a benefit of the MBSR class, as well as a positive impact of MBSR on activities of daily living, and on pain and anxiety. **CONCLUSIONS:** MBSR is a feasible and acceptable
intervention in adolescents with functional somatic syndromes and has preliminary evidence for improving functional disability, symptom impact, and anxiety, with consistency between parent and child measures. TRIAL REGISTRATION: ClinicalTrials.gov: NCT02190474.


OBJECTIVE: To determine if prenatal care affects adverse perinatal outcomes in pregnant women with Type-2 Diabetes Mellitus. STUDY DESIGN: This was a retrospective cohort study of pregnant women with pregestational diabetes mellitus pregnancies in the state of California between 1997 and 2006, using vital statistics data linked to birth certificates. Women were stratified by time of presentation to care and we compared those who presented in the first trimester, third trimester, and those who had no prenatal care prior to delivery. Perinatal outcomes looked at included: preeclampsia, macrosomia, preterm delivery, cesarean delivery and intrauterine fetal demise (IUFD). The two groups were compared with chi-squared testing to determine statistical significance. RESULTS: In women with pregestational diabetes those who presented at time of delivery had an 11.3% risk of IUFD compared to 0.9% in those who presented in the 1st trimester. There was also an increased rate of preterm birth in the late presentation cohort (29.4% at time of delivery vs 21.0% in the 1st trimester). After adjusting for possible confounding variables using logistic regression models, rates of IUFD and preterm delivery were still found to be statistically significant with adjusted odds ratios of 11.37 (95% CI: 6.10-21.16) and 1.55 (95% CI: 1.03-2.32), respectively. There were no differences in rates of macrosomia or preeclampsia between the three cohorts. CONCLUSION: Treatment of T2DM throughout pregnancy leads to improved maternal and neonatal outcomes.


BACKGROUND: Autologous cartilage tissue implants, including the NeoCart implant, are intended to repair focal articular cartilage lesions. Short-term results from United States Food and Drug Administration (FDA) phase I and phase II clinical trials indicated that the NeoCart implant was safe when surgically applied as a cell-based therapy and efficacious compared with microfracture. HYPOTHESIS: Quantitative magnetic resonance imaging (MRI) analysis would reveal NeoCart tissue maturation through to 60-month follow-up. STUDY DESIGN: Case series; Level of evidence, 4. METHODS: Patients with symptomatic full-thickness cartilage lesions of the distal femoral condyle were treated with NeoCart in FDA clinical trials. Safety and efficacy were evaluated prospectively by MRI and clinical patient-reported outcomes (PROs) through to 60-month follow-up. Qualitative MRI metrics were quantified according to modified MOCART (magnetic resonance observation of cartilage repair tissue) criteria, with an independent evaluation of repair tissue signal intensity. Subjective PROs and objective range of motion (ROM) were obtained at baseline and through to 60 months. RESULTS: Twenty-nine patients treated with NeoCart were observed over a mean of 52.0 +/- 15.5 months (median, 60 months). MOCART analyses indicated significant improvement (P < .001) in cartilage quality from 3 to 24 months, with stabilization from 24 to 60 months. Signal intensity of the repair tissue evolved from hyperintense at early follow-up to isointense after 6 months and to hypointense after 24 months. The temporal progression toward hypointense T2 signals at later time points observed here indicated a further reorganization of the repair tissue toward a dense tissue that was less similar to the surrounding native tissue. However, 80% of patients showed evidence of subchondral bone changes on MRI at all time points; 4 patients (14%) showed no improvement of MRI criteria. Compared with baseline values, significant improvement (P < .001) was seen in PROs (mean [+-SD] baseline to mean [+-SD] final follow-up), including the International Knee Documentation Committee score (47.9 +/- 17.4 to 75.5 +/- 22.1), physical component summary of the Short Form-36 (40.5 +/- 7.2 to 51.4 +/- 8.1), and all 5 domains of the Knee injury and Osteoarthritis Outcome Score (Pain: 64.8 +/- 12.1 to 86.1 +/- 17.3; Activities of Daily Living: 75.5 +/- 14.8 to 91.6 +/- 13.8; Quality of Life: 28.6 +/- 15.5 to 69.4 +/- 28.0; Symptoms: 65.8 +/- 13.8 to 86.6 +/- 13.4; Sports and Recreation: 41.4 +/- 24.3 to 72.4 +/- 28.8). Significant (P < .0001) decreases from
baseline scores for the visual analog scale for pain (34.6 +/- 22.5) were seen by 6 months and sustained at final follow-up (14.3 +/- 18.4). ROM significantly (P < .0001) improved from baseline (131.5 degrees +/- 7.9 degrees) to final follow-up (140.7 degrees +/- 6.3 degrees). CONCLUSION: Longitudinal MRI analysis demonstrated that NeoCart-based repair tissue is durable and evolves over time. For a majority of patients, this progression trended from an initial hyperintense signal to a hypointense signal at later follow-ups. Changes in radiographic measures over time corresponded with improvement in clinical measures, with maximum benefits experienced at 24-month follow-up. Similarly, clinical efficacy for the total cohort, determined by clinical outcome scores, reached a maximum at 24 months without decline to 60 months. Results from safety and exploratory clinical trials indicate that NeoCart is a safe and effective treatment for articular cartilage lesions through to 5-year follow-up. Registration: NCT00548119 (ClinicalTrials.gov identifier).


OBJECTIVE: We investigated the relationship between social support and health service use among men and women with depression. METHODS: Participants were 1379 adults with symptoms of depression (Patient Health Questionnaire-9 score >/= 5) in the National Health and Nutrition Examination Survey. Using the framework of the Andersen Behavioral Model of Health Services Use, multivariable regression models used social support, stratified by depression severity, to estimate association with utilization of mental health and nonmental health services. Partial F-tests examined a priori interactions between social support and gender. RESULTS: Among those with adequate social support, odds of seeing a nonmental health provider were much higher when depression was moderate [Odds Ratio (OR): 2.6 (1.3-5.3)] or severe [OR: 3.2 (1.2-8.7)], compared to those lacking social support. Conversely, odds of mental health service use were 60% lower among those with moderate depression [OR: 0.4 (0.2-1.0)] when social support was adequate as opposed to inadequate. Social support was unrelated to service use when depression was mild. Gender moderated the relationship between social support and health service use among individuals with severe depression. CONCLUSIONS: Social support has opposite associations with mental and nonmental health service use among adults with clinically significant depression. This association is largely attributable to the effect of male gender on the relationship between social support and health service use.


Introduction Desmoplastic small round cell tumor (DSRCT) is a rare mesenchymal malignancy. We describe our experience with treating DSRCT at a large sarcoma referral center. Methods A retrospective chart review was performed on DSRCT patients referred to our institution (1998–2014). Pathology specimens were reviewed to confirm the diagnosis. Clinical and imaging were extracted and summarized with descriptive statistics. Univariate analysis was performed to evaluate the association between patient, tumor, and treatment variables and overall survival (OS). Results In this study cohort of 20 patients, median age at presentation was 29 y (range 18–43) and 90% were male. Fifty-five percent were presented with metastasis. Patients underwent chemotherapy (n = 20), radiation therapy (n = 3), and cytoreductive surgery (CRS) (n = 5). Median OS was 22 m (interquartile range: 12–28 m). Five-year OS rate was 20%. Extra-abdominal metastasis was associated with a higher hazard ratio (HR) of mortality (HR: 3.1, 95% C.I. 1.0–9.4, p = 0.04), while CRS improved OS (HR: 0.1, 95% C.I. 0.03–0.7, p = 0.02). Conclusions Despite aggressive treatment, less than half of the patients were dead of DSRCT within 2 years of presentation. Although a select group of patients who underwent CRS had improved OS, novel treatments are urgently needed. © 2016 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology.


This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization potential, as well as, environmental safety. Data from the suitable read across analog isobornyl acetate (CAS # 125-12-2) show that this material is not genotoxic, provided a MOE> 100 for the repeated dose, developmental and reproductive endpoints, and does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (threshold of Toxicological Concern) for a Cramer Class II material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework. © 2016 Elsevier Ltd.


Background: Syncope has been associated with increased risk of sudden cardiac arrest (SCA) in specific patient populations, such as hypertrophic cardiomyopathy, heart failure, and long QT syndrome, but data are lacking on the risk of SCA associated with syncope among patients with coronary artery disease (CAD), the most common cause of SCA. We investigated this association among CAD patients in the community.

Methods: All cases of SCA due to CAD were prospectively identified in Portland, Oregon (population approximately 1 million) as part of the Oregon Sudden Unexpected Death Study 2002-2015, and compared to geographical controls. Detailed clinical information including history of syncope and cardiac investigations was obtained from medical records. Results: 2119 SCA cases (68.4. ±. 13.8. years, 66.9% male) and 746 controls (66.7. ±. 11.7. years, 67.0% male) were included in the analysis. 143 (6.8%) of cases had documented syncope prior to the SCA. SCA cases with syncope were > 5. years older and had more comorbidities than other SCA cases. After adjusting for clinical factors and left ventricular ejection fraction (LVEF), syncope was associated with increased risk of SCA (OR 2.8; 95%CI 1.68-4.85). When analysis was restricted to subjects with LVEF ≥ .50%, the risk of SCA associated with syncope remained significantly elevated (adjusted OR 3.1; 95%CI 1.68-5.79). Conclusions: Syncope was associated with increased risk of SCA in CAD patients even with preserved LV function. These findings suggest a role for this clinical marker among patients with CAD and normal LVEF, a large sub-group without any current means of SCA risk stratification. © 2016.


Sickle cell disease (SCD) is an inherited monogenic disease characterized by misshapen red blood cells that causes vaso-occlusive disease, vasculopathy, and systemic inflammation. Approximately 300,000 infants are born per year with SCD globally. Acute, chronic, and acute-on-chronic complications contribute to end-
organ damage and adversely affect quantity and quality of life. Hematopoietic stem cell transplantation is
the only cure available today, but is not feasible for the vast majority of people suffering from SCD.
Fortunately, new therapies are in late clinical trials and more are in the pipeline, offering hope for this
unfortunate disease, which has increasing global burden. © 2016 Elsevier Inc.

pretreatment CA125 at ovarian cancer diagnosis: a pooled analysis in the Ovarian Cancer Association

PURPOSE: Cancer antigen 125 (CA125) is a glycoprotein expressed by epithelial cells of several normal tissue
types and overexpressed by several epithelial cancers. Serum CA125 levels are mostly used as an aid in the
diagnosis of ovarian cancer patients, to monitor response to treatment and detect cancer recurrence. Besides
tumor characteristics, CA125 levels are also influenced by several epidemiologic factors, such as age, parity,
and oral contraceptive use. Identifying factors that influence CA125 levels in ovarian cancer patients could
aid in the interpretation of CA125 values for individuals. METHODS: We evaluated predictors of pretreatment
CA125 in 13 studies participating in the Ovarian Cancer Association Consortium. This analysis included a
total of 5,091 women with invasive epithelial ovarian cancer with pretreatment CA125 measurements. We
used probit scores to account for variability in CA125 between studies and linear regression to estimate the
association between epidemiologic factors and tumor characteristics and pretreatment CA125 levels.
RESULTS: In age-adjusted models, older age, history of pregnancy, history of tubal ligation, family history of
breast cancer, and family history of ovarian cancer were associated with higher CA125 levels while
endometriosis was associated with lower CA125 levels. After adjusting for tumor-related characteristics
(stage, histology, grade), body mass index (BMI) higher than 30 kg/m2 was associated with 10% (95% CI 2,
19%) higher CA125 levels, while race (non-white vs. white) was associated with 15% (95% CI 4, 27%) higher
CA125 levels. CONCLUSION: Our results suggest that high BMI and race may influence CA125 levels
independent of tumor characteristics. Validation is needed in studies that use a single assay for CA125
measurement and have a diverse study population.


Thio-urethanes were synthesized by combining 1,6-hexanediol-diisocyanate (aliphatic) with pentaerythritol
tetra-3-mercaptopropionate (PETMP) or 1,3-bis(1-isocyanato-1-methylethyl)benzene (aromatic) with
trimethylol-tris-3-mercaptopropionate (TMP), at 1:2 isocyanate:thiol, leaving pendant thiols. Oligomers were
added at 10-30 phr to BisGMA-UDMA-TEGDMA (5:3:2, BUT). 25 wt% silanated inorganic fillers were added.
Commercial cement (Relyx Veneer, 3M-ESPE) was also evaluated with 10-20 phr of aromatic oligomer. Near-
IR was used to follow methacrylate conversion (DC) and rate of polymerization (Rpmax). Mechanical
properties were evaluated in three-point bending (ISO 4049) for flexural strength/modulus (FS/FM, and
toughness), and notched specimens (ASTM Standard E399-90) for fracture toughness (KIC). Polymerization
stress (PS) was measured on the Bioman. Volumetric shrinkage (VS, %) was measured with the bonded disk
technique. Results were analyzed with ANOVA/Tukey’s test (alpha=5%). In general terms, for BUT cements,
conversion and mechanical properties in flexure increased for selected groups with the addition of thio-
urethane oligomers. The aromatic versions resulted in greater FS/FM than aliphatic. Fracture toughness
increased by two-fold in the experimental groups (from 1.17 +/- 0.36 MPam(1/2) to around 3.23 +/- 0.22
MPam(1/2)). Rpmax decreased with the addition of thio-urethanes, though the vitrification point was not
statistically different from the control. VS and PS decreased with both oligomers. For the commercial cement,
20 phr of oligomer increased DC, vitrification, reduced Rpmax and also significantly increased KIC, and
reduced PS and FM. Thio-urethane oligomers were shown to favorably modify conventional dimethacrylate
networks. Significant reductions in polymerization stress were achieved at the same time conversion and
fracture toughness increased.
BACKGROUND: The Monkey Alcohol and Tissue Research Resource (MATRR) is a repository and analytics platform for detailed data derived from well-documented Non-Human Primate (NHP) alcohol self-administration studies. This macaque model has demonstrated categorical drinking norms reflective of human drinking populations, resulting in consumption pattern classifications of Very Heavy Drinking (VHD), Heavy Drinking (HD), Binge Drinking (BD), and Low Drinking (LD) individuals. Here we expand on previous findings that suggest ethanol drinking patterns during initial drinking to intoxication can reliably predict future drinking category assignment. METHODS: The classification strategy uses a machine learning approach to examine an extensive set of daily drinking attributes during 90 sessions of induction across seven cohorts of five to eight monkeys for a total of 50 animals. A Random Forest classifier is employed to accurately predict categorical drinking after 12 months of self-administration. RESULTS: Predictive outcome accuracy is approximately 78% when classes are aggregated into two groups, “LD and BD” and “HD and VHD”. A subsequent two-step classification model distinguishes individual LD and BD categories with 90% accuracy and between HD and VHD categories with 95% accuracy. Average four-category classification accuracy is 74%, and provides putative distinguishing behavioral characteristics between groupings. CONCLUSION: We demonstrate that data derived from the induction phase of this ethanol self-administration protocol has significant predictive power for future ethanol consumption patterns. Importantly, numerous predictive factors are longitudinal, measuring the change of drinking patterns through three stages of induction. Factors during induction that predict future heavy drinkers include being younger at the time of first intoxication and developing a shorter latency to first ethanol drink. Overall, this analysis identifies predictive characteristics in future very heavy drinkers that optimize intoxication, such as having increasingly fewer bouts with more drinks. This analysis also identifies characteristic avoidance of intoxicating topographies in future low drinkers, such as increasing number of bouts and waiting longer before the first ethanol drink. This article is protected by copyright. All rights reserved.

Interferon-lambda (IFN-lambda) has potent antiviral effects against multiple enteric viral pathogens, including norovirus and rotavirus, in both preventing and curing infection. Because the intestine includes a diverse array of cell types, however, the cell(s) upon which IFN-lambda acts to exert its antiviral effects are unclear. Here, we sought to identify IFN-lambda responsive cells by generation of mice with lineage-specific deletion of the receptor for IFN-lambda, Ifnlr1. We found that expression of JFNLR1 on intestinal epithelial cells (IECs) in the small intestine and colon is required for enteric IFN-lambda antiviral activity. IEC Ifnlr1 expression also determines the efficacy of IFN-lambda in resolving persistent murine norovirus (MNoV) infection and regulates fecal shedding and viral titers in tissue. Expression of Ifnlr1 by IECs is thus necessary for the response to both endogenous and exogenous IFN-lambda. We further demonstrate that IEC Ifnlr1 expression is required for the sterilizing innate immune effects of IFN-lambda by extending these findings in Rag1-deficient mice. Finally, we assessed whether our findings pertained to multiple viral pathogens by infecting mice specifically lacking IEC Ifnlr1 expression with reovirus. These mice phenocopied Ifnlr1-null animals, exhibiting increased intestinal tissue titers and enhanced reovirus fecal shedding. IECs are thus the critical cell type responding to IFN-lambda to control multiple enteric viruses. This is the first genetic evidence that supports an essential role for IECs in IFN-lambda-mediated control of enteric viral infection, and these findings thus provide insight into the mechanism of IFN-lambda-mediated antiviral activity.

IMPORTANCE: Human noroviruses (HNoVs) are the leading cause of epidemic gastroenteritis worldwide. Type III interferons (IFN-lambda) control enteric viral infections in the gut, and have been shown to cure mouse norovirus, a small animal model for HNoVs. Using a genetic approach with conditional knock-out mice, we identified intestinal epithelial cells (IECs) as the dominant IFN-lambda-responsive cells in control of enteric virus infection in vivo. Upon murine norovirus or reovirus infection, Ifnlr1 depletion in IECs largely recapitulated the phenotype seen in Ifnlr1−/− mice of higher intestinal tissue viral titers and increased viral shedding in the stool. Moreover, IFN-lambda-mediated sterilizing immunity against murine norovirus requires the capacity of IECs to respond to IFN-lambda. These findings clarify the mechanism of action of this cytokine, and emphasize the therapeutic potential of IFN-lambda for treating mucosal viral infections.

Importance: Previous clinical trials showing the benefit of continuous glucose monitoring (CGM) in the management of type 1 diabetes predominantly have included adults using insulin pumps, even though the majority of adults with type 1 diabetes administer insulin by injection. Objective: To determine the effectiveness of CGM in adults with type 1 diabetes treated with insulin injections. Design, Setting, and Participants: Randomized clinical trial conducted between October 2014 and May 2016 at 24 endocrinology practices in the United States that included 158 adults with type 1 diabetes who were using multiple daily insulin injections and had hemoglobin A1c (HbA1c) levels of 7.5% to 9.9%. Interventions: Random assignment 2:1 to CGM (n = 105) or usual care (control group; n = 53). Main Outcomes and Measures: Primary outcome measure was the difference in change in central-laboratory-measured HbA1c level from baseline to 24 weeks. There were 18 secondary or exploratory end points, of which 15 are reported in this article, including duration of hypoglycemia at less than 70 mg/dL, measured with CGM for 7 days at 12 and 24 weeks. Results: Among the 158 randomized participants (mean age, 48 years [SD, 13]; 44% women; mean baseline HbA1c level, 8.6% [SD, 0.6%]; and median diabetes duration, 19 years [interquartile range, 10-31 years]), 155 (98%) completed the study. In the CGM group, 93% used CGM 6 d/wk or more in month 6. Mean HbA1c reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (repeated-measures model P < .001). At 24 weeks, the adjusted treatment-group difference in mean change in HbA1c level from baseline was -0.6% (95% CI, -0.8% to -0.3%; P < .001). Median duration of hypoglycemia at less than <70 mg/dL was 43 min/d (IQR, 27-69) in the CGM group vs 80 min/d (IQR, 36-111) in the control group (P = .002). Severe hypoglycemia events occurred in 2 participants in each group. Conclusions and Relevance: Among adults with type 1 diabetes who used multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects. Trial Registration: clinicaltrials.gov Identifier: NCT02282397.


Purpose Ipilimumab increases antitumor T-cell responses by binding to cytotoxic T-lymphocyte antigen 4. We evaluated treatment with ipilimumab in asymptomatic or minimally symptomatic patients with chemotherapy-naive metastatic castration-resistant prostate cancer without visceral metastases. Patients and Methods In this multicenter, double-blind, phase III trial, patients were randomly assigned (2:1) to ipilimumab 10 mg/kg or placebo every 3 weeks for up to four doses. Ipilimumab 10 mg/kg or placebo maintenance therapy was administered to nonprogressing patients every 3 months. The primary end point was overall survival (OS). Results Four hundred patients were randomly assigned to ipilimumab and 202 to placebo; 399 were treated with ipilimumab and 199 with placebo. Median OS was 28.7 months (95% CI, 24.5 to 32.5 months) in the ipilimumab arm versus 29.7 months (95% CI, 26.1 to 34.2 months) in the placebo arm (hazard ratio, 1.11; 95.87% CI, 0.88 to 1.39; P = .3667). Median progression-free survival was 5.6 months in the ipilimumab arm versus 3.8 with placebo arm (hazard ratio, 0.67; 95.87% CI, 0.55 to 0.81). Exploratory analyses showed a higher prostate-specific antigen response rate with ipilimumab (23%) than with placebo (8%). Diarrhea (15%) was the only grade 3 to 4 treatment-related adverse event (AE) reported in > = 10% of ipilimumab-treated patients. Nine (2%) deaths occurred in the ipilimumab arm due to treatment-related AEs; no deaths occurred in the placebo arm. Immune-related grade 3 to 4 AEs occurred in 31% and 2% of patients, respectively. Conclusion Ipilimumab did not improve OS in patients with metastatic castration-resistant prostate cancer. The observed increases in progression-free survival and prostate-specific antigen response rates suggest antitumor activity in a patient subset.

BACKGROUND: Posterior sternoclavicular dislocations can be challenging diagnostically, as traumatic force often happens to the lateral shoulder rather than directly to the sternoclavicular joint. Shoulder radiographs do not illustrate the sternoclavicular joint well, and can miss the diagnosis. This injury, however, has the potential for life-threatening complications due to proximity of mediastinal structures that might also be injured. CASE REPORT: The following case illustrates a delayed diagnosis of posterior sternoclavicular dislocation. It also shows how point-of-care ultrasound can diagnose a dislocation, confirm persistence of a dislocation diagnosis when patients are transported from a referring institution. Why should an emergency physician be aware of this? Point-of-care ultrasound can be used to rapidly diagnose posterior sternoclavicular dislocations and to provide patients education about their injury.


Fetal insulin secretion is inhibited by acute hypoxemia. The relationship between prolonged hypoxemia and insulin secretion, however, is less well defined. To test the hypothesis that prolonged fetal hypoxemia impairs insulin secretion, studies were performed in sheep fetuses that were bled to anemic conditions for 9 +/- 0 days (anemic, n=19) and compared to control fetuses (n=15). Arterial hematocrit and oxygen content were 34% and 52% lower, respectively, in anemic vs. control fetuses (P<0.0001). Plasma glucose concentrations were 21% higher in the anemic group (P<0.05). Plasma norepinephrine and cortisol concentrations increased 70% in the anemic group (P<0.05). Glucose-, arginine-, and leucine-stimulated insulin secretion all were lower (P<0.05) in anemic fetuses. No differences in pancreatic islet size or beta-cell mass were found. In vitro, isolated islets from fetuses secreted insulin in response to glucose and leucine as well as control fetal islets. These findings indicate a functional islet defect in anemic fetuses which likely involves direct effects of low oxygen and/or increased norepinephrine on insulin release. In pregnancies complicated by chronic fetal hypoxemia, increasing fetal oxygen concentrations may improve insulin secretion.


The rapid development of genomic sequencing technologies has decreased the cost of genetic analysis to the extent that it seems plausible that genome-scale sequencing could have widespread availability in pediatric care. Genomic sequencing provides a powerful diagnostic modality for patients who manifest symptoms of monogenic disease and an opportunity to detect health conditions before their development. However, many technical, clinical, ethical, and societal challenges should be addressed before such technology is widely deployed in pediatric practice. This article provides an overview of the Newborn Sequencing in Genomic Medicine and Public Health Consortium, which is investigating the application of genome-scale sequencing in newborns for both diagnosis and screening.


OBJECTIVE: The objective of this study was to compare glucose control in participants with type 1 diabetes receiving insulin glargine 300 U/mL (Gla-300) or glargine 100 U/mL (Gla-100) in the morning or evening, in combination with mealtime insulin. RESEARCH DESIGN AND METHODS: In this 16-week, exploratory, open-label, parallel-group, two-period crossover study (clinicaltrials.gov identifier NCT01658579), 59 adults with type 1 diabetes were randomized (1:1:1:1) to once-daily Gla-300 or Gla-100 given in the morning or evening (with crossover in the injection schedule). The primary efficacy end point was the mean percentage of time in the target glucose range (80-140 mg/dL), as measured using continuous glucose monitoring (CGM), during the last 2 weeks of each 8-week period. Additional end points included other CGM glycemic control parameters, hypoglycemia (per self-monitored plasma glucose [SMPG]), and adverse events. RESULTS: The
percentage of time within the target glucose range was comparable between the Gla-300 and Gla-100 groups. There was significantly less increase in CGM-based glucose during the last 4 h of the 24-h injection interval for Gla-300 compared with Gla-100 (least squares mean difference -14.7 mg/dL [95% CI -26.9 to -2.5]; P = 0.0192). Mean 24-h glucose curves for the Gla-300 group were smoother (lower glycemic excursions), irrespective of morning or evening injection. Four metrics of intrasubject interstitial glucose variability showed no difference between Gla-300 and Gla-100. Nocturnal confirmed (<54 mg/dL by SMPG) or severe hypoglycemia rate was lower for Gla-300 participants than for Gla-100 participants (4.0 vs. 9.0 events per participant-year; rate ratio 0.45 [95% CI 0.24-0.82]). CONCLUSIONS: Less increase in CGM-based glucose levels in the last 4 h of the 24-h injection interval, smoother average 24-h glucose profiles irrespective of injection time, and reduced nocturnal hypoglycemia were observed with Gla-300 versus Gla-100.


With extended life spans in modern humans, menopause has become a significant risk factor for depression, anxiety, loss of cognitive functions, weight gain, metabolic disease, osteoporosis, cardiovascular disease, and neurodegenerative diseases. Clinical studies have found beneficial neural effects of ovarian steroid hormone therapy (HT) during the menopausal transition and data are emerging that it can be continued long term. To further understand molecular underpinnings of the clinical studies, we used quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) to examine gene expression in the serotonergic dorsal raphe of old (>18 years) rhesus macaques, focusing on genes related to depression, cellular resilience, and neurodegenerative diseases. The animals were ovariectomized (Ovx, surgically menopausal) and subjected to either estradiol or estradiol plus progesterone HT, or to placebo, starting 2 months after Ovx and continuing for ~4 years. Significant changes were observed in 36 of 48 genes examined that encode proteins supporting serotonin neurotransmission, synapse assembly, glutamate neurotransmission, DNA repair, chaperones, ubiquinases and transport motors, as well as genes encoding proteins that have potential to delay the onset of neuropathologies. The data reveal important gene targets for chronic HT that contribute to neural health. Alternatively, the loss of ovarian steroids may lead to loss of functions at the gene level that contribute to many of the observable neural deficits after menopause. © 2016 Elsevier Inc.


Background: Rhesus macaques are widely used in biomedical research, but the application of genomic information in this species to better understand human disease is still in its infancy. Whole-genome sequence (WGS) data in large pedigreed macaque colonies could provide substantial experimental power for genetic discovery, but the collection of WGS data in large cohorts remains a formidable expense. Here, we describe a cost-effective approach that selects the most informative macaques in a pedigree for 30X WGS, followed by low-cost genotyping-by-sequencing (GBS) at 30X on the remaining macaques in order to generate sparse genotype data at high accuracy. Dense variants from the selected macaques with WGS data are then imputed into macaques having only sparse GBS data, resulting in dense genome-wide genotypes throughout the pedigree. Results: We developed GBS for the macaque genome using a digestion with PstI, followed by sequencing of size-selected fragments at 30X coverage. From GBS sequence data collected on all individuals in a 16-member pedigree, we characterized high-confidence genotypes at 22,455 single nucleotide variant (SNV) sites that were suitable for guiding imputation of dense sequence data from WGS. To characterize dense markers for imputation, we performed WGS at 30X coverage on nine of the 16 individuals, yielding 10,193,425 high-confidence SNVs. To validate the use of GBS data for facilitating

Gitelman syndrome (GS) is a rare, salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. The disease is recessively inherited, caused by inactivating mutations in the SLC12A3 gene that encodes the thiazide-sensitive sodium-chloride cotransporter (NCC). GS is usually detected during adolescence or adulthood, either fortuitously or in association with mild or nonspecific symptoms or both. The disease is characterized by high phenotypic variability and a significant reduction in the quality of life, and it may be associated with severe manifestations. GS is usually managed by a liberal salt intake together with oral magnesium and potassium supplements. A general problem in rare diseases is the lack of high quality evidence to inform diagnosis, prognosis, and management. We report here on the current state of knowledge related to the diagnostic evaluation, follow-up, management, and treatment of GS; identify knowledge gaps; and propose a research agenda to substantiate a number of issues related to GS. This expert consensus statement aims to establish an initial framework to enable clinical auditing and thus improve quality control of care. © 2016 International Society of Nephrology.


The current study sought to expand on prior reports of the validity and reliability of the CAINS (CAINS) by examining its performance across diverse non-academic clinical settings as employed by raters not affiliated with the scale’s developers and across a longer test-retest follow-up period. The properties of the CAINS were examined within the Management of Schizophrenia in Clinical Practice (MOSAIC) schizophrenia registry. A total of 501 participants with a schizophrenia spectrum diagnosis who were receiving usual care were recruited across 15 national Patient Assessment Centers and evaluated with the CAINS, other negative symptom measures, and assessments of functioning, quality of life and cognition. Temporal stability of negative symptoms was assessed across a 3-month follow-up. Results replicated the two-factor structure of the CAINS reflecting Motivation and Pleasure and expression symptoms. The CAINS scales exhibited high internal consistency and temporal stability. Convergent validity was supported by significant correlations between the CAINS subscales with other negative symptom measures. Additionally, the CAINS was significantly correlated with functioning and quality of life. Discriminant validity was demonstrated by small to moderate associations between the CAINS and positive symptoms, depression, and cognition (and these associations were comparable to those found with other negative symptom scales). Findings suggest that
the CAINS is a reliable and valid tool for measuring negative symptoms in schizophrenia across diverse clinical samples and settings.


Studies of Leishmania donovani have shown that both ornithine decarboxylase and spermidine synthase, two enzymes of the polyamine biosynthetic pathway, are critical for promastigote proliferation and required for maximum infection in mice. However, the importance of arginase (ARG), the first enzyme of the polyamine pathway in Leishmania, has not been analyzed in L. donovani. To test ARG function in intact parasites, we generated Δarg null mutants in L. donovani and evaluated their ability to proliferate in vitro and trigger infections in mice. The Δarg knockout was incapable of growth in the absence of polyamine supplementation, but the auxotrophic phenotype could be bypassed by addition of either millimolar concentrations of ornithine or micromolar concentrations of putrescine or by complementation with either glycosomal or cytosolic versions of ARG. Spermidine supplementation of the medium did not circumvent the polyamine auxotrophy of the Δarg line. Although ARG was found to be essential for ornithine and polyamine synthesis, ornithine decarboxylase appeared to be the rate-limiting enzyme for polyamine production. Mouse infectivity studies revealed that the Δarg lesion reduced parasite burdens in livers by an order of magnitude but had little impact on the numbers of parasites recovered from spleens. Thus, ARG is essential for proliferation of promastigotes but not intracellular amastigotes. Coupled with previous studies, these data support a model in which L. donovani amastigotes readily salvage ornithine and have some access to host spermidine pools, while host putrescine appears to be unavailable for salvage by the parasite. © 2016 Askarian et al. © 2016 American Society for Microbiology. All Rights Reserved.


Marriage and parenthood are associated with weight gain and residential mobility. Little is known about how obesity-relevant environmental contexts differ according to family structure. We estimated trajectories of neighborhood poverty, population density, and density of fast food restaurants, supermarkets, and commercial and public physical activity facilities for adults from a biracial cohort (CARDIA, n=4,174, aged 25-50) over 13 years (1992-93 through 2005-06) using latent growth curve analysis. We estimated associations of marriage, parenthood, and race with the observed neighborhood trajectories. Married participants tended to live in neighborhoods with lower poverty, population density, and availability of all types of food and physical activity amenities. Parenthood was similarly but less consistently related to neighborhood characteristics. Marriage and parenthood were more strongly related to neighborhood trajectories in whites (versus blacks), who, in prior studies, exhibit weaker associations between neighborhood characteristics and health. Greater understanding of how interactive family and neighborhood environments contribute to healthy living is needed.


Introduction Low-income populations have elevated exposure to early life risk factors for obesity, but are understudied in longitudinal research. Our objective was to assess the utility of a cohort derived from electronic health record data from safety net clinics for investigation of obesity emerging in early life. Methods We examined data from the PCORNet ADVANCE Clinical Data Research Network, a national network of Federally-Qualified Health Centers serving >1.7 million safety net patients across the US. This cohort includes patients who, in 2012-2014, had >/=1 valid body mass index measure when they were 0-5 years of age. We characterized the cohort with respect to factors required for early life obesity research in vulnerable subgroups: sociodemographic diversity, weight status based on World Health Organization (<2
Br ∫ Bramhall, N. F., Konrad ∫ auna, J., Baraliakos, X., Deodhar, A., Baeten, D., Sieper, J., Emery, P., . . . Richards, H. B. (2016). Effect of secukinumab mean change in mSASSS from baseline to week 104 was 0.30±2.53. Serious adverse events were reported in respectively. Among patients with evaluable X response rates at week 104 were 73.7% and 68.0% in the intravenous 150 mg and intravenous 75 mg groups, respectiv

Spine Score (mSASSS). Results 97 (77.6%) and 103 (83.1%) patients in the intravenous 150 mg and 104. Radiographic changes at week 104 were assessed using the modified Stoke Ankylosing Spondylitis Assessment of SpondyloArthritis international Society 20 (ASAS20 res

MEASURE 1 study. Objective To evaluate the effect of secukinumab, an interleukin-17A inhibitor, on clinical signs and symptoms and radiographic changes through 2 years in patients with ankylosing spondylitis (AS). Methods In the phase III MEASURE 1 study, patients were randomised to receive intravenous secukinumab 10 mg/kg (at baseline, week 2 and week 4) followed by subcutaneous secukinumab 150 mg (intravenous 150 mg; n=125) or 75 mg (intravenous 75 mg; n=124) every four weeks, or matched placebo (n=122). Placebotreated patients were re-randomised to subcutaneous secukinumab 150 or 75 mg from week 16. Clinical efficacy assessments included Assessment of SpondyloArthritis international Society 20 (ASAS20) response rates through week 104. Radiographic changes at week 104 were assessed using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Results 97 (77.6%) and 103 (83.1%) patients in the intravenous 150 mg and intravenous 75 mg groups, respectively, completed week 104. In the full analysis set (intent-to-treat), ASAS20 response rates at week 104 were 73.7% and 68.0% in the intravenous 150 mg and intravenous 75 mg groups, respectively. Among patients with evaluable X-rays who were originally randomised to secukinumab (n=168), mean change in mSASSS from baseline to week 104 was 0.30±2.53. Serious adverse events were reported in
12.2% and 13.4% of patients in the 150 mg and 75 mg groups, respectively. Conclusions Secukinumab improved AS signs and symptoms through 2 years of therapy, with no unexpected safety findings. Data from this study suggest a low mean progression of spinal radiographic changes, which will need to be confirmed in longer-term controlled studies. © 2016 BMJ Publishing Group Ltd & European League Against Rheumatism.


PROBLEM: To better prepare graduating medical students to transition to the professional responsibilities of residency, 10 medical schools are participating in an Association of American Medical Colleges pilot to evaluate the feasibility of explicitly teaching and assessing 13 Core Entrustable Professional Activities for Entering Residency. The authors focused on operationalizing the concept of entrustment as part of this process. APPROACH: Starting in 2014, the Entrustment Concept Group, with representatives from each of the pilot schools, guided the development of the structures and processes necessary for formal entrustment decisions associated with students’ increased responsibilities at the start of residency. OUTCOMES: Guiding principles developed by the group recommend that formal, summative entrustment decisions in undergraduate medical education be made by a trained group, be based on longitudinal performance assessments from multiple assessors, and incorporate day-to-day entrustment judgments by workplace supervisors. Key to entrustment decisions is evidence that students know their limits (discernment), can be relied on to follow through (conscientiousness), and are forthcoming despite potential personal costs (truthfulness), in addition to having the requisite knowledge and skills. The group constructed a developmental framework for discernment, conscientiousness, and truthfulness to pilot a model for transparent entrustment decision making. NEXT STEPS: The pilot schools are studying a number of questions regarding the pathways to and decisions about entrustment. This work seeks to inform meaningful culture change in undergraduate medical education through a shared understanding of the assessment of trust and a shared trust in that assessment. © 2017 by the Association of American Medical Colleges

Since 1992, the Speech Recognition in Noise Test, or SPRINT, has been the standard speech-in-noise test for assessing auditory fitness-for-duty of US Army Soldiers with hearing loss. The original SPRINT test consisted of 200 monosyllabic words presented at a Signal-to-Noise Ratio (SNR) of +9 dB in the presence of a six-talker babble noise. Normative data for the test was collected on 319 hearing impaired Soldiers, and a procedure for making recommendations about the disposition of military personnel on the basis of their SPRINT score and their years of experience was developed and implemented as part of US Army policy. In 2013, a new 100-word version of the test was developed that eliminated words that were either too easy or too hard to make meaningful distinctions among hearing impaired listeners. This paper describes the development of the original 200-word SPRINT test, along with a description of the procedure used to reduce the 200-word test to 100 words and the results of a validation study conducted to evaluate how well the shortened 100-word test is able to capture the results from the full 200-word version of the SPRINT.


Previously, we demonstrated the ability of the normal mammary microenvironment (niche) to direct non-mammary cells including testicular and embryonic stem cells (ESCs) to adopt a mammary epithelial cell (MEC) fate. These studies relied upon the interaction of transplanted normal MECs with non-mammary cells within the mammary fat-pads of recipient mice that had their endogenous epithelium removed. Here, we tested whether acellular mammary extracellular matrix (mECM) preparations are sufficient to direct differentiation of testicular-derived cells and ESCs to form functional mammary epithelial trees in vivo. We found that mECMs isolated from adult mice and rats were sufficient to redirect testicular derived cells to produce normal mammary epithelial trees within epithelial divested mouse mammary fat-pads. Conversely, ECMs isolated from omental fat and lung did not redirect testicular cells to a MEC fate, indicating the necessity of tissue specific components of the mECM. mECM preparations also completely inhibited teratoma formation from ESC inoculations. Further, a phenotypically normal ductal outgrowth resulted from a single inoculation of ESCs and mECM. To the best of our knowledge, this is the first demonstration of a tissue specific ECM driving differentiation of cells to form a functional tissue in vivo.


BACKGROUND: Advanced prostate cancer is a phenotypically diverse disease that evolves through multiple clinical courses. PSA level is the most widely used parameter for disease monitoring, but it has well-recognized limitations. Unlike in clinical trials, in practice, clinicians may rely on PSA monitoring alone to determine disease status on therapy. This approach has not been adequately tested. METHODS: Chemotherapy-naïve asymptomatic or mildly symptomatic men (n=872) with metastatic castration-resistant prostate cancer (mCRPC) who were treated with the androgen receptor inhibitor enzalutamide in the PREVAIL study were analyzed post hoc for rising versus nonrising PSA (empirically defined as >1.05 vs 1.05 times the PSA level from 3 months earlier) at the time of radiographic progression. Clinical characteristics and disease outcomes were compared between the rising and nonrising PSA groups. RESULTS: Of 265 PREVAIL patients with radiographic progression and evaluable PSA levels on the enzalutamide arm, nearly one-quarter had a nonrising PSA. Median progression-free survival in this cohort was 8.3 months versus 11.1 months in the rising PSA cohort (hazard ratio 1.68; 95% confidence interval 1.26-2.23); overall survival was similar between the two groups, although less than half of patients in either group were still at risk at 24 months. Baseline clinical characteristics of the two groups were similar. CONCLUSIONS: Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients treated with enzalutamide. As restaging in advanced prostate cancer patients is often guided by increases in PSA levels, our results demonstrate that disease progression on enzalutamide can occur without rising PSA levels. Therefore, a disease monitoring strategy that includes imaging not entirely reliant on serial serum PSA measurement may
more accurately identify disease progression. Prostate Cancer and Prostatic Diseases advance online publication, 24 January 2017; doi:10.1038/pcan.2016.71.


The neurotoxic effects of methamphetamine (MA) exposure in the developing and adult brain can lead to behavioral alterations and cognitive deficits in adults. Previous increases in the rates of adolescent MA use necessitate that we understand the behavioral and cognitive effects of MA exposure during adolescence on the adolescent brain. Adolescents using MA exhibit high rates of nicotine (NIC) use, but the effects of concurrent MA and NIC in the adolescent brain have not been examined, and it is unknown if NIC mediates any of the effects of MA in the adolescent. In this study, the long-term effects of a neurotoxic dose of MA with or without NIC exposure during early adolescence (postnatal day 30-31) were examined later in adolescence (postnatal day 41-50) in male C57BL/6J mice. Effects on behavioral performance in the open field, Porsolt forced swim test, and conditioned place preference test, and cognitive performance in the novel object recognition test and Morris water maze were assessed. Additionally, the effects of MA and/or NIC on levels of microtubule-associated-2 (MAP-2) protein in the nucleus accumbens and plasma corticosterone were examined. MA and NIC exposure during early adolescence separately decreased anxiety-like behavior in the open field test, which was not seen following co-administration of MA/NIC. There was no significant effect of early adolescent MA and/or NIC exposure on the intensity of MAP-2 immunoreactivity in the nucleus accumbens or on plasma corticosterone levels. These results show that early adolescent MA and NIC exposure separately decrease anxiety-like behavior in the open field, and that concurrent MA and NIC exposure does not induce the same behavioral change as either drug alone.


Physiological dependence and associated withdrawal episodes are thought to constitute a motivational force sustaining alcohol use/abuse and contributing to relapse in alcoholics. Although no animal model exactly duplicates alcoholism, models for specific factors, including the withdrawal syndrome, are useful for identifying potential genetic and neural determinants of liability in humans. We previously identified highly significant quantitative trait loci (QTLs) with large effects on predisposition to withdrawal after chronic and acute alcohol exposure in mice and mapped these loci to the same region of chromosome 1 (Alcp1 and Alcw1, respectively). The present studies utilize a novel Alcp1/Alcw1 congenic model (in which an interval spanning Alcp1 and Alcw1 from the C57BL/6J donor strain [build GRCm38 150.3–174.6 Mb] has been introgressed onto a uniform inbred DBA/2J genetic background) known to demonstrate significantly less severe chronic and acute withdrawal compared to appropriate background strain animals. Here, using c-Fos induction as a high-resolution marker of neuronal activation, we report that male Alcp1/Alcw1 congenic animals demonstrate significantly less alcohol withdrawal-associated neural activation compared to appropriate background strain animals in the prelimbic and cingulate cortices of the prefrontal cortex as well as discrete regions of the extended amygdala (i.e., basolateral) and extended basal ganglia (i.e., dorsolateral striatum, and caudal substantia nigra pars reticulata). These studies are the first to begin to elucidate circuitry by which this confirmed addiction-relevant QTL could influence behavior. This circuitry overlaps limbic circuitry involved in stress, providing additional mechanistic information. Alcp1/Alcw1 maps to a region syntenic with human chromosome 1q, where multiple studies find significant associations with risk for alcoholism. © 2016


This individual patient data meta-analysis aimed to evaluate the effects of exercise on quality of life (QoL) and physical function (PF) in patients with cancer, and to identify moderator effects of demographic (age,
sex, marital status, education), clinical (body mass index, cancer type, presence of metastasis), intervention-related (intervention timing, delivery mode and duration, and type of control group), and exercise-related (exercise frequency, intensity, type, time) characteristics. Relevant published and unpublished studies were identified in September 2012 via PubMed, EMBASE, PsycINFO, and CINAHL, reference checking and personal communications. Principle investigators of all 69 eligible trials were requested to share IPD from their study. IPD from 34 randomised controlled trials (n=4519 patients) that evaluated the effects of exercise compared to a usual care, wait-list or attention control group on QoL and PF in adult patients with cancer were retrieved and pooled. Linear mixed-effect models were used to evaluate the effects of the exercise on post-intervention outcome values (z-score) adjusting for baseline values. Moderator effects were studies by testing interactions. Exercise significantly improved QoL (beta=0.15, 95%CI=0.10;0.20) and PF (beta=0.18, 95%CI=0.13;0.23). The effects were not moderated by demographic, clinical or exercise characteristics. Effects on QoL (betadifference_in_effect=0.13, 95%CI=0.03;0.22) and PF (betadifference_in_effect=0.10, 95%CI=0.01;0.20) were significantly larger for supervised than unsupervised interventions. In conclusion, exercise, and particularly supervised exercise, effectively improves QoL and PF in patients with cancer with different demographic and clinical characteristics during and following treatment. Although effect sizes are small, there is consistent empirical evidence to support implementation of exercise as part of cancer care.


The metabolic roles of carnitine have been greatly clarified over the past 50 years, and it is now well established that carnitine is a key player in mitochondrial generation of energy and metabolism of acetyl coenzyme A. A therapeutic role for carnitine in treatment of nutritional deficiencies in infants and children was first demonstrated in 1958, and since that time it has been used to treat a number of inborn errors of metabolism. Carnitine was approved by the US Food and Drug Administration in 1985 for treatment of 'primary carnitine deficiency', and later in 1992 for treatment of 'secondary carnitine deficiency', a definition that included the majority of relevant metabolic disorders associated with low or abnormal plasma carnitine levels. Today, carnitine treatment of inborn errors of metabolism is a safe and integral part of many treatment protocols, and a growing interest in carnitine has resulted in greater recognition of many causes of carnitine depletion. Notwithstanding, there is still a lack of data from randomized clinical trials, even on the use of carnitine in inborn errors of metabolism, although ethical issues may be a contributing factor in this regard. © 2016 S. Karger AG, Basel.


A Measurement Tool to Assess Systematic Reviews (AMSTAR) is a commonly used tool to assess the quality of systematic reviews; however, modifications are needed to improve its usability, reliability, and validity. In this commentary, we summarize our experience and the experiences of others who have used AMSTAR and provide suggestions for its improvement. We propose that AMSTAR should modify a number of individual items and their instructions and responses to make them more congruent with an assessment of the methodologic quality of systematic reviews. We recommend adding new items and modifying existing items to assess the quality of the body of evidence and to address subgroup and sensitivity analyses. More detailed instructions are needed for scoring individual items across multiple reviewers, and we recommend that a total score should not be calculated. These suggestions need to be empirically tested prior to implementation.


Objectives: This study analyzed patient-provider dialogue regarding anti-retroviral therapy (ART) initiation, assessing the degree to which shared decision making (SDM) occurred. Methods: We analyzed 24 audio-recorded dialogues between 14 HIV providers and their patients regarding ART initiation. We coded transcribed dialogues for seven SDM elements. We stratified dialogues into three levels of decision complexity (basic, intermediate, complex) based on patient CD4 counts and evaluated SDM criteria fulfillment at each level of decision complexity. Results: There were five basic, twelve intermediate, and seven complex decisions in our sample. While only two met the defined criteria for SDM, the mean number of SDM elements present increased with each level of decision complexity. Discussion of the clinical issue requiring the decision occurred most frequently (88%), while discussion of pros/cons (13%), patient’s understanding (21%), and decision alternatives (29%) occurred least frequently. Conclusion/Practice implications: While few dialogues met the defined SDM criteria, providers are having conversations that respond to decision complexity. Clinicians should be aware that discussion of pros/cons, alternatives, and uncertainties are frequently skipped, even when these elements are clearly relevant, as in complex decisions. In addition, rhetorical questions to assess patient preferences and understanding are insufficient to fully engage patients in SDM. © 2016.


**PURPOSE:** Proper fluoroscopic education and protocols may reduce the patient radiation dose but few prospective studies in urology have been performed. Using optically stimulated luminescent dosimeters we tested whether fluoroscopy time and/or entrance skin dose would decrease after educational and radiation reduction protocols. **MATERIALS AND METHODS:** At default manufacturer settings fluoroscopy time and entrance skin dose were prospectively measured using optically stimulated luminescent dosimeters in patients undergoing ureteroscopy, retrograde pyelogram/stent or percutaneous nephrolithotomy with access for stone disease. A validated radiation safety competency test was administered to urology faculty and residents before and after web based, hands-on fluoroscopy training. Default fluoroscopy settings were changed from continuous to intermittent pulse rate and from standard to half-dose output. Fluoroscopy time and entrance skin dose were then measured again. **RESULTS:** The cohorts of 44 pre-protocol and 50 post-protocol patients with stones were similarly matched. The change in mean fluoroscopy time and entrance skin dose from pre-protocol to post-protocol was -0.6 minutes and -11.6 mGy (33%) for percutaneous nephrolithotomy (p = 0.62 and <0.001), 0.5 minutes and -0.1 mGy (34%) for ureteroscopy (p = 0.42 and 0.31), and 0.1 minute and -0.1 mGy (29%) for retrograde pyelogram/stent (p = 0.85 and 0.49, respectively). Urologist post-training test scores increased 30% from pretraining scores (p = 0.1). **CONCLUSIONS:** Radiation safety training protocols improved clinical knowledge but did not significantly alter fluoroscopy time. Changing equipment default settings to intermittent pulse rate (12 frames per second) and half-dose lowered the entrance skin dose by 30% across all endourology patients but most significantly during percutaneous nephrolithotomy. To limit patient radiation exposure fluoroscopy default settings should be decreased before all endourology procedures and image equipment manufacturers should consider lowering standard default renal settings.


Part 3 of this 4-part continuing medical education series reviews several important infectious complications of corticosteroid use, including a focus on pneumocystis pneumonia (PCP) prophylaxis, tuberculosis, viral hepatitis, and other infections, followed by a discussion of vaccination recommendations in immunosuppressed patients.

PURPOSE: This policy study analyzed states’ residential care and assisted living (RC/AL) regulations for dementia care requirements. Estimates suggest that at least half of RC/AL residents have dementia, and 22% of settings provide or specialize in dementia care. Residents with dementia might benefit from regulations that account for specific behaviors and needs associated with dementia, making states’ RC/AL regulations address dementia care an important policy topic. DESIGN AND METHODS: This study examined RC/AL regulations in all 50 states and the District of Columbia for regulatory requirements on five topics important to the quality of life of RC/AL residents with dementia: pre-admission assessment, consumer disclosure, staffing types and levels, administrator training, and physical environment. RESULTS: Sixteen states license or certify dementia care units within RC/AL settings. All states had at least one dementia care requirement, though only four states had requirements for all five of the topics reviewed. Most states addressed administrator training, consumer disclosure, and physical environment, 17 addressed staffing types and levels, and 14 addressed pre-admission assessment for dementia. Thus, most states rely on general RC/AL regulations to cover dementia care policies and practices. IMPLICATIONS: This policy study provides a resource for researchers who do cross-state studies of dementia care in RC/AL settings and state policymakers who are updating RC/AL regulations, including those responding to a 2014 Centers for Medicare and Medicaid Services rule change.


BACKGROUND AND OBJECTIVES: Evolutions in care delivery toward the patient-centered medical home have influenced important aspects of care continuity. Primary responsibility for a panel of continuity patients is a foundational requirement in family medicine residencies. In this paper we characterize challenges in measuring continuity of care in residency training in this new era of primary care. METHODS: We synthesized the literature and analyzed information from key informant interviews and group discussions with residency faculty and staff to identify the challenges and possible solutions for measuring continuity of care during family medicine training. We specifically focused on measuring interpersonal continuity at the patient level, resident level, and health care team level. RESULTS: Challenges identified in accurately measuring interpersonal continuity of care during residency training include: (1) variability in empanelment approaches for all patients, (2) scheduling complexity in different types of visits, (3) variability in ability to attain continuity counts at the level of the resident, and (4) shifting make-up of health care teams, especially in residency training. Possible solutions for each challenge are presented. Philosophical issues related to continuity are discussed, including whether true continuity can be achieved during residency training and whether qualitative rather than quantitative measures of continuity are better suited to residencies. CONCLUSIONS: Measuring continuity of care in residency training is challenging but possible, though improvements in precision and assessment of the comprehensive nature of the relationships are needed. Definitions of continuity during training and the role continuity measurement plays in residency need further study.


Background: Implementation science (IS) is the study of methods that successfully integrate best evidence into practice. Although typically applied in healthcare settings to improve patient care and subsequent outcomes, IS also has immediate and practical applications to medical education toward improving physician training and educational outcomes. The objective of this article is to illustrate how to build a research agenda that focuses on applying IS principles in medical education. Approach: We examined the literature to construct a rationale for using IS to improve medical education. We then used a generalizable scenario to step through a process for applying IS to improve team-based care. Perspectives: IS provides a valuable
approach to medical educators and researchers for making improvements in medical education and overcoming institution-based challenges. It encourages medical educators to systematically build upon the research outcomes of others to guide decision-making while evaluating the successes of best practices in individual environments and generate additional research questions and findings. Conclusions: IS can act as both a driver and a model for educational research to ensure that best educational practices are easier and faster to implement widely. © 2016 Patricia A. Carney et al.


Subdivision-based image registration has previously been applied to co-localize digital information extracted from rigid structures in biological specimens, such as the brain. Here, we describe and demonstrate the creation and application of a two-dimensional subdivision-based atlas representing a dynamic structure: the outflow tract of the developing chicken heart. The atlas is designed to segment three different anatomical layers of the outflow tract, and is demonstrated on the characterization of collagen XIV in both control and induced abnormal flow specimens. Abnormal blood flow in the embryonic developing heart can lead to congenital heart disease. Comparing local cellular and sub-cellular changes that are caused by abnormal flow can assist in understanding the molecular pathways involved in maladaptations of the heart and congenital defects. This study demonstrates the approach and potential for more extensive applications of the subdivision-based atlas for the embryonic chicken heart. © 2016 IEEE.


Anemia is among the most common medical problems and clinical and laboratory evaluation need to be approached logically. The complete blood count with red cell indices offers clues to diagnosis. Many anemias have characteristic red cell morphology. The reticulocyte count serves as a useful screen for hemolysis or blood loss. Testing for specific causes of the anemia is performed. Occasionally, examination of the bone marrow is required for diagnosis. Molecular testing is increasingly being used to aid the diagnostic process. This article reviews diagnostic tests for anemia and suggests a rational approach to determining the etiology of a patient’s anemia. © 2016 Elsevier Inc.


Oxidative stress plays a role in UV-induced melanoma, which may arise from melanocytic nevi. We investigated whether oral administration of the antioxidant N-acetylcysteine (NAC) could protect nevi from oxidative stress in vivo in the setting of acute UV exposure. The minimal erythemal dose (MED) was determined for 100 patients at increased risk for melanoma. Patients were randomized to receive a single dose (1,200 mg) of NAC or placebo, in double-blind fashion, and then one nevus was irradiated (1–2 MED) using a solar simulator. One day later, the MED was redetermined and the irradiated nevus and a control unirradiated nevus were removed for histologic analysis and examination of biomarkers of NAC metabolism and UV-induced oxidative stress. Increased expression of 8-oxoguanine, thioredoxin reductase-1, and g-glutamylcysteine synthase modifier subunit were consistently seen in UV-treated compared with unirradiated nevi. However, no significant differences were observed in these UV-induced changes or in the pre- and postintervention MED between those patients receiving NAC versus placebo. Similarly, no significant differences were observed in UV-induced changes between subjects with germline wild-type versus loss-of-function mutations in the melanocortin-1 receptor. Nevi showed similar changes of UV-induced oxidative stress in an open-label post-trial study in 10 patients who received NAC 3 hours before nevus irradiation. Thus, a single oral dose of NAC did not effectively protect nevi from UV-induced oxidative stress under the conditions examined. © 2017 American Association for Cancer Research.

The p53 tumor suppressor protein plays a critical role in orchestrating the genomic response to various stress signals by acting as a master transcriptional regulator. Differential gene activity is controlled by transcription factors but also dependent on the underlying chromatin structure, especially on covalent histone modifications. After screening different histone lysine methyltransferases and demethylases, we identified JMJD2B/KDM4B as a p53-inducible gene in response to DNA damage. p53 directly regulates JMJD2B gene expression by binding to a canonical p53-consensus motif in the JMJD2B promoter. JMJD2B induction attenuates the transcription of key p53 transcriptional targets including p21, PIG3 and PUMA, and this modulation is dependent on the catalytic capacity of JMJD2B. Conversely, JMJD2B silencing led to an enhancement of the DNA-damage driven induction of p21 and PIG3. These findings indicate that JMJD2B acts in an auto-regulatory loop by which p53, through JMJD2B activation, is able to influence its own transcriptional program. Functionally, exogenous expression of JMJD2B enhanced subcutaneous tumor growth of colon cancer cells in a p53-dependent manner, and genetic inhibition of JMJD2B impaired tumor growth in vivo. These studies provide new insights into the regulatory effect exerted by JMJD2B on tumor growth through the modulation of p53 target genes.


UNLABELLED: Human cytomegalovirus (HCMV), a beta-herpesvirus, persists indefinitely in the human host through poorly understood mechanisms. The UL136 gene is carried within a genetic locus important to HCMV latency termed the UL133/8 locus, which also carries UL133, UL135, and UL138. Previously, we demonstrated that UL136 is expressed as five protein isoforms ranging from 33-kDa to 19-kDa, arising from alternative transcription and, likely, translation initiation mechanisms. We previously showed that the UL136 isoforms are largely dispensable for virus infection in fibroblasts, a model for productive virus replication. In our current work, UL136 has emerged as a complex regulator of HCMV infection in multiple contexts of infection relevant to HCMV persistence: in an endothelial cell (EC) model of chronic infection, in a CD34(+) hematopoietic progenitor cell (HPC) model of latency, and in an in vivo NOD-scid IL2Rgamma (null) humanized (huNSG) mouse model for latency. The 33- and 26-kDa isoforms promote replication, while the 23- and 19-kDa isoforms suppress replication in ECs, in CD34(+) HPCs, and in huNSG mice. The role of the 25-kDa isoform is context dependent and influences the activity of the other isoforms. These isoforms localize throughout the secretory pathway, and loss of the 33- and 26-kDa UL136 isoforms results in virus maturation defects in ECs. This work reveals an intriguing functional interplay between protein isoforms that impacts virus replication, latency, and dissemination, contributing to the overall role of the UL133/8 locus in HCMV infection. IMPORTANCE: The persistence of DNA viruses, and particularly of herpesviruses, remains an enigma because we have not completely defined the viral and host factors important to persistence. Human cytomegalovirus, a herpesvirus, persists in the absence of disease in immunocompetent individuals but poses a serious disease threat to transplant patients and the developing fetus. There is no vaccine, and current therapies do not target latent reservoirs. In an effort to define the viral factors important to persistence, we have studied viral genes with no known viral replication function in contexts important to HCMV persistence. Using models relevant to viral persistence, we demonstrate opposing roles of protein isoforms encoded by the UL136 gene in regulating latent and replicative states of infection. Our findings reveal an intriguing interplay between UL136 protein isoforms and define UL136 as an important regulator of HCMV persistence.
Diabetes care: "Taking it to the limit one more time". *Diabetes Care, 40*(1), 3-6. doi:10.2337/dc16-2326


Alcohol use disorders encompass a range of drinking levels and behaviors, including low, binge and heavy drinking. In this regard, investigating the neural state of individuals who chronically self-administer lower doses of alcohol may provide insight into mechanisms that prevent the escalation of alcohol use. DNA methylation is one of the epigenetic mechanisms that stabilizes adaptations in gene expression and has been associated with alcohol use. Thus, we investigated DNA methylation, gene expression and the predicted neural effects in the nucleus accumbens core (NAcc) of male rhesus macaques categorized as low or binge drinkers, compared to alcohol-naïve and heavy drinkers based on drinking patterns during a 12 month alcohol self-administration protocol. Using genome-wide CpG-rich region enrichment and bisulfite sequencing, the methylation levels of 2.6 million CpGs were compared between alcohol naïve (AN), low/binge (L/BD) and heavy/very heavy (H/VHD) drinking subjects (n = 24). Through regional clustering analysis, we identified nine significant differential methylation regions (DMRs) that specifically distinguished ANs and L/BDs, and then compared those DMRs among H/VHDs. The DMRs mapped to genes encoding ion channels, receptors, cell adhesion molecules and cAMP, NF-κβ and Wnt signaling pathway proteins. Two of the DMRs, linked to . PDE10A and . PKD2L2, were also differentially methylated in H/VHDs, suggesting an alcohol-dose independent effect. However two other DMRs, linked to the . CCBE1 and . FZD5 genes, had L/BD methylation levels that significantly differed from both ANs and H/VHDs. The remaining 5 DMRs also differentiated L/BDs and ANs, however H/VHDs methylation levels were not distinguishable from either of the two groups. Functional validation of two DMRs, linked to . FZD5 and . PDE10A, support their role in regulating gene expression and exon usage, respectively. In summary, the findings demonstrate that L/BD is associated with unique DNA methylation signatures in the primate NAcc, and identifies synaptic genes that may play a role in preventing the escalation of alcohol use. © 2016.


Alterations in DNA methylation have been associated with alcohol exposure and proposed to contribute to continued alcohol use; however, the molecular mechanisms involved remain obscure. We investigated the escalating effects of alcohol use on DNA methylation, gene expression and predicted neural effects in the nucleus accumbens of rhesus macaques that self-administered 4% alcohol for over 12 months. Using an exploratory approach to identify CpG-rich regions, followed by bisulfite sequencing, the methylation levels of 2.7 million CpGs were compared between seven low-binge drinkers and nine heavy-very heavy drinking subjects. We identified 17 significant differential methylation regions (DMRs), including 14 with methylation levels that were correlated with average daily alcohol consumption. The size of the DMRs ranged from 29 to 158 bp (mean=63.7), included 4-19 CpGs per DMR (mean=8.06) and spanned a range of average methylation values from 5 to 34%. Eight of the DMRs mapped to genes implicated in modulating synaptic plasticity. Six of the synaptic genes have not previously been linked to alcohol use. Validation studies of these eight DMRs using bisulfite amplicon sequencing and an expanded set of 30 subjects confirmed the significant alcohol-dose-associated methylation of the DMRs. Expression analysis of three of the DMR-associated genes, LRP5, GPR39 and JAKMIP1, revealed significant correlations between DMR methylation and whole-gene or alternative transcript expression, supporting a functional role in regulating gene expression. Together, these studies suggest that alcohol-associated synaptic remodeling may be regulated and coordinated at the level of DNA methylation.

The role of the monoamines dopamine (DA) and serotonin (5HT) and the monoamine-metabolizing enzyme monoamine oxidase A (MAOA) have been repeatedly implicated in studies of alcohol use and dependence. Genetic investigations of MAOA have yielded conflicting associations between a common polymorphism (MAOA-LPR) and risk for alcohol abuse. The present study provides direct comparison of tissue-specific MAOA expression and the level of alcohol consumption. We analyzed rhesus macaque MAOA (rhMAOA) expression in blood from males before and after 12 months of alcohol self-administration. In addition, nucleus accumbens core (NAC core) and cerebrospinal fluid (CSF) were collected from alcohol access and control (no alcohol access) subjects at the 12-month time point for comparison. The rhMAOA expression level in the blood of alcohol-naive subjects was negatively correlated with subsequent alcohol consumption level. The mRNA expression was independent of rhMAOA-LPR genotype and global promoter methylation. After 12 months of alcohol use, blood rhMAOA expression had decreased in an alcohol dose-dependent manner. Also after 12 months, rhMAOA expression in the NAC core was significantly lower in the heavy drinkers, as compared with control subjects. The CSF measured higher levels of DA and lower DOPAC/DA ratios among the heavy drinkers at the same time point. These results provide novel evidence that blood MAOA expression predicts alcohol consumption and that heavy alcohol use is linked to low MAOA expression in both the blood and NAC core. Together, the findings suggest a mechanistic link between dampened MAOA expression, elevated DA and alcohol abuse.

Chang, Y. H., Thibault, G., Azimi, V., Johnson, B., Jorgens, D., Link, J., . . . Gray, J. W. (2016). Quantitative analysis of histological tissue image based on cyto logical profiles and spatial statistics. Paper presented at the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2016. The cellular heterogeneity and complex tissue architecture of most tumor samples is a major obstacle in image analysis on standard hematoxylin and eosin-stained (H&E) tissue sections. A mixture of cancer and normal cells complicates the interpretation of their cytological profiles. Furthermore, spatial arrangement and architectural organization of cells are generally not reflected in cellular characteristics analysis. To address these challenges, first we describe an automatic nuclei segmentation of H&E tissue sections. In the task of deconvoluting cellular heterogeneity, we adopt Landmark based Spectral Clustering (LSC) to group individual nuclei in such a way that nuclei in the same group are more similar. We next devise spatial statistics for analyzing spatial arrangement and organization, which are not detectable by individual cellular characteristics. Our quantitative, spatial statistics analysis could benefit H&E section analysis by refining and complementing cellular characteristics analysis. © 2016 IEEE.


Background Patients with bladder cancer undergoing radical cystectomy (RC) experience high rates of perioperative blood transfusions (PBTs) and morbidity. The aim of this study was to evaluate the effect of blood storage duration on the risk of adverse perioperative outcomes in this high-risk patient population. Materials and methods In a retrospective review of RC patients from 2010 to 2014 who received PBTs, the average storage duration for all units transfused was used to classify patients as receiving older blood using 3 different definitions (≥21 days, ≥28 days, and ≥35 days). Multivariable Poisson regression models were used to determine the adjusted relative risk of perioperative infections and overall morbidity in those given older blood compared to fresher blood. Results Of the 451 patients undergoing RC, 205 (45%) received nonirradiated PBTs. In multivariable modeling, increasing average blood storage duration, as a continuous variable, was associated with an increased risk of infections (risk ratio [RR] = 1.08 per day, 95% CI: 1.01–1.17) and overall morbidity (RR = 1.08 per day, 95% CI: 1.01–1.15). Furthermore, ≥28-day blood storage (vs. <28) was associated with increased infections (RR = 2.69, 95% CI: 1.18–6.14) and morbidity (RR = 2.54, 95% CI: 1.31–4.95), and ≥35-day blood storage (vs. <35) was also associated with increased infections (RR = 2.83, 95% CI: 1.42–5.66) and morbidity (RR = 3.35, 95% CI: 1.95–5.77). Conclusions Although blood is stored up to
42 days, storage≥28 days may expose RC patients to increased perioperative infections and overall morbidity compared with storage<28 days. Prospective cohort studies are warranted in cystectomy and other high-risk surgical oncology patients to better determine the effect of blood storage duration. © 2017 Elsevier Inc.


INTRODUCTION: Gunshot wounds to the head are more common in military settings. Recently, a damage control (DC) approach for the management of these lesions has been used in combat areas. The aim of this study was to evaluate the results of civilian patients with penetrating gunshot wounds to the head, managed with a strategy of early cranial decompression (ECD) as a DC procedure in a university hospital with few resources for intensive care unit (ICU) neuro-monitoring in Colombia. MATERIALS AND METHODS: Fifty-four patients were operated according to the DC strategy (<12 h after injury), over a 4-year period. Variables were analysed and results were evaluated according to the Glasgow Outcome Scale (GOS) at 12 months post injury; a dichotomous variable was established as 'favourable' (GOS 4-5) or 'unfavourable' (GOS 1-3). A univariate analysis was performed using a chi(2) test. RESULTS: Forty (74.1%) of the patients survived and 36 (90%) of them had favourable GOS. Factors associated with adverse outcomes were: Injury Severity Score (ISS) greater than 25, bi-hemispheric involvement, intra-cerebral haematoma on the first CT, closed basal cisterns and non-reactive pupils in the emergency room. CONCLUSION: DC for neurotrauma with ECD is an option to improve survival and favourable neurological outcomes 12 months after injury in patients with penetrating traumatic brain injury treated in a university hospital with few resources for ICU neuro-monitoring.


PURPOSE: Oscillatory dynamics in acute hypoxia have been observed, but poorly understood. They have mostly been attributed to vascular perturbations, but no link has yet been made to metabolic causes. We set out to determine the fundamental frequencies and test for coherence in tumor oxygen dynamics and spatial properties. METHODS: Severe combined immunodeficient (SCID) mice were inoculated onto bilateral flanks with human derived head and neck carcinoma (UW-SCC22) cell line xenografts. Oxygen dynamics were monitored in the tumor every minute for an hour using three modalities: blood oxygen level dependent magnetic resonance imaging (BOLD-MRI), hemoglobin oxygen saturation photoacoustic, and locally manufactured optical probes for spectral fitting. A statistical test was used to separate fluctuating from non-fluctuating voxels and pixels in BOLD-MRI and photoacoustic data respectively. The power spectrum density (PSD) and the autocorrelation functions were calculated for the time series of each voxel, pixel and region, of the BOLD-MRI, photoacoustic or fiber optic data respectively. RESULTS: Using all three techniques, intermittent oxygen dynamics with both coherent and incoherent signatures was observed in the tumors. Upon averaging the PSDs of fluctuating voxels and pixels, it was found that these oscillations occurred with periods of minutes to tens of minutes from all three approaches. Observations from the BOLD-MRI and photoacoustic data showed that clusters of voxels oscillated in a synchronized manner. CONCLUSION: We were able to use three different modalities to show that fluctuation in tumor oxygen is both coherent and incoherent, with periods of minutes to tens of minutes. These periods are very similar to those from the well-established metabolic, non-linear biomechanical phenomenon called the glycolytic oscillator. This may provide an additional explanation to the cause of cyclic hypoxia. Such dynamics could have profound implications in hypofractionated radiotherapy regiments and could help guide treatment and make it more patient specific. The authors would like to thank the University of Wisconsin Carbone Cancer Center (UWCCC) for the funds to complete this project. This work is also supported in part by NIH/NCI P30 CA014520- UW Comprehensive Cancer Center Support*.
Despite the immunosuppressive treatment, the destruction of the retinal photoreceptors progressed, and it was supported by positive Western blots for 23-kDa proteins and by immunohistochemical staining of human retinal bipolar and ganglion cells. Despite the immunosuppressive treatment, the destruction of the retinal photoreceptors progressed, and


Multi-parent populations (MPPs) capture and maintain the genetic diversity from multiple inbred founder strains to provide a resource for high-resolution genetic mapping through the accumulation of recombination events over many generations. Breeding designs that maintain a large effective population size with randomized assignment of breeders at each generation can minimize the impact of selection, inbreeding, and genetic drift on allele frequencies. Small deviations from expected allele frequencies will have little effect on the power and precision of genetic analysis, but a major distortion could result in reduced power and loss of important functional alleles. We detected strong transmission ratio distortion in the Diversity Outbred (DO) mouse population on chromosome 2, caused by meiotic drive favoring transmission of the WSB/EiJ allele at the R2d2 locus. The distorted region harbors thousands of polymorphisms derived from the seven non-WSB founder strains and many of these would be lost if the sweep was allowed to continue. To ensure the utility of the DO population to study genetic variation on chromosome 2, we performed an artificial selection against WSB/EiJ alleles at the R2d2 locus.Here, we report that we have purged the WSB/EiJ allele from the drive locus while preserving WSB/EiJ alleles in the flanking regions. We observed minimal disruption to allele frequencies across the rest of the autosomal genome. However, there was a shift in haplotype frequencies of the mitochondrial genome and an increase in the rate of an unusual sex chromosome aneuploidy. The DO population has been restored to genome-wide utility for genetic analysis, but our experience underscores that vigilant monitoring of similar genetic resource populations is needed to ensure their long-term utility. © 2016 by the Genetics Society of America.


Autoimmune retinopathy (AIR) is an immune-mediated retinopathy, resulting from an immunologic process caused by the aberrant recognition of retinal antigens as autoantigens. The diagnosis of AIR involves the detection of antiretinal antibodies with concurrent clinical and electrophysiological evidence of retinopathy. A 40-year-old patient presented with progressive loss of bilateral vision over several months. A fundus examination was unremarkable. Spectral domain optical coherence tomography revealed a blurred photoreceptor ellipsoid zone at the subfoveal region in both eyes with more prominent disruption in the left eye. Full-field electroretinography (ERG) showed relatively normal rod and cone responses in the right eye, and decreased photopic b-waves with minimal attenuation of a-waves in the left eye. Multifocal ERG demonstrated slightly reduced amplitude of the inner segment ring in the right eye and decreased amplitudes and delayed latencies of all modalities in the left eye. The patient was suspected to have AIR and it was supported by positive Western blots for 23-kDa protein, enolase (46-kDa), aldolase (40-kDa), 62-kDa and 78-kDa proteins and by immunohistochemical staining of human retinal bipolar and ganglion cells. Despite the immunosuppressive treatment, the destruction of the retinal photoreceptors progressed, and

As states increasingly liberalize marijuana laws, high-quality research is needed that will inform the public and policymakers about the health and societal impact of these laws. However, there are many challenges to studying marijuana policy, including the heterogeneity of the drug and its use, the variability in the laws and their implementation from state to state, the need to capture a wide variety of relevant outcomes, and the poorly understood influence of marijuana commercialization. Furthermore, current instruments generally fail to distinguish between types of users and lack accurate and detailed measures of use. This review provides a background on marijuana laws in the United States and an overview of existing policy research, discusses methodological considerations when planning analysis of state marijuana laws, and highlights specific topics needing further development and investigation. © 2016 The New York Academy of Sciences.


STUDY OBJECTIVE: The motor component of the Glasgow Coma Scale (mGCS) has been proposed as an easier-to-use alternative to the total GCS (tGCS) for field assessment of trauma patients by emergency medical services. We perform a systematic review and meta-analysis to compare the predictive utility of the tGCS versus the mGCS or Simplified Motor Scale in field triage of trauma for identifying patients with adverse outcomes (inhospital mortality or severe brain injury) or who underwent procedures (neurosurgical intervention or emergency intubation) indicating need for high-level trauma care. METHODS: Ovid MEDLINE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, Health and Psychosocial Instruments, and the Cochrane databases were searched through June 2016 for English-language cohort studies. We included studies that compared the area under the receiver operating characteristic curve (AUROC) of the tGCS versus the mGCS or Simplified Motor Scale assessed in the field or shortly after arrival in the emergency department for predicting the outcomes described above. Meta-analyses were performed with a random-effects model, and subgroup and sensitivity analyses were conducted. RESULTS: We included 18 head-to-head studies of predictive utility (n=1,703,388). For inhospital mortality, the tGCS was associated with slightly greater discrimination than the mGCS (pooled mean difference in [AUROC] 0.015; 95% confidence interval [CI] 0.009 to 0.022; I²=85%; 12 studies) or the Simplified Motor Scale (pooled mean difference in AUROC 0.030; 95% CI 0.024 to 0.036; I²=0%; 5 studies). The tGCS was also associated with greater discrimination than the mGCS or Simplified Motor Scale for nonmortality outcomes (differences in AUROC from 0.03 to 0.05). Findings were robust in subgroup and sensitivity analyses. CONCLUSION: The tGCS is associated with slightly greater discrimination than the mGCS or Simplified Motor Scale for identifying severe trauma. The small differences in discrimination are likely to be clinically unimportant and could be offset by factors such as convenience and ease of use.


Therapy by blocking tumor necrosis factor (TNF) activity is highly efficacious and profoundly changed the paradigm of several inflammatory diseases. However, a significant proportion of patients with inflammatory diseases do not respond to TNF inhibitors (TNFi). Prediction of therapeutic response is required for TNFi therapy. Isotope labeled anti-TNF antibodies or TNF receptor have been investigated to localize TNF production at inflammatory tissue in animal models and in patients with inflammatory diseases. The in vivo detection of TNF has been associated with treatment response. Recently, fluorophore labeled anti-TNF antibody in combination with confocal laser endomicroscopy in patients with Crohn’s disease yielded more accurate and quantitative in vivo detection of TNF in the diseased mucosa. More importantly, this method
demonstrated high therapeutic predication value. Fluorophore labeled TNF binding aptamers in combination with modern imaging technology offers additional tools for in vivo TNF probing. © 2016 Elsevier Ltd.


Background: Aesthetic facial appearance following neurosurgical ablation of frontal fossa tumors is a primary concern for patients and neurosurgeons alike. Craniofacial reconstruction procedures have drastically evolved since the development of three-dimensional computed tomography imaging and computer-assisted programming. Traditionally, two-stage approaches for resection and reconstruction were used; however, these two-stage approaches have many complications including cerebrospinal fluid leaks, necrosis, and pneumocephalus. Case Description: We present two successful cases of single-stage osteoma resection and craniofacial reconstruction in a 26-year-old female and 65-year-old male. The biopolymer implants were preselected and contoured based on imaging prior to surgery. The ideal selection of appropriate flaps for reconstruction was imperative. The flaps were well vascularized and included a pedicle for easy translocation. Using a titanium mesh biopolymer implant for reconstruction in conjunction with a forehead flap proved advantageous, and the benefits of single-stage approaches were apparent. The patients recovered quickly after the surgery with complete resection of the osteoma and good aesthetic appearance. The flap adhered to the biopolymer implant, and the cosmetic appearance years after surgery remained decent. The gap between the bone and implant was less than 2 mm. The patients are highly satisfied with the symmetrical appearance of the reconstruction. Conclusions: Advances in technology are allowing neurosurgeons unprecedented opportunities to design complex yet feasible single-stage craniofacial reconstructions that improve a patient’s quality of life by enhancing facial contours, aesthetics, and symmetry. © 2016 Surgical Neurology International.


Purpose Simulation training offers a useful opportunity to appreciate vascular anatomy and develop the technical expertise required to clip intracranial aneurysms of the posterior circulation. Materials and Methods In cadavers, a comparison was made between the endoscopic transclival approach (ETA) alone and a combined multiportal approach using the ETA and a transorbital precaruncular approach (TOPA) to evaluate degrees of freedom, angles of visualization, and ergonomics of aneurysm clip application to the posterior circulation depending on basilar apex position relative to the posterior clinoids. Results ETA alone provided improved access to the posterior circulation when the basilar apex was high riding compared with the posterior clinoids. ETA + TOPA provided a significantly improved functional working area for instruments and visualization of the posterior circulation for a midlevel basilar apex. A single-shaft clip applier provided improved visualization and space for instruments. Proximal and distal vascular control and feasibility of aneurysmal clipping were demonstrated. Conclusions TOPA is a medial orbital approach to the central skull base; a transorbital neuroendoscopic surgery approach. This anatomical simulation provides surgical teams an alternative to the ETA approach alone to address posterior circulation aneurysms, and a means to preoperatively prepare for intraoperative anatomical and surgical instrumentation challenges. Copyright © 2016, Georg Thieme Verlag KG. All rights reserved.

An individual is typically considered an adult at age 18, although the age of adulthood varies for different legal and social policies. A key question is how cognitive capacities relevant to these policies change with development. The current study used an emotional go/no-go paradigm and functional neuroimaging to assess cognitive control under sustained states of negative and positive arousal in a community sample of one hundred ten 13- to 25-year-olds from New York City and Los Angeles. The results showed diminished cognitive performance under brief and prolonged negative emotional arousal in 18- to 21-year-olds relative to adults over 21. This reduction in performance was paralleled by decreased activity in fronto-parietal circuitry, implicated in cognitive control, and increased sustained activity in the ventromedial prefrontal cortex, involved in emotional processes. The findings suggest a developmental shift in cognitive capacity in


Objective Endoscopic surgical treatment of pituitary tumors, lateral invading tumors, or aneurysms requires surgeons to operate adjacent to the cavernous sinus. During these endoscopic endonasal procedures, the carotid artery is vulnerable to surgical injury at its genu. The objective of this simulation model was to evaluate trainees regarding management of a potentially life-threatening vascular injury. Methods Cadaveric heads were prepared in accordance with the Oregon Health & Science University body donation program. An endoscopic endonasal approach was used, and a perfusion pump with a catheter was placed in the ipsilateral common carotid artery at its origin in the neck. Learners used a muscle graft to establish vascular control and were evaluated over 3 training sessions. Simulation assessment, blood loss during sessions, and performance metric data were collected for learners. Results Vascular control was obtained at a mean arterial pressure of 65 mm Hg using a muscle graft correctly positioned at the arteriotomy site. Learners improved over the course of training, with senior residents (n = 4) performing better across all simulation categories (situation awareness, decision making, communications and teamwork, and leadership); the largest mean difference was in communication and teamwork. Additionally, learner performance concerning blood loss improved between sessions (t = 3.667, P < 0.01). Conclusions In this pilot endoscopic endonasal simulation study, we successfully demonstrate a vascular complication perfusion model. Learners were able to gain direct applicable expertise in endoscopic endonasal techniques, instrumentation use, and teamwork required to optimize the technique. Learners gained skills of vascular complication management that transcend this model. © 2016 Elsevier Inc.
emotional situations that coincides with dynamic changes in prefrontal circuitry. These findings may inform age-related social policies.


Previous studies on changes in murine brain gene expression associated with the selection for ethanol preference have used F2 intercross or heterogeneous stock (HS) founders, derived from standard laboratory strains. However, these populations represent only a small proportion of the genetic variance available in Mus musculus. To investigate a wider range of genetic diversity, we selected mice for ethanol preference using a HS derived from the eight strains of the Collaborative Cross. These heterogeneous stock mice were selectively bred (four generations) for High and Low ethanol preference. The nucleus accumbens shell of naive S4 mice was interrogated using RNA-Seq. Gene networks were constructed using the weighted gene coexpression network analysis assessing both coexpression and cosplicing. Selection targeted one of the network coexpression modules (greenyellow) that was significantly enriched in genes associated with receptor signaling activity including ChRNA7, Grin2a, Htr2a, and Oprd1. Connectivity in the module as measured by changes in the hub nodes was significantly reduced in the Low preference line. Of particular interest was the observation that selection had marked effects on a large number of cell adhesion molecules, including cadherins and protocadherins. In addition the coexpression data revealed that selection had marked effects on long non-coding RNA hub nodes. Analysis of the cosplicing network data revealed a significant effect of selection on a large cluster of RasGTPase binding genes including Cdkl5, Cyfip1, Ndrg1, Sod1, and Stxbp5. These data in part support the earlier observation of Mulligan et al. (2006) that preference is linked to Ras/Mapk pathways.


Study objective Prior research has indicated that children with developmental delay (DD) experience qualitative and quantitative differences in health care (Boulet et al., 2009). In the perioperative setting, there is concern that children with DD may be more likely to experience postoperative complications including agitation and nausea/vomiting than typically developing patients (TDP). Differences in the administration and dosage of perioperative opioids may contribute to this, however, empirical investigations are lacking. The purpose of this research was to compare the experience of postoperative nausea/vomiting and agitation, as well as to examine perioperative opioid administration, among children with DD as compared to TDP. Design Retrospective original research. Setting Operating room, postanesthesia care unit. Patients 1145 patients (1–20.9 years, ASA I-III, 23.9% with a history of DD) who had undergone outpatient dental surgery involving extraction/restorations under general anesthesia. Measurements Data was obtained and analyzed from the medical records of both DD and TDP across a five-year period. Data included the experience of agitation, nausea/vomiting, as well as perioperative medication administration. Main results Postoperative agitation and nausea/vomiting did not differ significantly between the DD and TDP groups. Children with DD were significantly less likely to receive opioids during both the intra and postoperative period ($\chi^2 = 10.02, p = 0.001$ and $\chi^2 = 8.08, p = 0.003$, respectively). Further, higher dosage of intraoperative opioids was predictive of reduced administration of postoperative opioids among TDP; however, no significant association was observed between the dosage of intraoperative opioids and administration of postoperative opioids in the DD group. Conclusions Children with DD experience similar rates of postoperative complications including nausea/vomiting and agitation as TDP. DD children were less likely to receive both intra and postoperative opioids than TDP. Importantly, while the dosage of intraoperative opioids was predictive of administration of postoperative opioids in the TDP group, this was not the case for the DD group. Clinical implications are discussed. © 2016
OBJECTIVE: Parkinson’s disease (PD) presents clinically with several motor subtypes that exhibit variable treatment response and prognosis. Here, we investigated genetic variants for their potential association with PD motor phenotype and progression. METHODS: We screened 10 SNPs, previously associated with PD risk, for association with tremor-dominant (TD) versus postural-instability gait disorder (PIGD) motor subtypes. SNPs that correlated with the TD/PIGD ratio in a discovery cohort of 251 PD patients were then evaluated in a multi-site replication cohort of 559 PD patients. SNPs associated with motor phenotype in both cross-sectional cohorts were next evaluated for association with (1) rates of motor progression in a longitudinal subgroup of 230 PD patients and (2) brain alpha-synuclein (SNCA) expression in the GTEx (Genotype-Tissue Expression project) consortium database. RESULTS: Genotype at rs356182, near SNCA, correlated with the TD/PIGD ratio in both the discovery (Bonferroni-corrected P = 0.04) and replication cohorts (P = 0.02). The rs356182 GG genotype was associated with a more tremor-dominant phenotype and predicted a slower rate of motor progression (1-point difference in annual rate of UPDRS-III motor score change, P = 0.01). The rs356182 genotype was associated with SNCA expression in the cerebellum (P = 0.005). INTERPRETATION: Our study demonstrates that the GG genotype at rs356182 provides molecular definition for a clinically important endophenotype associated with (1) more tremor-dominant motor phenomenology, (2) slower rates of motor progression, and (3) decreased brain expression of SNCA. Such molecularly defined endophenotyping in PD may benefit both clinical trial design and tailoring of clinical care as we enter the era of precision medicine.


BACKGROUND: Challenges of recruiting participants into pragmatic trials, particularly at the level of the health system, remain largely unexplored. As part of Strategies and Opportunities to STOP Colon Cancer in Priority Populations (STOP CRC), we recruited eight separate community health centers (consisting of 26 individual safety net clinics) into a large comparative effectiveness pragmatic study to evaluate methods of raising the rates of colorectal cancer screening. METHODS: In partnership with STOP CRC’s advisory board, we defined criteria to identify eligible health centers and applied these criteria to a list of health centers in Washington, Oregon, and California affiliated with Oregon Community Health Information Network, a 16-state practice-based research network of federally sponsored health centers. Project staff contacted centers that met eligibility criteria and arranged in-person meetings of key study investigators with health center leadership teams. We used the Consolidated Framework for Implementation Research to thematically analyze the content of discussions during these meetings to identify major facilitators of and barriers to health center participation. RESULTS: From an initial list of 41 health centers, 11 met the initial inclusion criteria. Of these, leaders at three centers declined and at eight centers (26 clinic sites) agreed to participate (73%). Participating and nonparticipating health centers were similar with respect to clinic size, percent Hispanic patients, and percent uninsured patients. Participating health centers had higher proportions of Medicaid patients and higher baseline colorectal cancer screening rates. Common facilitators of participation were perception by center leadership that the project was an opportunity to increase colorectal cancer screening rates and to use electronic health record tools for population management. Barriers to participation were concerns of center leaders about ability to provide fecal testing to and assure follow-up of uninsured patients, limited clinic capacity to prepare mailings required by the study protocol, discomfort with randomization, and concerns about delaying program implementation at some clinics due to the research requirements. CONCLUSION: Our findings address an important research gap and may inform future efforts to recruit community health centers into pragmatic research.

Importance: Mechanical thrombectomy (MT) improves clinical outcomes in patients with acute ischemic stroke (AIS) caused by a large vessel occlusion. However, it is not known whether intravenous thrombolysis (IVT) is of added benefit in patients undergoing MT. Objective: To examine whether treatment with IVT before MT with a stent retriever is beneficial in patients undergoing MT. Design, Setting, and Participants: This post hoc analysis used data from 291 patients treated with MT included in 2 large, multicenter, prospective clinical trials that evaluated MT for AIS (Solitaire With the Intention for Thrombectomy performed from January 1, 2010, through December 31, 2011, and Solitaire Flow Restoration Thrombectomy for Acute Revascularization from January 1, 2010, through December 31, 2012). An independent core laboratory scored the radiologic outcomes in each trial. Interventions: Patients were treated with IVT with tissue plasminogen activator followed by MT (IVT and MT group) with the use of a stent retriever or MT with a stent retriever alone (MT group). Main Outcomes and Measures: Successful reperfusion, functional independence (modified Rankin Scale score of 0-2) and mortality at 90 days, symptomatic intracranial hemorrhage, emboli to new territory, and vasospasm were compared. Results: Of 291 patients included in the analysis, 160 (55.0%) underwent IVT and MT (mean [SD] age, 67 [13] years; 97 female [60.6%]), and 131 (45.0%) underwent MT alone (mean [SD] age, 69 [12] years; 71 [55.7%] female). Median Alberta Stroke Program Early CT Score at baseline was lower in the IVT and MT group (8 vs 9, P = .04). There was no statistically significant difference in the duration from symptom onset to groin puncture (254 minutes for the IVT and MT group vs 262 minutes for the MT group, P = .10). The number of passes, rate of successful reperfusion, functional independence at 90 days, mortality at 90 days, and emboli to new territory were also similar among groups. Symptomatic intracranial hemorrhage (1% vs 4%) and parenchymal hemorrhages type 1 (1% vs 3%) or type 2 (1% vs 2%) did not differ significantly (P = .25). Vasospasm occurred more often in patients who received IVT and MT vs MT alone (27% vs 14%, P = .006). In multivariate analysis, no statistically significant association was observed between IVT and MT vs MT alone for any of the outcomes. Conclusions and Relevance: The results indicate that treatment of patients experiencing AIS due to a large vessel occlusion with IVT before MT does not appear to provide a clinical benefit over MT alone. A randomized clinical trial seems warranted. Trial Registration: clinicaltrials.gov Identifiers: NCT01054560 and NCT01327989.


**BACKGROUND:** Protein kinase C epsilon (PKCepsilon) is emerging as a potential target for the development of pharmacotherapies to treat alcohol use disorders, yet little is known regarding how a history of a highly prevalent form of drinking, binge alcohol intake, influences enzyme priming or the functional relevance of kinase activity for excessive alcohol intake. **METHODS:** Immunoblotting was employed on tissue from subregions of the nucleus accumbens (NAc) and the amygdala to examine both idiopathic and binge drinking-induced changes in constitutive PKCepsilon priming. The functional relevance of PKCepsilon translocation for binge drinking and determination of potential upstream signaling pathways involved were investigated using neuropharmacologic approaches within the context of two distinct binge drinking procedures, drinking in the dark and scheduled high alcohol consumption. **RESULTS:** Binge alcohol drinking elevated p(Ser729)-PKCepsilon levels in both the NAc and the central nucleus of the amygdala (CeA). Moreover, immunoblotting studies of selectively bred and transgenic mouse lines revealed a positive correlation between the propensity to binge drink alcohol and constitutive p(Ser729)-PKCepsilon levels in the NAc and CeA. Finally, neuropharmacologic inhibition of PKCepsilon translocation within both regions reduced binge alcohol consumption in a manner requiring intact group 1 metabotropic glutamate receptors, Homer2, phospholipase C, and/or phosphotidylinositol-3 kinase function. **CONCLUSIONS:** Taken together, these data indicate that PKCepsilon signaling in both the NAc and CeA is a major contributor to binge alcohol drinking and to the genetic propensity to consume excessive amounts of alcohol.

Millions of archived formalin-fixed, paraffin-embedded (FFPE) specimens contain valuable molecular insight into healthy and diseased states persevered in their native ultrastructure. To diagnose and treat diseases in tissue on the nanoscopic scale, pathology traditionally employs electron microscopy (EM), but this platform has significant limitations including cost and painstaking sample preparation. The invention of single molecule localization microscopy (SMLM) optically overcame the diffraction limit of light to resolve fluorescently labeled molecules on the nanoscale, leading to many exciting biological discoveries. However, applications of SMLM in preserved tissues has been limited. Through adaptation of the immunofluorescence workflow on FFPE sections milled at histological thickness, cellular architecture can now be visualized on the nanoscale using SMLM including individual mitochondria, undulations in the nuclear lamina, and the HER2 receptor on membrane protrusions in human breast cancer specimens. Using astigmatism imaging, these structures can also be resolved in three dimensions to a depth of ~800 nm. These results demonstrate the utility of SMLM in efficiently uncovering ultrastructural information of archived clinical samples, which may offer molecular insights into the physiopathology of tissues to assist in disease diagnosis and treatment using conventional sample preparation methods.


The mammalian distal convoluted tubule (DCT) makes an important contribution to potassium homeostasis by modulating NaCl transport. The thiazide-sensitive Na+/Cl- cotransporter (NCC) is activated by low potassium intake and by hypokalemia. Coupled with suppression of aldosterone secretion, activation of NCC helps to retain potassium by increasing electroneutral NaCl reabsorption, therefore reducing Na+/K+ exchange. Yet the mechanisms by which DCT cells sense plasma potassium concentration and transmit the information to the apical membrane are not clear. Here, we tested the hypothesis that the potassium channel Kir4.1 is the potassium sensor of DCT cells. We generated mice in which Kir4.1 could be deleted in the kidney after the mice are fully developed. Deletion of Kir4.1 in these mice led to moderate salt wasting, low BP, and profound potassium wasting. Basolateral membranes of DCT cells were depolarized, nearly devoid of conductive potassium transport, and unresponsive to plasma potassium concentration. Although renal WNK4 abundance increased after Kir4.1 deletion, NCC abundance and function decreased, suggesting that membrane depolarization uncouples WNK kinases from NCC. Together, these results indicate that Kir4.1 mediates potassium sensing by DCT cells and couples this signal to apical transport processes.


Purpose There is only one prior report associating mutations in BEST1 with a diagnosis of retinitis pigmentosa (RP). The imaging studies presented in that report were more atypical of RP and shared features of autosomal recessive bestrophinopathy and autosomal dominant vitreoretinaldophopathoy. Here, we present a patient with a clinical phenotype consistent with classic features of RP. Observations The patient in this report was diagnosed with simplex RP based on clinically-evident bone spicules with characteristic ERG and EOG findings. The patient had associated massive cystoid macular edema which resolved following a short course of oral acetazolamide. Genetic testing revealed that the patient carries a novel heterozygous deletion mutation in BEST1 which is not carried by either parent. While this suggests BEST1 is causative, the patient also inherited heterozygous copies of several mutations in other genes known to cause recessive retinal degenerative disease. Conclusions and Importance How some mutations in BEST1 associate with peripheral retinal degeneration phenotypes, while others manifest as macular degeneration phenotypes is currently unknown. We speculate that RP due to BEST1 mutation requires mutations in other modifier genes.

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Exosomes are small extracellular vesicles (EVs) secreted by many cell types in both normal and pathogenic circumstances. Because EVs, particularly exosomes, are known to transfer biologically active proteins, RNAs and lipids between cells, they have recently become the focus of intense interest as potential mediators of cell-cell communication, particularly in long-range and juxtacrine signaling events associated with adaptive immune function and progression of cancer. Among the EVs, exosomes appear particularly adapted for long-range delivery of cargoes between cells. Because of their association with disease states, the exciting potential for exosomes to serve as diagnostic biomarkers and as target-specific biomolecule delivery vehicles has stimulated a broad range of biomedical investigations to learn how exosomes are generated, what their cargoes are, and how they might be tailored for uptake by remote targets. Addressing these questions requires experimental models in which biochemically useful amounts of material can be harvested, gene expression easily manipulated, and interpretable biological assays developed. The early Xenopus embryo fulfills these model-system ideals in an in vivo context: during morphogenesis the embryo develops several large, fluid-filled extracellular compartments across which numerous tissue-specifying signals must cross, and which are abundantly endowed with exosomes and other EVs. Importantly, certain surface-facing tissues avidly ingest EVs during gastrulation. Recent work has demonstrated that EVs can be isolated from these interstitial spaces in amounts suitable for proteomic and transcriptomic analysis. With its large numbers, great cell size, well-understood fate map, and tolerance of a variety of experimental approaches, the Xenopus embryo provides a unique opportunity to both understand and manipulate the basic cell biology of exosomal trafficking in the context of an intact organism.


OBJECTIVE: The Institute of Medicine and the draft National Pain Strategy recently called for better training for health care clinicians. This was the first high-level needs assessment for pain psychology services and resources in the United States. DESIGN: Prospective, observational, cross-sectional. METHODS: Brief surveys were administered online to six stakeholder groups (psychologists/therapists, individuals with chronic pain, pain physicians, primary care physicians/physician assistants, nurse practitioners, and the directors of graduate and postgraduate psychology training programs). RESULTS: 1,991 responses were received. Results revealed low confidence and low perceived competency to address physical pain among psychologists/therapists, and high levels of interest and need for pain education. We found broad support for pain psychology across stakeholder groups, and global support for a national initiative to increase pain training and competency in U.S. therapists. Among directors of graduate and postgraduate psychology training programs, we found unanimous interest for a no-cost pain psychology curriculum that could be integrated into existing programs. Primary barriers to pain psychology include lack of a system to identify qualified therapists, paucity of therapists with pain training, limited awareness of the psychological treatment modality, and poor insurance coverage. CONCLUSIONS: This report calls for transformation within psychology predoctoral and postdoctoral education and training and psychology continuing education to include and emphasize pain and pain management. A system for certification is needed to facilitate quality control and appropriate reimbursement. There is a need for systems to facilitate identification and access to practicing psychologists and therapists skilled in the treatment of pain.


BACKGROUND: Little is known about the relationship between disability and mode of delivery. Prior research has indicated elevated risk of cesarean delivery among women with certain disabilities, but has not examined patterns across multiple types of disability or by parity. OBJECTIVE: This study sought to determine whether physical, sensory, or intellectual and developmental disabilities are independently associated with primary cesarean delivery. METHODS: We conducted a retrospective cohort study of all deliveries in California from 2000 to 2010 using linked birth certificate and hospital discharge data. We identified physical, sensory, and intellectual and developmental disabilities using International Classification of Diseases, 9th revision, clinical modification codes. We used logistic regression to examine the association of these disabilities and primary
cesarean delivery, controlling for sociodemographic characteristics and comorbidities, and stratified by parity. RESULTS: In our sample, 0.45% of deliveries (20,894/4,610,955) were to women with disabilities. A greater proportion of women with disabilities were nulliparous, had public insurance, and had comorbidities (e.g., gestational diabetes) compared with women without disabilities (p < .001 for all). The proportion of primary cesarean in women with disabilities was twice that in women without disabilities (32.7% vs. 16.3%; p < .001; adjusted odds ratio, 2.05; 95% confidence interval, 1.94-2.17). The proportion of deliveries by cesarean was highest among women with physical disabilities due to injuries compared with women without disabilities (57.8% vs. 16.3%; p < .001; adjusted odds ratio, 6.83; 95% confidence interval, 5.46-8.53).

CONCLUSIONS: Women across disability subgroups have higher odds of cesarean delivery, and there is heterogeneity by disability type. More attention is needed to this population to ensure better understanding of care practices that may impact maternal and perinatal outcomes.


BACKGROUND: The Romhilt-Estes point score system (RE) is an established ECG criterion for diagnosing left ventricular hypertrophy (LVH). In this study, we assessed for the first time, whether RE and its components are predictive of sudden cardiac arrest (SCA) independent of left ventricular (LV) mass. METHODS: Sudden cardiac arrest (SCA) cases occurring between 2002 and 2014 in a Northwestern US metro region (catchment area approx. 1 million) were compared to geographic controls. ECGs and echocardiograms performed prior to the SCA and those of controls were acquired from the medical records and evaluated for the ECG criteria established in the RE score and for LV mass. RESULTS: Two hundred forty-seven SCA cases (age 68.3 +/- 14.6, male 64.4%) and 330 controls (age 67.4 +/- 11.5, male 63.6) were included in the analysis. RE scores were greater in cases than controls (2.5 +/- 2.1 vs. 1.9 +/- 1.7, p < .001), and SCA cases were more likely to meet definite LVH criteria (18.6% vs. 7.9%, p < .001). In a multivariable model including echocardiographic LVH and LV function, definite LVH remained independently predictive of SCA (OR 2.04, 95% CI 1.16-3.59, p = .013). The model was replicated with the individual ECG criteria, and only SV1.2 >/= 30 mm and delayed intrinsicoid deflection remained significant predictors of SCA. CONCLUSION: Left ventricular hypertrophy (LVH) as defined by the RE point score system is associated with SCA independent of echocardiographic LVH and reduced LV ejection fraction. These findings support an independent role for purely electrical LVH, in the genesis of lethal ventricular arrhythmias.


Many processes lead to anemia. This review covers anemias that are less commonly encountered in the United States. These anemias include hemoglobin defects like thalassemia, bone marrow failure syndromes like aplastic anemia and pure red cell aplasia, and hemolytic processes such as paroxysmal nocturnal hemoglobinuria. The pathogenesis, diagnostic workup, and treatment of these rare anemias are reviewed. © 2016 Elsevier Inc.


Purpose: The zonule of Zinn (ciliary zonule) is a system of fibers that centers the crystalline lens on the optical axis of the eye. Mutations in zonule components underlie syndromic conditions associated with a broad range of ocular pathologies, including microspherophakia and ectopia lentis. Here, we used HPLC-mass spectrometry to determine the molecular composition of the zonule. Methods: Tryptic digests of human and bovine zonular samples were analyzed by HPLC-mass spectrometry. The distribution of selected components was confirmed by immunofluorescence confocal microscopy. In bovine samples, the composition of the equatorial zonule was compared to that of the hyaloid zonule and vitreous humor. Results: The 52 proteins common to the zonules of both species accounted for >95% of the zonular protein. Glycoproteins constituted the main structural components, with two proteins, FBN1 and LTBP2, constituting

Despite this study’s limitations, it presents a viable basis for future human studies looking at the efficacy of topical treatments for jellyfish stings.


Objective: To evaluate the influence of phenyl-propanedione on yellowing and chemical-mechanical properties of experimental resin-based materials photoactivated using different light curing units (LCUs).

Material and Methods: Experimental resin-based materials with the same organic matrix (60:40 wt% BisGMA:TEGDMA) were mechanically blended using a centrifugal mixing device. To this blend, different photoinitiator systems were added in equimolar concentrations with aliphatic amine doubled by wt%: 0.4 wt% CQ; 0.38 wt% PPD; or 0.2 wt% CQ and 0.19 wt% PPD. The degree of conversion (DC), flexural strength (FS), Young’s modulus (YM), Knoop hardness (KNH), crosslinking density (CLD), and yellowing (Y) were evaluated (n=10). All samples were light cured with the following LCUs: A halogen lamp (XL 2500), a monowave LED (Radii), or a polywave LED (Valo) with 16 J/cm2. The results were analysed by two-way ANOVA and Tukey’s test (a=0.05). Results: No statistical differences were found between the different photoinitiator systems to KNH, FS, FS, and YM properties (p≥0.05). PPD/CQ association showed the higher DC values compared with CQ and PPD isolated systems when photoactivated by a polywave LED (P≤0.05). Y values were highest for the CQ compared with the PPD systems (p≤0.05). Conclusion: PPD isolated system promoted similar chemical and mechanical properties and less yellowing compared with the CQ isolated system, regardless of the LCU used. © 2016, Faculdade de Odontologia de Bauru. All rights reserved.


OBJECTIVES: This study sought to create a model for testing topical treatment of jellyfish stings. It sought to determine which treatments 1) stimulate/inhibit nematocyst discharge; 2) decrease pain; and 3) decrease skin inflammation; it also sought to discover whether there is a clinical correlation between stimulated nematocyst discharge observed in vitro to the pain and erythema experienced by humans stung by a particular species of jellyfish, C chinensis. METHODS: Chrysaora chinensis stung 96 human subjects, who were then treated with isopropyl alcohol, hot water, acetic acid, papain meat tenderizer, lidocaine, or sodium bicarbonate. Pain and erythema were measured. In a separate experiment, nematocysts were examined microscopically after exposure to the same topical treatments used in the human experiment. RESULTS: Forearms treated with papain showed decreased mean pain over the first 30 minutes after being stung, relative to placebo, although only by a small amount. The other topical treatments tested did not reach statistical significance. Sodium bicarbonate may reduce erythema after 30 minutes of treatment; sodium bicarbonate and papain may reduce erythema at 60 minutes. The other topical treatments tested did not reach statistical significance. Nematocyst discharge in vitro occurred when tentacles of C chinensis were exposed to acetic acid or isopropyl alcohol. Sodium bicarbonate, papain, heated water, and lidocaine did not induce nematocyst discharge. CONCLUSIONS: Papain-containing meat tenderizer used as a topical treatment for C chinensis stings may decrease pain. Although there is published experimental support for the concept that in vitro nematocyst discharge correlates with in vivo human pain perception, no definitive randomized controlled trial, including ours, has yet provided incontrovertible evidence of this assertion. Despite this study’s limitations, it presents a viable basis for future human studies looking at the efficacy of topical treatments for jellyfish stings.

Background: Individualized education is emerging as an innovative model for physician training. This requires faculty coaching to guide learners' achievements in academic performance, competency development, and career progression. In addition, coaching can foster self-reflection and self-monitoring using a data-guided approach to support lifelong learning. Context: Coaching differs from mentoring or advising, and its application in medical education is novel. Because of this, definitions of the concept and the constructs of coaching as applied to medical education are needed to accurately assess the coaching relationship and coaching processes. These can then be linked to learner outcomes to inform how coaching serves as a modifier of academic and competency achievement and career satisfaction. Innovation: We developed definitions and constructs for academic coaching in medical education based on review of existing education and non-education coaching literature. These constructs focus on 1) establishing relationship principles, 2) conducting learner assessments, 3) developing and implementing an action plan, and 4) assessing results and revising plans accordingly. Implication: Coaching is emerging as an important construct in the context of medical education. This article lays the vital groundwork needed for evaluation of coaching programs aimed at producing outstanding physicians. © 2016 Nicole M. Deiorio et al.


Cytomegalovirus (CMV) elicits long-term T-cell immunity of unparalleled strength, which has allowed the development of highly protective CMV-based vaccine vectors. Counterintuitively, experimental vaccines encoding a single MHC-I restricted epitope offered better immune protection than those expressing entire proteins, including the same epitope. To clarify this conundrum, we generated recombinant murine CMVs (MCMVs) encoding well-characterized MHC-I epitopes at different positions within viral genes and observed strong immune responses and protection against viruses and tumor growth when the epitopes were expressed at the protein C-terminus. We used the M45-encoded conventional epitope HGIRNASFI to dissect this phenomenon at the molecular level. A recombinant MCMV expressing HGIRNASFI on the C-terminus of M45, in contrast to wild-type MCMV, enabled peptide processing by the constitutive proteasome, direct antigen presentation, and an inflation of antigen-specific effector memory cells. Consequently, our results indicate that constitutive proteasome processing of antigenic epitopes in latently infected cells is required for robust inflationary responses. This insight allows utilizing the epitope positioning in the design of CMV-based vectors as a novel strategy for enhancing their efficacy. © 2016 Dekhtiarenko et al.


Iron deficiency is one of the most common causes of anemia. The 2 main etiologies of iron deficiency are blood loss due to menstrual periods and blood loss due to gastrointestinal bleeding. Beyond anemia, lack of iron has protean manifestations, including fatigue, hair loss, and restless legs. The most efficient test for the diagnosis of iron deficiency is the serum ferritin. Iron replacement can be done orally, or in patients in whom oral iron is not effective or contraindicated, with intravenous iron. © 2016 Elsevier Inc.


BACKGROUND: Adult congenital heart disease (ACHD) patients with moderate or great defect complexity are at risk for premature death. Although early engagement in advance care planning (ACP) is recommended, previous research suggests that it seldom occurs. METHODS: This study investigated ACHD patient preferences for ACP and factors that impact preferences. ACHD patients completed an ACP preferences questionnaire, the Hospital Anxiety and Depression Scale and a measure of attachment styles. RESULTS: Of 152 ACHD patients (median age 33 years, 50% female), 13% reported previous ACP discussions
with providers and 21% had completed advance directives. On a 0-10 scale, the median rating for the importance of discussing ACP with providers was 7; 18 years was identified as the most appropriate age to initiate this dialogue. Higher ratings for the importance of discussing ACP with providers was observed in patients who were female (p=0.03), had lower disease complexity (p=0.03), and had elevated anxiety symptoms (p=0.001); elevated anxiety remained significant in a multivariable model. Interest in receiving information about life expectancy (61% overall) was greater among patients with lower disease complexity (p=0.04) and a history of >/=2 cardiac surgeries (p=0.01); disease complexity remained significant in a multivariable model. CONCLUSIONS: As a group, ACHD patients value the opportunity for ACP discussions and prefer earlier communication. Although some clinicians might avoid ACP discussions in patients who are generally more anxious or have less complex CHD, such avoidance does not appear to be warranted.


Curiosity, the tendency to engage in novel and challenging opportunities, may be an important source of resilience for those at risk for suicide. We hypothesized that curiosity would have a buffering effect against risk conferred by multiple sources of distress, whereby curiosity would be associated with reduced suicidal ideation and increased coping efficacy. As part of a larger intervention trial designed to improve coping skills and reduce suicidal ideation, 117 military veterans with suicidal ideation completed measures of curiosity and distress (perceived stress, depression, anxiety, and sleep disturbances) at baseline, and completed measures of suicidal ideation and coping efficacy (to stop negative thoughts, to enlist support from friends and family) at baseline and 3-, 6-, and 12-week follow up. Growth curve models showed that curiosity moderated the association between distress and suicidal ideation at baseline and that curiosity moderated the association between distress and increased coping efficacy to stop negative thoughts over time. Findings suggest that curiosity may buffer against the effect of heightened levels of distress on suicidal ideation and help facilitate stronger gains in coping efficacy over time. Additional work should further examine the role of curiosity as a protective factor for veterans with suicidal ideation.


Background: The Cell Ontology (CL) is an OBO Foundry candidate ontology covering the domain of canonical, natural biological cell types. Since its inception in 2005, the CL has undergone multiple rounds of revision and expansion, most notably in its representation of hematopoietic cells. For in vivo cells, the CL focuses on vertebrates but provides general classes that can be used for other metazoans, which can be subtyped in species-specific ontologies. Construction and content: Recent work on the CL has focused on extending the representation of various cell types, and developing new modules in the CL itself, and in related ontologies in coordination with the CL. For example, the Kidney and Urinary Pathway Ontology was used as a template to populate the CL with additional cell types. In addition, subtypes of the class ‘cell in vitro’ have received improved definitions and labels to provide for modularity with the representation of cells in the Cell Line Ontology and Reagent Ontology. Recent changes in the ontology development methodology for CL include a switch from OBO to OWL for the primary encoding of the ontology, and an increasing reliance on logical definitions for improved reasoning. Utility and discussion: The CL is now mandated as a metadata standard for large functional genomics and transcriptomics projects, and is used extensively for annotation, querying, and analyses of cell type specific data in sequencing consortia such as FANTOMS and ENCODE, as well as for the NIAID ImmPort database and the Cell Image Library. The CL is also a vital component used in the modular construction of other biomedical ontologies—for example, the Gene Ontology and the cross-species anatomy ontology, Uberon, use CL to support the consistent representation
of cell types across different levels of anatomical granularity, such as tissues and organs. Conclusions: The ongoing improvements to the CL make it a valuable resource to both the OBO Foundry community and the wider scientific community, and we continue to experience increased interest in the CL both among developers and within the user community. © 2016 The Author(s).


The placement of a resorbable suture on one edge of a wound can effectively retard the mucosal closure of the defect and thereby duplicate the function of a passive surgical drain. The placement of a double or triple loop of a resorbable suture such as chromic gut on one side of the wound edge can provide an inexpensive and self-eliminating wound drain.


OBJECTIVES: Neuropathy and its associated pain pose great therapeutic challenges. While there has been a recent surge in acupuncture use and research, little remains known about its effects on nerve function. This review aims to assess the efficacy of acupuncture in the treatment of neuropathy of various etiologies.

METHODS: The Medline, AMED, Cochrane, Scopus, CINAHL, and clintrials.gov databases were systematically searched from inception to July 2015. Randomized controlled trials (RCTs) assessing acupuncture’s efficacy for poly- and mononeuropathy were reviewed. Parallel and crossover RCTs focused on acupuncture’s efficacy were reviewed and screened for eligibility. The Scale for Assessing Scientific Quality of Investigations in Complementary and Alternative Medicine was used to assess RCT quality. RCTs with score of >9 and active control treatments such as sham acupuncture or medical therapy were included.

RESULTS: Fifteen studies were included: 13 original RCTs, a long-term follow-up, and a re-analysis of a prior RCT. The selected RCTs studied acupuncture for neuropathy caused by diabetes, Bell’s palsy, carpal tunnel syndrome, human immunodeficiency virus (HIV), and idiopathic conditions. Acupuncture regimens, control conditions, and outcome measures differed among studies, and various methodological issues were identified. Still, the majority of RCTs showed benefit for acupuncture over control in the treatment of diabetic neuropathy, Bell’s palsy, and carpal tunnel syndrome. Acupuncture is probably effective in the treatment of HIV-related neuropathy, and there is insufficient evidence for its benefits in idiopathic neuropathy. Acupuncture appears to improve nerve conduction study parameters in both sensory and motor nerves. Meta-analyses were conducted on all diabetic neuropathy and Bell’s palsy individual subject data (six RCTs; a total of 680 subjects) using a summary estimate random effects model, which showed combined odds ratio of 4.23 (95% confidence interval 2.3-7.8; p < 0.001) favoring acupuncture over control for neuropathic symptoms.

CONCLUSIONS: Acupuncture is beneficial in some peripheral neuropathies, but more rigorously designed studies using sham-acupuncture control are needed to characterize its effect and optimal use better.


Background: In many developed countries, cognitive functioning (as measured by neuropsychological tests) appears to be improving over time in the population at large, in parallel with the declining age-specific incidence of dementia. Here, we investigated cohort effects in the age-associated trajectories of verbal memory function in older adults. We sought to determine whether they varied by decade of birth and, if so, whether the change would be explained by increasing educational attainment. Methods: Pooling data from two prospective US population-based studies between 1987 and 2015, we identified four birth cohorts born 1902-1911, 1912-1921, 1922-1931, and 1932-1943. Among these cohorts, we compared age-associated trajectories both of performance and of practice effects on immediate and delayed recall of a 10-item Word List. We used mixed effects models, first including birth cohorts and cohort X age interaction terms, and then controlling for education and education X age interaction. Results: We observed significant cohort effects in performance (baseline and age-associated trajectories) in both immediate recall and delayed recall, with
function improving between the earliest- and latest-born cohorts. For both tests, we also observed cohort effects on practice effects with the highest levels in the latest-born cohorts. Including education in the models did not attenuate these effects. Conclusions: In this longitudinal population study, across four decade-long birth cohorts, there were significant improvements in test performance and practice effects in verbal memory tests, not explained by education. Whether this reflects declining disease incidence or other secular trends awaits further investigation. © International Psychogeriatric Association 2016.


Importance As the problem of obesity continues to grow, more patients are choosing to undergo bariatric surgery to lose weight and treat comorbidities, such as diabetes. Of the more than 200,000 procedures performed each year, 80% are in women, many of reproductive age. Taking care of a pregnant woman who has undergone bariatric surgery requires understanding of the risks, the need for additional surveillance, and the limitations of our knowledge about how bariatric surgery affects pregnancy. Objective The aims of this study were to review the current literature on bariatric surgery and pregnancy and summarize the important evidence to help the obstetrician care for a pregnant woman after bariatric surgery. Evidence Acquisition Evidence for this review was acquired using PubMed. Conclusions Pregnancy after bariatric surgery is safe and may be associated with improved pregnancy outcomes; however, more research is needed to better understand how to manage pregnant women with a history of bariatric surgery. Relevance Obstetricians will increasingly be caring for women who have undergone bariatric surgery and subsequently become pregnant. Target Audience Obstetricians and gynecologists, family physicians. Learning Objectives After participating this activity, the learner should be better able to understand the indications for bariatric surgery and how different types of bariatric procedures change gastrointestinal physiology and nutrient metabolism; appropriately counsel patients about the risks and benefits of pregnancy after bariatric surgery; and understand the importance of monitoring nutritional status and supplementation in pregnancies after bariatric surgery. © 2016 Wolters Kluwer Health, Inc.


The inaugural Starfield Summit was hosted in April 2016 by the Robert Graham Center for Policy Studies in Family Medicine and Primary Care with additional partners and sponsors, including the Pisacano Leadership Foundation (PLF). The Summit addressed critical topics in primary care and health care delivery, including payment, measurement, and team-based care. Invited participants included an interdisciplinary group of pediatricians, family physicians, internists, behaviorists, trainees, researchers, and advocates. Among the family physicians invited were both current and past PLF (Pisacano) scholars. After the Summit, a small group of current and past Pisacano scholars formed a writing group to reflect on and summarize key lessons and conclusions from the Summit. A Summit participant’s statement, “a paradox persists when the paradigm is wrong,” became a repeated theme regarding the paradox of primary care within the context of the health care system in the United States. The Summit energized participants to renew their commitment to Dr. Starfield’s 4 C’s of Primary Care (first contact access, continuity, comprehensiveness, and care coordination) and to the Quadruple Aim (quality, value, and patient and physician satisfaction) and to continue to explore how primary care can best shape the future of the nation’s health care system.


Trauma is the leading cause of pediatric mortality and abdominal injury is a significant contributor to morbidity. The assessment of abdominal trauma in children must be conducted expeditiously and thoroughly. Physical examination, laboratory testing, and imaging are central to trauma evaluation. In children with minor injury, protocols may help to limit the use of ionizing radiation. Children with significant
abdominal injury who are unstable should be resuscitated with blood products and undergo emergent surgical intervention.


Introduction: Prior research has shown that advanced stage nonsmall cell lung cancer (NSCLC) patients enrolled in hospice care receive less aggressive treatment at the end of life (EOL) without compromising survival. Our purpose was to profile the continuum of care of these patients, exploring the connection between hospice enrollment and quality indicators for excellence in EOL cancer care. Methods: One hundred ninety-seven deceased stage IV NSCLC patients diagnosed between 2008 and 2010 at two separate tertiary care centers within the same county were identified. A retrospective review was conducted, collecting data from electronic medical records regarding antitumor treatment, postdiagnosis hospital visits and admissions, hospice referrals and enrollments, and circumstances surrounding the patient’s death. Patients were grouped by their status of hospice enrollment, and the remainder of the measures compared accordingly. Results: There was no significant difference found in total number of postdiagnosis hospital admissions between the patients who were enrolled in hospice and those who were not. However, the group who received hospice services had a significantly lower number of hospitalizations (p < 0.001), emergency department visits (p < 0.01), and intensive care unit admissions in the last 30 days of life (p < 0.001). The number of lines of chemotherapy received did not differ significantly between the groups. Median survival, measured by the length of time between diagnosis and death, was significantly longer for hospice patients (p = 0.02).

Conclusions: This study demonstrates that, among patients with metastatic NSCLC, hospice enrollment was associated with optimized EOL oncological care and a significantly longer median survival. © Copyright 2016, Mary Ann Liebert, Inc. 2016.


Background: Adolescence is a developmental period associated with increased difficulty managing diabetes. During adolescence family functioning, including miscarried helping, family conflict, and acceptance of illness, is an important predictor of adherence to treatment recommendations. Multiple barriers exist to receiving behavioral health interventions to address suboptimal adherence. We hypothesized that behavioral family systems therapy-diabetes (BFST-D) delivered via telehealth would yield changes in family functioning that were not significantly different than changes in clinic-based treatment. Furthermore, that BFST-D would significantly improve overall family functioning. Methods: Ninety adolescent participants and their parents were randomized to receive BFST-D via telehealth or traditional (Clinic) treatment conditions. Repeated measures ANOVAs were used to assess changes in mean scores across pre, post, and follow-up assessments. Mediation analyses were conducted using methods outlined by Sobel and were confirmed by bootstrapping. Results: Changes in miscarried helping, family conflict and adjustment to illness were not significantly different across groups. Overall, clinically significant improvements were identified in youth- and parent-reported miscarried helping, family conflict, and acceptance of illness. Reductions in family conflict mediated the relationship between changes in miscarried helping and acceptance of illness. In addition, improvements in family functioning were associated with changes in adherence and glycemic control. Conclusions: Results provide strong support for BFST-D (and similar interventions) delivered via telehealth as yielding outcomes no different than clinic-based treatment. In addition, further support was provided for the effectiveness of BFST-D. © 2015 Diabetes Technology Society.


INTRODUCTION: Polyneuropathy signs (Neuropathy Impairment Score, NIS), neurophysiologic tests (m+7Ionis), disability, and health scores were assessed in baseline evaluations of 100 patients entered into an oligonucleotide familial amyloidotic polyneuropathy (FAP) trial. METHODS: We assessed: 1) Proficiency of
grading neurologic signs and correlation with neurophysiologic tests, and 2) clinometric performance of mNIS+7Ionis and its subscores and correlation with disability and health scores. RESULTS: The modified Neuropathy Impairment Score + 7 neurophysiologic tests (mNIS+7Ionis) sensitively detected, characterized and broadly scaled diverse polyneuropathy impairments. Polyneuropathy signs (NIS and subscores) correlated with neurophysiology tests, disability, and health scores. Smart Somatotopic Quantitative Assessment of Heat as Pain 5 provided a needed measure of small fiber involvement not adequately assessed by other tests. DISCUSSION: Specially trained neurologists accurately assessed neuropathy signs as compared to referenced neurophysiologic tests. The score, mNIS+7Ionis, broadly detected, characterized, and scaled polyneuropathy abnormality in FAP, which correlated with disability and health scores. This article is protected by copyright. All rights reserved.


In 2002, the Physician Charter on Medical Professionalism was published to provide physicians with guidance for decision making in a rapidly changing environment. Feedback from physicians indicated that they were unable to fully live up to the principles in the 2002 charter partly because of their employing or affiliated health care organizations. A multistakeholder group has developed a Charter on Professionalism for Health Care Organizations, which may provide more guidance than charters for individual disciplines, given the current structure of health care delivery systems. This article contains the Charter on Professionalism for Health Care Organizations, as well as the process and rationale for its development. For hospitals and hospital systems to effectively care for patients, maintain a healthy workforce, and improve the health of populations, they must attend to the four domains addressed by the Charter: patient partnerships, organizational culture, community partnerships, and operations and business practices. Impacting the social determinants of health will require collaboration among health care organizations, government, and communities. Transitioning to the model hospital described by the Charter will challenge historical roles and assumptions of both its leadership and staff. While the Charter is aspirational, it also outlines specific institutional behaviors that will benefit both patients and workers. Lastly, this article considers obstacles to implementing the Charter and explores avenues to facilitate its dissemination. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.


Initiating joint attention (IJA), the behavioral instigation of coordinated focus of 2 people on an object, emerges over the first 2 years of life and supports social-communicative functioning related to the healthy development of aspects of language, empathy, and theory of mind. Deficits in IJA provide strong early indicators for autism spectrum disorder, and therapies targeting joint attention have shown tremendous promise. However, the brain systems underlying IJA in early childhood are poorly understood, due in part to significant methodological challenges in imaging localized brain function that supports social behaviors during the first 2 years of life. Herein, we show that the functional organization of the brain is intimately related to the emergence of IJA using functional connectivity magnetic resonance imaging and dimensional behavioral assessments in a large semilongitudinal cohort of infants and toddlers. In particular, though functional connections spanning the brain are involved in IJA, the strongest brain-behavior associations cluster within connections between a small subset of functional brain networks; namely between the visual network and dorsal attention network and between the visual network and posterior cingulate aspects of the default mode network. These observations mark the earliest known description of how functional brain systems underlie a burgeoning fundamental social behavior, may help improve the design of targeted therapies for neurodevelopmental disorders, and, more generally, elucidate physiological mechanisms essential to healthy social behavior development.
The newer and emerging treatments for atopic dermatitis (AD) focus on blockade of inflammatory cytokines, especially those that derive from T helper cell type 2 (TH2) and are associated with a pathway of immunoglobulin E (IgE) sensitization. Among the proinflammatory cytokines that have been identified as promising therapeutic targets are chemoattractant receptor-homologous molecule expressed on TH2 cells (CRTH2), IgE, thymic stromal lymphopoietin (TSLP), and several monoclonal antibodies that block key cytokine pathways in the innate immune response. Two agents that have been studied in phase III clinical trials are the boron-based phosphodiesterase-4 (PDE-4) inhibitor, crisaborole, and dupilumab, an antibody that inhibits the interleukin-4/IL-13 receptor alpha chain. Semin Cutan Med Surg 35(supp5):S92-S96.

To be healthy, support their families, and be productive members of their communities, women must have access to comprehensive reproductive health services including treatment of miscarriage and ectopic pregnancy and access to abortion, sterilization, and other contraceptive methods. However, in the United States, hospitals and legislative bodies are erecting barriers and limiting access to these basic health care services. These barriers are caused by factors such as hospital mergers (specifically those that are religiously affiliated); federal, state, and local legislation; hospital policies; and business-related decisions are threatening reproductive health care. Such barriers, of which women are often not even aware, put women at real risk of harm. This commentary provides clinical examples of these harms and recommends ways that obstetrician-gynecologists can get involved to publicize the consequences of these barriers and, hopefully, prevent them from occurring or break them down to promote women's health. © 2016 Elsevier Inc.

BACKGROUND: Sleep impairment is highly prevalent in patients with chronic rhinosinusitis (CRS). Although endoscopic sinus surgery (ESS) has been shown to improve overall patient-reported sleep quality, the postoperative impact on individual sleep symptoms remains unclear. METHODS: Patients with medically-recalcitrant CRS who elected to undergo ESS were prospectively enrolled into a multi-institutional, observational cohort study. Sleep-related symptom severity and treatment outcomes were assessed using the sleep domain questions within the 22-item Sino-Nasal Outcome Test (SNOT-22). RESULTS: A total of 334 participants met criteria and were followed postoperatively for an average of 14.5 +/- 4.9 months (mean +/- standard deviation [SD]). Mean SNOT-22 sleep domain scores improved from 13.7 +/- 6.8 to 7.7 +/- 6.6 (p < 0.001). Significant mean relative improvements were reported for "difficulty falling asleep" (45%; p < 0.001), "waking up at night" (40%; p < 0.001), "lack of a good night's sleep" (43%; p < 0.001), "waking up tired" (40%; p < 0.001), and "fatigue" (42%; p < 0.001) scores. A total of 66% of study participants reported postoperative improvement in "lack of a good night's sleep," "waking up tired," and "fatigue"; 62% reported improvement in "waking up at night"; and 58% reported improvement in "difficulty falling asleep." CONCLUSION: Patients with CRS report significant and sustained improvements following ESS in common sleep-related symptoms as assessed by the SNOT-22 sleep domain. Despite these significant improvements, some degree of persistent postoperative sleep impairment was reported. Further study is necessary to determine what factors are associated with continued sleep dysfunction after sinus surgery.

Hereditary tyrosinemia type 1 (HT1) is an autosomal recessive disease caused by deficiency in fumarylacetacetate hydrolase, the last enzyme in the tyrosine catabolic pathway. In this study, we
investigated whether fumarylacetoacetate hydrolase deficient (FAH−/−) pigs, a novel large-animal model of HT1, develop fibrosis and cirrhosis characteristic of the human disease. FAH−/− pigs were treated with the protective drug 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3 cyclohexandione (NTBC) at a dose of 1 mg/kg per day initially after birth. After 30 days, they were assigned to one of three groups based on dosing of NTBC. Group 1 received ≥0.2 mg/kg per day, group 2 cycled on/off NTBC (0.05 mg/kg per day × 1 week/0 mg/kg per day × 3 weeks), and group 3 received no NTBC thereafter. Pigs were monitored for features of liver disease. Animals in group 1 continued to have weight gain and biochemical analyses comparable to wild-type pigs. Animals in group 2 had significant cessation of weight gain, abnormal biochemical test results, and various grades of fibrosis and cirrhosis. No evidence of hepatocellular carcinoma was detected. Group 3 animals declined rapidly, with acute liver failure. In conclusion, the FAH−/− pig is a large-animal model of HT1 with clinical characteristics that resemble the human phenotype. Under conditions of low-dose NTBC, FAH−/− pigs developed liver fibrosis and portal hypertension, and thus may serve as a large-animal model of chronic liver disease. © 2017 American Society for Investigative Pathology


BACKGROUND: To evaluate the impact of depression before autologous and allogeneic hematopoietic cell transplantation (HCT) on clinical outcomes posttransplantation. METHODS: We analyzed data from the Center for International Blood and Marrow Transplant Research to compare outcomes after autologous (n = 3786) or allogeneic (n = 7433) HCT for adult patients with hematologic malignancies with an existing diagnosis of pre-HCT depression requiring treatment versus those without pre-HCT depression. Using Cox regression models, we compared overall survival (OS) between patients with or without depression. We compared the number of days alive and out of the hospital in the first 100 days post-HCT using Poisson models. We also compared the incidence of grade 2-4 acute and chronic graft-versus-host disease (GVHD) in allogeneic HCT. RESULTS: The study included 1116 (15%) patients with pre-transplant depression and 6317 (85%) without depression who underwent allogeneic HCT between 2008 and 2012. Pre-transplant depression was associated with lower OS (hazard ratio [HR], 1.13; 95% confidence interval [CI], 1.04-1.23; P = 0.004) and a higher incidence of grade 2-4 acute GVHD (HR, 1.25; 95% CI, 1.14-1.37; P < 0.0001), but similar incidence of chronic GVHD. Pre-transplant depression was associated with fewer days-alive-and-out-of-the-hospital (means ratio [MR] = 0.97; 95% CI, 0.95-0.99; P = 0.004). There were 512 (13.5%) patients with Pre-transplant depression and 3274 (86.5%) without depression who underwent autologous HCT. Pre-transplant depression in autologous HCT was not associated with OS (HR, 1.15; 95% CI, 0.98-1.34; P = 0.096) but was associated with fewer days alive and out of the hospital (MR, 0.98; 95% CI, 0.97-0.99; P = 0.002).

CONCLUSION: Pre-transplant depression was associated with lower OS and higher risk of acute GVHD among allogeneic HCT recipients and fewer days alive and out of the hospital during the first 100 days after autologous and allogeneic HCT. Patients with pre-transplant depression represent a population that is at risk for post-transplant complications. Cancer 2017. (c) 2017 American Cancer Society.


Aberrations in metabolism contribute to a large number of diseases, such as diabetes, obesity, cancer, and cardiovascular diseases, that have a substantial impact on the mortality rates and quality of life worldwide. However, the mechanisms leading to these changes in metabolic state—and whether they are conserved between diseases—is not well understood. Changes in metabolism similar to those seen in pathological conditions are observed during normal development in a number of different cell types. This provides hope that understanding the mechanism of these metabolic switches in normal development may provide useful insight in correcting them in pathological cases. Here, we focus on the metabolic remodeling observed both in early stage embryonic stem cells and during the maturation of cardiomyocytes.
Hyperkalemia is common in patients with impaired kidney function or who take drugs that inhibit the renin-angiotensin-aldosterone axis. During the past decade, substantial advances in understanding how the body controls potassium excretion have been made, which may lead to improved standard of care for these patients. Renal potassium disposition is primarily handled by a short segment of the nephron, comprising part of the distal convoluted tubule and the connecting tubule, and regulation results from the interplay between aldosterone and plasma potassium. When dietary potassium intake and plasma potassium are low, the electroneutral sodium chloride cotransporter is activated, leading to salt retention. This effect limits sodium delivery to potassium secretory segments, limiting potassium losses. In contrast, when dietary potassium intake is high, aldosterone is stimulated. Simultaneously, potassium inhibits the sodium chloride cotransporter. Because more sodium is then delivered to potassium secretory segments, primed by aldosterone, kaliuresis results. When these processes are disrupted, hyperkalemia results. Recently, new agents capable of removing potassium from the body and treating hyperkalemia have been tested in clinical trials. This development suggests that more effective and safer approaches to the prevention and treatment of hyperkalemia may be on the horizon. Copyright © 2015 by the American Society of Nephrology.


BACKGROUND: Withdrawing life-sustaining therapy because of perceived poor neurological prognosis (WLST-N) is a common cause of hospital death after out-of-hospital cardiac arrest (OHCA). Although current guidelines recommend against WLST-N before 72h (WLST-N<72), this practice is common and may increase mortality. We sought to quantify these effects. METHODS: In a secondary analysis of a multicenter OHCA trial, we evaluated survival to hospital discharge and survival with favorable functional status (modified Rankin Score ≤3) in adults alive >1h after hospital admission. Propensity score modeling the probability of exposure to WLST-N<72 based on pre-exposure covariates was used to match unexposed subjects with those exposed to WLST-N<72. We determined the probability of survival and functionally favorable survival in the unexposed matched cohort, fit adjusted logistic regression models to predict outcomes in this group, and then used these models to predict outcomes in the exposed cohort. Combining these findings with current epidemiologic statistics we estimated mortality nationally that is associated with WLST-N<72. RESULTS: Of 16,875 OHCA subjects, 4265 (25%) met inclusion criteria. WLST-N<72 occurred in one-third of subjects who died in-hospital. Adjusted analyses predicted that exposed subjects would have 26% survival and 16% functionally favorable survival if WLST-N<72 did not occur. Extrapolated nationally, WLST-N<72 may be associated with mortality in approximately 2300 Americans each year of whom nearly 1500 (64%) might have had functional recovery. CONCLUSIONS: After OHCA, death following WLST-N<72 may be common and is potentially avoidable. Reducing WLST-N<72 has national public health implications and may afford an opportunity to decrease mortality after OHCA.


PURPOSE: This study aims to determine whether radiologists who perform well in screening also perform well in interpreting diagnostic mammography. MATERIALS AND METHODS: We evaluated the accuracy of 468 radiologists interpreting 2,234,947 screening and 196,164 diagnostic mammograms. Adjusting for site, radiologist, and patient characteristics, we identified radiologists with performance in the highest tertile and compared to those with lower performance. RESULTS: A moderate correlation was noted for radiologists’ accuracy when interpreting screening versus their accuracy on diagnostic examinations: sensitivity (rspearman=0.51, 95% CI: 0.22, 0.80; P=.0006) and specificity (rspearman=0.40, 95% CI: 0.30, 0.49; P<.0001).

CONCLUSION: Different educational approaches to screening and diagnostic imaging should be considered.

Within the first three weeks of human immunodeficiency virus (HIV) infection, virus replication peaks in peripheral blood. Despite the critical, causal role of virus replication in determining transmissibility and kinetics of progression to acquired immune deficiency syndrome (AIDS), there is limited understanding of the conditions required to transform the small localized transmitted founder virus population into a large and heterogeneous systemic infection. Here we show that during the hyperacute “pre-peak” phase of simian immunodeficiency virus (SIV) infection in macaques, high levels of microbial DNA transiently translocate into peripheral blood. This, heretofore unappreciated, hyperacute-phase microbial translocation was accompanied by sustained reduction of lipopolysaccharide (LPS)-specific antibody titer, intestinal permeability, increased abundance of CD4+CCR5+ T cell targets of virus replication, and T cell activation. To test whether increasing gastrointestinal permeability to cause microbial translocation would amplify viremia, we treated two SIV-infected macaque ‘elite controllers’ with a short-course of dextran sulfate sodium (DSS)–stimulating a transient increase in microbial translocation and a prolonged recrudescence viremia. Altogether, our data implicates translocating microbes as amplifiers of immunodeficiency virus replication that effectively undermine the host’s capacity to contain infection. © 2016 Public Library of Science. All Rights Reserved.


BACKGROUND: Adults with congenital heart disease (CHD) face unique life courses and challenges that may negatively influence their psychological functioning. The aims of this study were to (1) examine the level of hopelessness among adults with CHD in comparison with non-CHD participants and (2) identify correlates of elevated hopelessness among adults with CHD. METHODS: We enrolled 347 patients with CHD (18-64 years, 52.2% female) and 353 matched (by sex/age) non-CHD persons in this cross-sectional study. Hopelessness was assessed by Beck Hopelessness Scale. Hierarchical multiple logistic regression analyses were performed to explore correlates of elevated hopelessness. RESULTS: The mean total hopelessness score did not significantly differ between the CHD and non-CHD groups. Twenty-eight percent of CHD patients had elevated hopelessness scores. Within the CHD patient sample, regression analyses revealed that being male (odds ratio=2.62), not having children (odds ratio=3.57), being unemployed (odds ratio=2.27), and elevated depressive symptoms (odds ratio=1.21) were significantly associated with hopelessness. Regular physical activity (odds ratio=0.36) emerged as a protective factor and all CHD disease parameters were unrelated to hopelessness. The final model explained 43% of the variance in hopelessness. CONCLUSIONS: Adult CHD teams are encouraged to continue to explore strategies to support patients to live as rich and full as lives as possible by pursuing relationships, employment and physical activity, as well as managing depression and hopelessness.


PURPOSE: Morbidity of free tissue transfer in the extremes of age is controversial and not well studied in patients aged 90 years or older because of the rarity of these patients and many clinicians’ natural hesitancy to perform such a large operation in patients of this group. The purpose of this study was to answer the following clinical question: Do patients aged 90 years or older who undergo free flap reconstruction have worse functional outcomes than their younger counterparts? MATERIALS AND METHODS: We performed a retrospective chart review of patients aged 90 years or older who underwent free flap reconstruction at Oregon Health and Science University Hospital from 2000 to 2015. All patients aged 90 years or older undergoing free flap reconstruction were included. Patients younger than 90 years during the same period were randomly selected to serve as controls. RESULTS: Free flap reconstructions were performed in 14 patients aged 90 years or older, who were then compared with their randomly selected controls. The only statistically significant difference observed in the outcome variables analyzed was the location of discharge.
from the hospital, with the older patients more likely to be discharged to a skilled nursing facility (P = .002). However, there was no difference in return-to-baseline level of care at last follow-up between the 2 groups. There also was no statistically significant difference in major or minor medical or surgical complication rates, duration of hospitalization, duration of tracheostomy, return to baseline respiratory status, or return to baseline feeding status between the 2 groups. CONCLUSIONS: Patients aged 90 years or older are more likely to be discharged to a skilled nursing facility than their younger counterparts but otherwise have similar outcomes in terms of complications and return to baseline function. The results of this study suggest that age 90 years or older should not be a direct contraindication for free flap reconstruction in the head and neck.


Health extension programs represent an opportunity for practice-based research networks (PBRNs) and primary care practices to develop collaborations reaching beyond the clinic walls to address the upstream social determinants of health and engage in community-based research. The Health Extension Regional Officers (HEROs) program at the University of New Mexico described in this issue of the JABFM is an innovative model with a bidirectional approach to linking academic health centers to community-based practices and organizations. Health extension programs are local, influenced by history, relationships, and support. Oregon’s health extension workforce represents a diverse group that includes practice facilitators, community health workers, and Cooperative Extension agents. PBRNs are measuring success in terms of collaboration across a spectrum of health activities. The Oregon Rural Practice-based Research Network uses a “Four Pillars” model of community engagement, practice transformation, research, and education to involve researchers, health policy experts, educators, and health extension workers to improve community health.


Although prematurity and hypoxic-ischaemic injury are well-recognized contributors to the pathogenesis of cerebral palsy (CP), as many as one-third of children with CP may lack traditional risk factors. For many of these children, a genetic basis to their condition is suspected. Recent findings have implicated copy number variants and mutations in single genes in children with CP. Current studies are limited by relatively small patient numbers, the underlying genetic heterogeneity identified, and the paucity of validation studies that have been performed. However, several genes mapping to intersecting pathways controlling neurodevelopment and neuronal connectivity have been identified. Analogous to other neurodevelopmental disorders such as autism and intellectual disability, the genomic architecture of CP is likely to be highly complex. Although we are just beginning to understand genetic contributions to CP, new insights are anticipated to serve as a unique window into the neurobiology of CP and suggest new targets for intervention.


In 2014, the Association of American Medical Colleges identified 13 Core Entrustable Professional Activities for Entering Residency (Core EPAs), which are activities that entering residents might be expected to perform without direct supervision. This work included the creation of an interinstitutional concept group focused on faculty development efforts, as the processes and tools for teaching and assessing entrustability in undergraduate medical education (UME) are still evolving. In this article, the authors describe a conceptual framework for entrustment that they developed to better prepare all educators involved in entrustment decision making in UME. This framework applies to faculty with limited or longitudinal contact with medical students and to those who contribute to entrustment development or render summative entrustment decisions. The authors describe a shared mental model for entrustment that they developed, based on a

OBJECTIVES: Wideband acoustic immittance (WAI) measures such as pressure reflectance, parameterized by absorbance and group delay, equivalent admittance at the tympanic membrane (TM), and acoustic stapedius reflex threshold (ASRT) describe middle ear function across a wide frequency range, compared with traditional tests employing a single frequency. The objective of this study was to obtain normative data using these tests for a group of normal-hearing adults and investigate test-retest reliability using a longitudinal design. DESIGN: A longitudinal prospective design was used to obtain normative test and retest data on clinical and WAI measures. Subjects were 13 males and 20 females (mean age = 26 years). Inclusion criteria included normal audiometry and clinical immittance. Subjects were tested on two separate visits approximately 1 month apart. Reflectance and equivalent admittance at the TM were measured from 0.25 to 8.0 kHz under three conditions: at ambient pressure in the ear canal and with pressure sweeps from positive to negative pressure (downswept) and negative to positive pressure (upswept). Equivalent admittance at the TM was calculated using admittance measurements at the probe tip that were adjusted using a model of sound transmission in the ear canal and acoustic estimates of ear-canal area and length. Wideband ASRTs were measured at tympanometric peak pressure (TPP) derived from the average TPP of downswept and upswept tympanograms. Descriptive statistics were obtained for all WAI responses, and wideband and clinical ASRTs were compared. RESULTS: Mean absorbance at ambient pressure and TPP demonstrated a broad band-pass pattern typical of previous studies. Test-retest differences were lower for absorbance at TPP for the downswept method compared with ambient pressure at frequencies between 1.0 and 1.26 kHz. Mean tympanometric peak-to-tail differences for absorbance were greatest around 1.0 to 2.0 kHz and similar for positive and negative tails. Mean group delay at ambient pressure and at TPP were greatest between 0.32 and 0.6 kHz at 200 to 300 musec, reduced at frequencies between 0.8 and 1.5 kHz, and increased above 1.5 kHz to around 150 musec. Mean equivalent admittance at the TM had a lower level for the ambient method than at TPP for both sweep directions below 1.2 kHz, but the difference between methods was only statistically significant for the comparison between the ambient method and TPP for the upswept tympanogram. Mean equivalent admittance phase was positive at all frequencies. Test-retest reliability of the equivalent admittance level ranged from 1 to 3 dB at frequencies below 1.0 kHz, but increased to 8 to 9 dB at higher frequencies. The mean wideband ASRT for an ipsilateral broadband noise activator was 12 dB lower than the clinical ASRT, but had poorer reliability. CONCLUSIONS: Normative data for the WAI test battery revealed minor differences for results at ambient pressure compared with tympanometric methods at TPP for reflectance, group delay, and equivalent admittance level at the TM for subjects with middle ear pressure within +/-100 daPa. Test-retest reliability was better for absorbance at TPP for the downswept tympanogram compared with ambient pressure at frequencies around 1.0 kHz. Large peak-to-tail differences in absorbance combined with good reliability at frequencies between about 0.7 and 3.0 kHz suggest that this may be a sensitive frequency range for interpreting absorbance at TPP. The mean wideband ipsilateral ASRT was lower than the clinical ASRT, consistent with previous studies. Results are promising for the use of a wideband test battery to evaluate middle ear function.

An increasing number of studies have implicated the role of network functional connectivity in addiction. Yet, none have examined functional connectivity as a potential mechanism of adolescent behavior change. We examined the underlying neural mechanism of a promising treatment for adolescents, motivational interviewing (MI). We began by employing psychophysiological interaction (PPI) to evaluate network response in a sample of adolescent cannabis users (N=30). Next, we examined correlations between network connectivity and clinical metrics of treatment outcome. PPI analyses seeded on the orbitofrontal cortex (OFC) showed significant increases in functional connectivity across the inferior frontal gyrus (IFG), precentral gyrus, anterior and posterior cingulate gyrus, supplementary motor area (SMA), superior frontal gyrus, pallidus, caudate, and parahippocampal gyrus. Further, greater functional connectivity between the OFC and anterior cingulate/medial frontal gyrus was associated with less behavior change (e.g., greater post-treatment cannabis problems). These data support the role of the OFC network as a mechanism of adolescent treatment response.


Background Pharmacologic inhibitors of proprotein convertase subtilisin-kexin type 9 (PCSK9) are being evaluated in clinical trials for the treatment of cardiovascular disease. The effect of lowering low-density lipoprotein (LDL) cholesterol levels by inhibiting PCSK9 on the risk of cardiovascular events or diabetes is unknown. Methods We used genetic scores consisting of independently inherited variants in the genes encoding PCSK9 and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR; the target of statins) as instruments to randomly assign 112,772 participants from 14 studies, with 14,120 cardiovascular events and 10,635 cases of diabetes, to groups according to the number of LDL cholesterol-lowering alleles that they had inherited. We compared the effects of lower LDL cholesterol levels that were mediated by variants in PCSK9, HMGCR, or both on the risk of cardiovascular events and the risk of diabetes. Results Variants in PCSK9 and HMGCR were associated with nearly identical protective effects on the risk of cardiovascular events per decrease of 10 mg per deciliter (0.26 mmol per liter) in the LDL cholesterol level: odds ratio for cardiovascular events, 0.81 (95% confidence interval [CI], 0.74 to 0.89) for PCSK9 and 0.81 (95% CI, 0.72 to 0.90) for HMGCR. Variants in these two genes were also associated with very similar effects on the risk of diabetes: odds ratio for each 10 mg per deciliter decrease in LDL cholesterol, 1.11 (95% CI, 1.04 to 1.19) for PCSK9 and 1.13 (95% CI, 1.06 to 1.20) for HMGCR. The increased risk of diabetes was limited to persons with impaired fasting glucose levels for both scores and was lower in magnitude than the protective effect against cardiovascular events. When present together, PCSK9 and HMGCR variants had additive effects on the risk of both cardiovascular events and diabetes. Conclusions In this study, variants in PCSK9 had approximately the same effect as variants in HMGCR on the risk of cardiovascular events and diabetes per unit decrease in the LDL cholesterol level. The effects of these variants were independent and additive. (Funded by the Medical Research Council and the National Heart, Lung, and Blood Institute.).


Purpose: This study was intended to evaluate a series of algorithms developed to perform automatic classification of paraphasic errors (formal, semantic, mixed, neologistic, and unrelated errors). Method: We analyzed 7, 111 paraphasias from the Moss Aphasia Psycholinguistics Project Database (Mirman et al., 2010) and evaluated the classification accuracy of 3 automated tools. First, we used frequency norms from the SUBTLEXus database (Brysbaert & New, 2009) to differentiate nonword errors and real-word productions.
Then we implemented a phonological-similarity algorithm to identify phonologically related real-word errors. Last, we assessed the performance of a semantic-similarity criterion that was based on word2vec (Mikolov, Yih, & Zweig, 2013). Results: Overall, the algorithmic classification replicated human scoring for the major categories of paraphasias studied with high accuracy. The tool that was based on the SUBTLEXus frequency norms was more than 97% accurate in making lexicality judgments. The phonological-similarity criterion was approximately 91% accurate, and the overall classification accuracy of the semantic classifier ranged from 86% to 90%. Conclusion: Overall, the results highlight the potential of tools from the field of natural language processing for the development of highly reliable, cost-effective diagnostic tools suitable for collecting high-quality measurement data for research and clinical purposes. © 2016 American Speech-Language-Hearing Association.


INTRODUCTION: Childhood obesity disproportionately affects rural populations; therefore, promoting healthy eating among rural children is essential. Teachers are important role models for children and can influence children's eating behaviors through their own behaviors and beliefs about food. This study examined the food-related practices and beliefs of rural elementary and middle school teachers. METHODS: Data were used from the SNACZ study, a school- and community-based trial conducted in rural Oregon. Kindergarten through eighth-grade teachers (n=87), teaching students usually aged 5-14 years, from eight rural school districts completed a baseline survey in November 2012 concerning their classroom food practices, eating behaviors at school, beliefs about the school food environment, and nutrition knowledge. Frequencies of responses to each item were calculated. RESULTS: Nearly all teachers (97.6%) agreed that a healthy school food environment is important, but fewer agreed that teachers' behaviors and the foods available at school influence students' eating behaviors (71.0% and 67.0%, respectively). Nearly 86% of teachers used candy as a reward for students, while 78.2% consumed unhealthy snacks and 42.5% consumed sweetened beverages in the classroom. CONCLUSIONS: The results suggest that most rural teachers recognize that having a healthy school food environment is important, but are less aware of factors within the school that influence students' eating behaviors - including their own eating behaviors and classroom food practices - and, perhaps for this reason, many rural teachers engage in classroom practices and behaviors that do not promote healthy eating. Teacher training and expanded school policies that focus on teacher behavior may be needed to ensure a healthier rural school food environment.


BACKGROUND: Taenia solium inflicts substantial neurologic disease and economic losses on rural communities in many developing nations. “Ring-strategy” is a control intervention that targets treatment of humans and pigs among clusters of households (rings) that surround pigs heavily infected with cysticerci. These pigs are typically identified by examining the animal's tongue for cysts. However, as prevalence decreases in intervened communities, more sensitive methods may be needed to identify these animals and to maintain control pressure. The purpose of this study was to evaluate ultrasonography as an alternative method to detect pigs heavily infected with T. solium cysts. METHODOLOGY/PRINCIPAL FINDINGS: We purchased 152 pigs representing all seropositive animals villagers were willing to sell from eight...

OBJECTIVE: We examined associations of clinicians’ empathy with patient-clinician communication behaviors, patients’ rating of care, and medication self-efficacy. METHODS: We analyzed 435 adult patients and 45 clinicians at four outpatient HIV care sites in the United States. Negative binomial regressions investigated associations between clinician empathy and patient-clinician communication, assessed using the Roter Interaction Analysis System (RIAS). Logistic regressions investigated associations between clinician empathy and patient ratings of clinician communication, overall satisfaction, and medication self-efficacy. RESULTS: Clinicians in the highest vs. lowest empathy tertile engaged in less explicitly emotional talk (IRR 0.79, p < 0.05), while clinicians in the middle vs. lowest engaged in more positive talk (IRR 1.31, p < 0.05), more questions (IRR 1.42, p < 0.05), and more patient activating talk (IRR 1.43, p < 0.05). Patients of higher empathy clinicians disclosed more psychosocial and biomedical information. Patients of clinicians in both the middle and highest (vs. lowest) empathy tertiles had greater odds of reporting highest medication self-efficacy (OR 1.80, 95% CI 1.16–2.80; OR 2.13, 95% CI 1.37–3.32). CONCLUSIONS: Clinician empathy may be expressed through addressing patient engagement in care, by fostering cognitive, rather than primarily emotional, processing. PRACTICE IMPLICATIONS: Clinicians should consider enhancing their own empathic capacity, which may encourage patients’ self-efficacy in medication adherence.


OBJECTIVE: Attitudes towards patients may influence how clinicians interact. We investigated whether respect for patients was associated with communication behaviors during HIV care encounters. METHODS: We analyzed audio-recordings of visits between 413 adult HIV-infected patients and 45 primary HIV care providers. The independent variable was clinician-reported respect for the patient and outcomes were clinician and patient communication behaviors assessed by the Roter Interaction Analysis System (RIAS). We performed negative binomial regressions for counts outcomes and linear regressions for global outcomes. RESULTS: When clinicians had higher respect for a patient, they engaged in more rapport-building, social chitchat, and positive talk. Patients of clinicians with higher respect for them engaged in more rapport-building, social chitchat, positive talk, and gave more psychosocial information. Encounters between patients and clinicians with higher respect for them had more positive clinician emotional tone [regression coefficient 2.97 (1.92–4.59)], more positive patient emotional tone [2.71 (1.75–4.21)], less clinician verbal dominance [0.81 (0.68–0.96)] and more patient-centeredness [1.28 (1.09–1.51)]. CONCLUSIONS: Respect is associated with positive and patient-centered communication behaviors during encounters. PRACTICE IMPLICATIONS: Clinicians should be mindful of their respectful attitudes and work to foster positive regard for patients. Educators should consider methods to enhance trainees’ respect in communication skills training.

PURPOSE: The purpose of this study was to describe how novice physician assistants (PAs) transfer learning from formal training into clinical practice. METHODS: This Q study was conducted as a part of a larger mixed-interpretive investigation of the experiences of novice PAs during the first 2 years of practice. A set of 45 statements was naturally sampled from 10 previously conducted semi-structured qualitative interviews with novice PAs. Fifteen different novice PAs then sorted the statements. The data were analyzed using by-person factor analysis (Q methodology). The resultant factor array was used to generate a summary, a sketch, and a monologue for each shared social perspective. RESULTS: Three shared social perspectives concerning transfer of learning during the transition to practice emerged: (1) partnership, (2) self-reliant, and (3) insecure perspectives. Novice PAs sharing the partnership perspective experienced few, if any, individual or environmental obstacles to transfer of learning. Novice PAs sharing the self-reliant perspective experienced environmental obstacles but few, if any, individual obstacles to transfer of learning. Novice PAs who shared the insecure perspective experienced both individual and environmental obstacles to transfer of learning. CONCLUSIONS: The results of this study describe variability in the novice PA experiences of learning transfer during the first 2 years of practice. The results have implications for PA educators and those involved in helping novice PAs develop as clinicians.


OBJECTIVE: To evaluate the interaction and contribution of maternal and fetal risk factors associated with neonatal brachial plexus injury (BPI). METHODS: In a case-control study, matched maternal and neonatal discharge records were accessed from US State Inpatient Databases for New Jersey (2010-2012), Michigan (2010-2011), and Hawaii (2010-2011). Univariate and multivariate logistic regressions were used to evaluate associations between risk factors and BPI. Area under the receiver operating characteristic curve was used to build predictive models, including two stratified models evaluating deliveries among obese and diabetic cohorts. RESULTS: Among 376,325 deliveries, BPI was diagnosed in 274 (0.1%). Significant BPI risk factors included maternal obesity (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.7-4.4), maternal diabetes (OR 4.6, 95% CI 3.0-7.0), use of forceps (OR 4.6, 95% CI 2.3-9.0), and vacuum assistance (OR 2.3, 95% CI 1.7-3.3). After adjusting for shoulder dystocia and other predictive factors, cesarean reduced the risk of BPI by 88% (OR 0.1, 95% CI 0.07-0.2). When stratified by obesity and diabetes, the ORs for BPI increased significantly for macrosomia, forceps, and vacuum assistance. CONCLUSION: The analysis confirms and quantifies more precisely the impact of risk factors for neonatal BPI, and provides a reliable basis for evidence-based clinical decision-making models.


Background Sodium thiosulfate is an antioxidant shown in preclinical studies in animals to prevent cisplatin-induced hearing loss with timed administration after cisplatin without compromising the antitumour efficacy of cisplatin. The primary aim of this study was to assess sodium thiosulfate for prevention of cisplatin-induced hearing loss in children and adolescents. Methods ACCL0431 was a multicentre, randomised, open-label, phase 3 trial that enrolled participants at 38 participating Children’s Oncology Group hospitals in the USA and Canada. Eligible participants aged 1–18 years with newly diagnosed cancer and normal audiometry were randomly assigned (1:1) to receive sodium thiosulfate or observation (control group) in addition to their planned cisplatin-containing chemotherapy regimen, using permuted blocks of four. Randomisation was initially stratified by age and duration of cisplatin infusion. Stratification by previous cranial irradiation was added later as a protocol amendment. The allocation sequence was computer-generated centrally and concealed to all personnel. Participants received sodium thiosulfate 16 g/m2 intravenously 6 h after each
cisplatin dose or observation. The primary endpoint was incidence of hearing loss 4 weeks after final cisplatin dose. Hearing was measured using standard audiometry and reviewed centrally by audiologists masked to allocation using American Speech-Language-Hearing Association criteria but treatment was not masked for participants or clinicians. Analysis of the primary endpoint was by modified intention to treat, which included all randomly assigned patients irrespective of treatment received but restricted to those assessable for hearing loss. Enrolment is complete and this report represents the final analysis. This trial is registered with ClinicalTrials.gov, number NCT00716976. Findings Between June 23, 2008, and Sept 28, 2012, 125 eligible participants were randomly assigned to either sodium thiosulfate (n=61) or observation (n=64). Of these, 104 participants were assessable for the primary endpoint (sodium thiosulfate, n=49; control, n=55). Hearing loss was identified in 14 (28·6%; 95% CI 16·6–43·3) participants in the sodium thiosulfate group compared with 31 (56·4%; 42·3–69·7) in the control group (p=0·00022). Adjusted for stratification variables, the likelihood of hearing loss was significantly lower in the sodium thiosulfate group compared with the control group (odds ratio 0·31, 95% CI 0·13–0·73; p=0·0036). The most common grade 3–4 haematological adverse events reported, irrespective of attribution, were neutropenia (117 [66%] of 177 participant cycles in the sodium thiosulfate group vs 145 [65%] of 223 in the control group), whereas the most common non-haematological adverse event was hypokalaemia (25 [17%] of 147 vs 22 [12%] of 187). Of 194 serious adverse events reported in 26 participants who had received sodium thiosulfate, none were deemed probably or definitely related to sodium thiosulfate; the most common serious adverse event was decreased neutrophil count: 26 episodes in 14 participants. Interpretation Sodium thiosulfate protects against cisplatin-induced hearing loss in children and is not associated with serious adverse events attributed to its use. Further research is needed to define the appropriate role for sodium thiosulfate among emerging otoprotection strategies. Funding US National Cancer Institute. © 2017 Elsevier Ltd


The pathophysiology of atopic dermatitis (AD) is complex, and future treatment options will likely be incorporated in a multimodal approach to management. The new, directed therapies that have been developed will likely be used in conjunction with concomitant continuous or intermittent use of standard therapies; the goal is to optimize therapeutic outcomes while minimizing adverse impacts on safety and cost. Current data regarding disease course and expression throughout life suggest that treatment strategies also will need to be adjusted as a patient grows. Research also indicates that interventions begun in infancy—such as the use of emollients—may mitigate or prevent AD signs and symptoms in children at high risk for the disease. Semin Cutan Med Surg 35(supp5):S97-S99.


Drug sensitivity and resistance testing on diagnostic leukemia samples should provide important functional information to guide actionable target and biomarker discovery. We provide proof of concept data by profiling 60 drugs on 68 acute lymphoblastic leukemia (ALL) samples mostly from resistant disease in co-cultures on bone marrow stromal cells. Patient-derived xenografts retained the original pattern of mutations found in the matched patient material. Stromal co-culture did not prevent leukemia cell cycle activity, while a specific sensitivity profile to cell cycle related drugs identified samples with higher cell proliferation both in vitro and in vivo as leukemia xenografts. In cases with refractory relapses, individual patterns of marked drug resistance, but also exceptional responses to new agents of immediate clinical relevance were detected. The BCL2-inhibitor venetoclax was highly active below 10 nM in BCP-ALL subsets including MLL-AF4 and TCF3-HLF ALL, and in some T-ALLs, predicting in vivo activity as a single agent and in combination with
Dexamethasone and vincristine. Unexpected sensitivity to dasatinib with IC50 values below 20 nM was detected in two independent T-ALL cohorts, which correlated with similar cytotoxic activity of the SRC Inhibitor KX2-391 and inhibition of SRC phosphorylation. A patient with refractory T-ALL was treated with dasatinib based on drug profiling information and achieved a five-month remission. Thus, drug profiling captures disease-relevant features and unexpected sensitivity to relevant drugs, which warrants further exploration of this functional assay in the context of clinical trials in order to develop drug repurposing strategies for patients with urgent medical needs.


The absence of sperm in the ejaculate after vasectomy reversal is commonly caused by failure to recognize and subsequently bypass epididymal or proximal vasal obstruction at the time of vasectomy reversal. If intraoperative proximal obstruction is suspected, vasopididymostomy (VE) is recommended rather than vasovasostomy (VV). We sought to calculate the associated risk of needing VE, rather than VV with time from original vasectomy (obstructive interval) using a large cohort of vasectomy reversal patients. We reviewed the electronic and paper vasectomy reversal database by a single surgeon from 1978 through 2012. We performed univariate analysis to identify variables that predicted the need for VE rather than VV, and then combined only significant univariates into our multi-variable analysis. 2697 total men underwent vasectomy reversal, and 239 were repeat procedures. Of the 5296 individual testes operated on, 1029 were VE. Significant variables that predicted the need for VE on univariate analysis included: age, obstructive time interval, vasectomy reversal after previous VV (repeat vasectomy reversal), and year the procedure was performed. On multi-variable analysis significant risk factors for VE were age above 50 (OR 1.36), repeat vasectomy reversal (OR 5.78), and greater obstructive time interval (OR 1.56). For every 3 years since original vasectomy, the risk of needing VE increases by 56%. There is a linear relationship between obstructive interval and need for VE. Men undergoing repeat vasectomy reversal have five times greater risk of requiring VE and men greater than 50 years of age are also at higher risk. Using these pre-operative predictors is helpful in identifying patients who will benefit from referral to an experienced surgeon who can perform VE.


BACKGROUND: Alcohol is an important nonessential component of diet, but the overall impact of drinking on bone health, especially at moderate levels, is not well understood. Bone health is important because fractures greatly reduce quality of life and are a major cause of morbidity and mortality in the elderly. Regular alcohol consumption is most common following skeletal maturity, emphasizing the importance of understanding the skeletal consequences of drinking in adults. METHODS: This review focuses on describing the complex effects of alcohol on the adult skeleton. Studies assessing the effects of alcohol on bone in adult humans as well as skeletally mature animal models published since the year 2000 are emphasized. RESULTS: Light to moderate alcohol consumption is generally reported to be beneficial, resulting in higher bone mineral density (BMD) and reduced age-related bone loss, whereas heavy alcohol consumption is generally associated with decreased BMD, impaired bone quality, and increased fracture risk. Bone remodeling is the principal mechanism for maintaining a healthy skeleton in adults and dysfunction in bone remodeling can lead to bone loss and/or decreased bone quality. Light to moderate alcohol may exert beneficial effects in older individuals by slowing the rate of bone remodeling, but the impact of light to moderate alcohol on bone remodeling in younger individuals is less certain. The specific effects of alcohol on bone remodeling in heavy drinkers are even less certain because the effects are often obscured by unhealthy lifestyle choices, alcohol-associated disease, and altered endocrine signaling. CONCLUSIONS: Although there
have been advances in understanding the complex actions of alcohol on bone, much remains to be determined. Limited evidence implicates age, skeletal site evaluated, duration, and pattern of drinking as important variables. Few studies systematically evaluating the impact of these factors have been conducted and should be made a priority for future research. In addition, studies performed in skeletally mature animals have potential to reveal mechanistic insights into the precise actions of alcohol and associated comorbidity factors on bone remodeling.


The choriocapillaris plays an important role in supporting the metabolic demands of the retina. Studies of the choriocapillaris in disease states with optical coherence tomography angiography (OCTA) have proven insightful. However, image artifacts complicate the identification and quantification of the choriocapillaris in degenerative diseases such as choroideremia. Here, we demonstrate a supervised machine learning approach to detect intact choriocapillaris based on training with results from an expert grader. We trained a random forest classifier to evaluate en face structural OCT and OCTA information along with spatial image features. Evaluation of the trained classifier using previously unseen data showed good agreement with manual grading.


Importance: Skin cancer is the most common malignancy occurring after organ transplantation. Although previous research has reported an increased risk of skin cancer in solid organ transplant recipients (OTRs), no study has estimated the posttransplant population-based incidence in the United States. Objective: To determine the incidence and evaluate the risk factors for posttransplant skin cancer, including squamous cell carcinoma (SCC), melanoma (MM), and Merkel cell carcinoma (MCC) in a cohort of US OTRs receiving a primary organ transplant in 2003 or 2008. Design, Setting, and Participants: This multicenter retrospective cohort study examined 10649 adult recipients of a primary transplant performed at 26 centers across the United States in the Transplant Skin Cancer Network during 1 of 2 calendar years (either 2003 or 2008) identified through the Organ Procurement and Transplantation Network (OPTN) database. Recipients of all organs except intestine were included, and the follow-up periods were 5 and 10 years. Main Outcomes and Measures: Incident skin cancer was determined through detailed medical record review. Data on predictors were obtained from the OPTN database. The incidence rates for posttransplant skin cancer overall and for SCC, MM, and MCC were calculated per 100000 person-years. Potential risk factors for posttransplant skin cancer were tested using multivariate Cox regression analysis to yield adjusted hazard ratios (HR). Results: Overall, 10649 organ transplant recipients (mean [SD] age, 51 [12] years; 3873 women [36%] and 6776 men [64%]) contributed 59923 years of follow-up. The incidence rates for posttransplant skin cancer was 1408 per 100000 person-years. Specific subtype rates for SCC, MM, and MCC were 1328, 122, and 4 per 100000 person-years, respectively. Statistically significant risk factors for posttransplant skin cancer included pretransplant skin cancer (HR, 4.69; 95% CI, 3.26-6.73), male sex (HR, 1.56; 95% CI, 1.34-1.81), white race (HR, 9.04; 95% CI, 6.20-13.18), age at transplant 50 years or older (HR, 2.77; 95% CI, 2.20-3.48), and being transplanted in 2008 vs 2003 (HR, 1.53; 95% CI, 1.22-1.94). Conclusions and Relevance: Posttransplant skin cancer is common, with elevated risk imparted by increased age, white race, male sex, and thoracic organ transplantation. A temporal cohort effect was present. Understanding the risk factors and trends in posttransplant skin cancer is fundamental to targeted screening and prevention in this population.


PURPOSE: The objective of this study was to examine the attitudes of baccalaureate nursing students toward their role in pressure injury prevention (PIP) and describe how clinical experiences influence their attitudes.
Understanding students' attitudes and experiences related to PIP may facilitate development of evidence-based interventions for PIP by nurses. DESIGN: Qualitative exploratory descriptive design. SETTING AND SUBJECTS: Participants were 16 senior nursing students enrolled in a prelicensure baccalaureate nursing program in an accredited school of nursing. Half of the participants had completed their first 2 years of the nursing major in the baccalaureate program. The remaining participants completed their first 2 years in a community college associate degree nursing program. METHOD: Semistructured, in-depth, open-ended interviews were conducted. Interviews were digitally recorded and transcribed verbatim; data were analyzed for key themes using content analysis. RESULTS: Four categories of attitudes about PIP were identified: (1) ambivalence, (2) emerging awareness, (3) committed, and (4) passionate. Diverse clinical experiences in pediatrics, the operating room, trauma units, and long-term care facilities enhanced nursing students' learning related to PIP. Experiences observing WOC nurses and other staff role models engaged in PIP were associated with student commitment and passion for PIP. CONCLUSIONS: Findings from this study can be used to guide interventions to enhance attitudes of commitment to PIP. WOC nurses, clinical preceptors, and clinical staff can involve nursing students in intentional PIP learning activities to improve clinical practice and patient outcomes. Intentionally incorporating key learning activities about PIP in the nursing curriculum is recommended.


OBJECTIVES: Extracapsular extension (ECE) in cervical metastatic lymph nodes remains an indication for adding chemotherapy for patients with oropharyngeal squamous cell carcinoma (OPSCC). The aim of this study is to identify specific imaging characteristics on computed tomography (CT) scan that are predictive of ECE in order to better risk stratify patients preoperatively. MATERIALS AND METHODS: A single cohort study was performed using a prospectively collected database of patients with HPV-related OPSCC who underwent transoral robotic surgery with cervical lymphadenectomy. CT scans were assessed for the presence of multiple imaging characteristics, including lymph node size, number of nodes positive, cystic appearance, and border irregularity. Univariable and multivariable analyses were performed to analyze each variable's predictability of pathologic ECE. RESULTS: 100 patients underwent TORS with cervical lymphadenectomy for OPSCC from 2010 to 2015. Ninety-one percent (21/23) of patients with 3 or more radiologically suspicious nodes were found to have pathologic ECE, which was a significantly greater proportion than patients with fewer suspicious nodes (p<0.001). CT scans with 3 or more radiologically suspicious nodes displayed a sensitivity and specificity of 55% and 94%, respectively with a positive predictive value (PPV) of 91% for ECE. Irregular borders and age were also correlated with ECE on multivariable analysis. CONCLUSION AND RELEVANCE: The presence of 3 or more radiologically suspicious lymph nodes on CT scan has a 91% PPV for any histologic evidence of ECE. The absolute number of radiographically suspicious lymph node metastases may be a useful method for risk-stratifying patients for the presence of ECE.


Molecular networks governing cellular responses to targeted therapies are complex dynamic systems with non-intuitive behaviors. Here we applied a novel computational strategy to infer probabilistic causal relationships between network components based on gene expression. We constructed a model comprised of an ensemble of networks using multidimensional data from cell line models of cell cycle arrest caused by inhibition of MEK1/2. Through simulation of reverse-engineered Bayesian network modeling, we generated predictions of G1-S transition. The model identified known components of the cell cycle machinery, such as CCND1, CCNE2 and CDC25A, as well as novel regulators of G1-S transition IER2, TRIB1 and TRIM27. Experimental validation of this model confirmed 10 of 12 predicted genes to have a role in progression through the G1-S phase transition of the cell cycle. Further analysis showed that TRIB1 regulated the cyclin D1 promoter via NF-kappaB and AP-1 sites and sensitized cells to TRAIL-induced apoptosis. In clinical specimens of breast cancer, TRIB1 levels correlated with expression of NF-kappaB and its target genes IL-8
and CSF2, and TRIB1 copy number and expression were predictive of clinical outcome. Together, our results establish a critical role for TRIB1 in cell cycle and survival that is mediated via the modulation of NF-kappaB signaling.


The myeloproliferative neoplasms, including polycythemia vera, essential thrombocythemia and myelofibrosis, are distinguished by their debilitating symptom profiles, life-threatening complications and profound impact on quality of life. The role gender plays in the symptomatology of myeloproliferative neoplasms remains underinvestigated. In this study we evaluated how gender relates to patients’ characteristics, disease complications and overall symptom expression. A total of 2,006 patients (polycythemia vera=711, essential thrombocythemia= 830, myelofibrosis=460, unknown=5) were prospectively evaluated, with patients completing the Myeloproliferative Neoplasm-Symptom Assessment Form and Brief Fatigue Inventory Patient Reported Outcome tools. Information on the individual patients’ characteristics, disease complications and laboratory data was collected. Consistent with known literature, most female patients were more likely to have essential thrombocytemia (48.6% versus 33.0%; P<0.001) and most male patients were more likely to have polycythemia vera (41.8% versus 30.3%; P<0.001). The rate of thrombocytopenia was higher among males than females (13.9% versus 8.2%; P<0.001) and males also had greater redblood cell transfusion requirements (7.3% versus 4.9%; P=0.02) with shorter mean disease duration (6.4 versus 7.2 years, P=0.03). Despite there being no statistical differences in risk scores, receipt of most therapies or prior complications (hemorrhage, thrombosis), females had more severe and more frequent symptoms for most individual symptoms, along with overall total symptom score (22.8 versus 20.3; P<0.001). Females had particularly high scores for abdominal-related symptoms (abdominal pain/discomfort) and microvascular symptoms (headache, fatigue, insomnia, concentration difficulties, dizziness; all P<0.01). Despite complaining of more severe symptom burden, females had similar quality of life scores to those of males. The results of this study suggest that gender contributes to the heterogeneity of myeloproliferative neoplasms by influencing phenotypic profiles and symptom expression. © 2017 Ferrata Storti Foundation.


The cultivation and consumption of grasspea (Lathyrus sativus) in Spain probably dates back centuries, especially during times of famine when the neurotoxic potential of this legume was expressed in the form of a spastic paraparesis known as neurolathyrism. Little known outside the country, the epidemic of neurolathyrism in the years following the Spanish Civil War (1936–1939) came to affect more than a thousand people. In late 1872, during the Six Years Revolutionary Term, young Alejandro San Martín Satrústegui (1847–1908), then editor of the popular weekly El Siglo Médico, travelled to Azañón, a remote village in the province of Guadalajara, to clarify a so-far unknown disease. We analysed the original article published in 1873 by San Martin, as well as communications sent by El Siglo Médico readers reporting similar cases in many other Castilian provinces. San Martin’s neurological findings in seven personally examined cases were astonishingly accurate; he concluded the subjects’ neurological deficits resulted from injury to the lateral columns in the lower portion of the spinal cord. Description of the clinical findings provided both by San Martin, and by the readers of El Siglo Médico, leave no doubt as to the diagnosis of neurolathyrism. However, none suspected the patient’s staple food was the determinant cause of the disease. San Martin proposed the eponym Azañón’s disease for lack of a better name the same year (1873) in which Cantani in Italy introduced the term lathyrism. The epidemic of neurolathyrism that affected many Castilian towns represents one of the best-documented in Europe during the last third of the 19th century. © 2016 Elsevier Masson SAS
INTRODUCTION: Women experiencing intimate partner violence (IPV) navigate complex, dangerous decisions. Tailored safety information and safety planning, typically provided by domestic violence service providers, can prevent repeat IPV exposure and associated adverse health outcomes; however, few abused women access these services. The Internet represents a potentially innovative way to connect abused women with tailored safety planning resources and information. The purpose of this study was to compare safety and mental health outcomes at baseline, 6 months, and 12 months among abused women randomized to: (1) a tailored, Internet-based safety decision aid; or (2) control website (typical safety information available online). DESIGN: Multistate, community-based longitudinal RCT with one-to-one allocation ratio and blocked randomization. Data were collected March 2011-May 2013 and analyzed June-July 2015.

SETTING/PARTICIPANTS: Currently abused Spanish- or English-speaking women (N=720). INTRODUCTION: A tailored Internet-based safety decision aid included priority-setting activities, risk assessment, and tailored feedback and safety plans. A control website offered typical safety information available online. MAIN OUTCOME MEASURES: Primary outcomes were decisional conflict, safety behaviors, and repeat IPV; secondary outcomes included depression and post-traumatic stress disorder. RESULTS: At 12 months, there were no significant group differences in IPV, depression, or post-traumatic stress disorder. Intervention women experienced significantly less decisional conflict after one use (beta= -2.68, p=0.042) and greater increase in safety behaviors they rated as helpful from baseline to 12 months (12% vs 9%, p=0.033) and were more likely to have left the abuser (63% vs 53%, p=0.008). Women who left had higher baseline risk (14.9 vs 13.1, p=0.003) found more of the safety behaviors they tried helpful (61.1% vs 47.5%, p<0.001), and had greater reductions in psychological IPV ((11.69 vs 7.5, p=0.001) and sexual IPV (2.41 vs 1.25, p=0.001) than women who stayed. CONCLUSIONS: Internet-based safety planning represents a promising tool to reduce the public health impact of IPV.
We conducted a qualitative study to evaluate the experiences of 20 clinicians caring for patients with clinical Stage I NSCLC prior to treatment, focusing on communication practices. We used directed content analysis and a patient-centered communication theoretical model to guide understanding of communication strategies. RESULTS: All clinicians expressed the importance of providing information, especially for mitigating patient worry, despite recognition that patients recall only a small amount of the information given. When patients expressed distress, clinicians exhibited empathy but preferred to provide more information in order to address patient concerns. Most clinicians reported practicing SDM, however, they also reported not clearly eliciting patient preferences and values, a key part of SDM. CONCLUSION: Communication with patients about treatment options for early stage NSCLC primary includes information giving. We found that only a few communication domains associated with SDM occurred regularly, and SDM may not be necessary in this clinical context. PRACTICE IMPLICATIONS: Clinicians may need to incorporate nurse navigators or more written materials for effectively discussing potentially equivalent treatment options with their patients.


INTRODUCTION: In two, 6-month, randomized, double-blind Phase 3 trials, PA32540 (enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) compared to aspirin alone was associated with fewer endoscopic gastric and duodenal ulcers in patients requiring aspirin therapy for secondary cardiovascular disease (CVD) prevention who were at risk for upper gastrointestinal (UGI) events. AIMS: In this 12-month, open-label, multicenter Phase 3 study, we evaluated the long-term cardiovascular and gastrointestinal safety of PA32540 in subjects who were taking aspirin 325 mg daily for >3 months for secondary CVD prevention and were at risk for aspirin-associated UGI events. Enrolled subjects received PA32540 once daily for up to 12 months and were assessed at baseline, month 1, month 6, and month 12. RESULTS: The overall safety population consisted of 379 subjects, and 290 subjects (76%) were on PA32540 for >348 days (12-month completers). Adverse events (AEs) caused study withdrawal in 13.5% of subjects, most commonly gastroesophageal reflux disease (1.1%). Treatment-emergent AEs occurred in 76% of the safety population (11% treatment-related) and 73% of 12-month completers (8% treatment-related). The most common treatment-related AE was dyspepsia (2%). One subject had a gastric ulcer observed on for-cause endoscopy. There were five cases of adjudicated nonfatal myocardial infarction, one nonfatal stroke, and one cardiovascular death, but none considered treatment-related. CONCLUSIONS: Long-term treatment with PA32540 once daily for up to 12 months in subjects at risk for aspirin-associated UGI events is not associated with any new or unexpected safety events.


Military Service Members are often exposed to high levels of occupational noise, solvents, and other exposures that can be damaging to the auditory system. Little is known about hearing loss and how it progresses in Veterans following military service. This epidemiology study is designed to evaluate and monitor a cohort of Veterans for 20 years or more to determine how hearing loss changes over time and how those changes are related to noise exposure and other ototoxic exposures encountered during military service. Data reported here are from baseline assessments of the first 100 study participants (84 males; 16 females; mean age 33.5 years; SD 8.8; range 21-58). Each participant was asked to complete a comprehensive audiologic examination and self-report questionnaires regarding sociodemographic characteristics, noise and solvent exposures, health conditions common among post-deployment Veterans, and the social and emotional consequences of hearing loss. For this relatively young cohort, 29% exhibited hearing loss, defined as average hearing threshold >20 dB HL in the conventional audiometric range. Forty-two percent exhibited hearing loss in the extended-high-frequency audiometric range using the same criterion (average hearing threshold >20 dB HL). Certain factors were found to be associated with poorer hearing in both
conventional and extended-high-frequency ranges, including age, type of military branch, years of military service, number of military deployments, noise exposure, tinnitus, and a positive screen for post-traumatic stress disorder. Although the majority of participants had hearing within normal limits, 27% reported a self-perceived mild/moderate hearing handicap and 14% reported a significant handicap. Further research is needed to identify a cause for this discrepancy in audiologic results versus self-report. The information obtained from this longitudinal study could be used in future resource planning with the goal of preventing, as much as possible, the development of hearing loss during military service, and the exacerbation of prevalent hearing loss after military service and over Veterans’ lifetimes. © 2016.


Purpose Identify AML patients most likely to respond to CPX-351, a nano-scale liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio. Methods We examined the ex vivo cytotoxic activity of CPX-351 against leukemic cells isolated from 53 AML patients and an additional 127 samples including acute lymphoblastic leukemia, myelodysplastic syndrome/myeloproliferative neoplasms, or chronic lymphocytic leukemia/lymphoma. We assessed activity with respect to common molecular lesions and used flow cytometry to assess CPX-351 cellular uptake. Results AML specimen sensitivity to CPX-351 was similar across conventional risk groups. FLT3-ITD cases were five-fold more sensitive to CPX-351. CPX-351 was active across other indications with nearly all cases exhibiting IC50 values markedly lower than reported 72-h plasma drug concentration in patients receiving CPX-351. The range and distribution of CPX-351 IC50 values were comparable for AML, CLL, and ALL, whereas MDS/MPN cases were less sensitive. CPX-351 uptake analysis revealed a correlation between uptake of CPX-351 and cytotoxic potency. Conclusions Our findings are consistent with clinical data, in which CPX-351 activity is retained in high-risk AML patients. Ex vivo analysis of cytotoxic potency may provide a means to identify specific AML subsets, such as FLT3-ITD, that benefit most from CPX-351 and warrant additional clinical evaluation. © 2016 Elsevier Ltd


PURPOSE: OSLDs made of Al2O3:C have many useful dosimetric characteristics including their ability to be reused. The signal on an OSLD can be removed through heat or light. The objective of this study was to characterize the change in sensitivity associated with annealing OSLDs with light and in doing so define a range through which reuse is viable. METHODS: Four groups of nanoDot OSLDs were repeatedly irradiated and bleached to create accumulated dose history. Each group’s repeated irradiation remained constant at either 50, 100, 200, or 500 cGy. Before both irradiation and bleaching the OSLDs were read out, giving the dose reading and ensuring that ample bleaching had occurred, respectively. New and used OSLDs were compared in several clinical situations to verify accuracy. One final test involved correcting the readout dose based on the loss of sensitivity seen in the accumulated dose data. RESULTS: In the first 40 Gy of accumulated dose the sensitivity can be broken into two regions: a region of sensitivity change and a region of no sensitivity change. From 0 cGy to an average of 1080 cGy the sensitivity does not change. After 1080 cGy the sensitivity begins to decrease linearly with an average slope of 0.00456 cGy lost per cGy accumulated after the cutoff point. The slope and cutoff point were used to correct readings in the final test, reducing the error from 6.8% to 3.9%. CONCLUSION: In the region of no sensitivity change OSLDs can be reused without concern to the validity of their result. Readings must be corrected if OSLDs are to be used in the region of sensitivity change, above 1080 cGy. After 40 Gy OSLDs must be retired because the sensitivity change reverses, making linear correction no longer feasible.

**BACKGROUND:** Twins have a higher-than-expected risk of infantile hemangiomas (IHs), but the exact reasons for this association are not clear. Comparing concordant and discordant twin pairs might help elucidate these factors and yield more information about IH risk factors. **METHODS:** A prospective cohort study of twin pairs from 12 pediatric dermatology centers in the United States, Canada, Argentina, and Spain was conducted. Information regarding maternal pregnancy history, family history of vascular birthmarks, zygosity (if known), and pregnancy-related information was collected. Information regarding twins (N = 202 sets) included birthweight, gestational age (GA), presence or absence of IHs, numbers and subtypes of IHs, presence of other birthmarks, and other medical morbidities. **RESULTS:** Two hundred two sets of twins were enrolled. Concordance for IH was present in 37% of twin pairs. Concordance for IH was inversely related to gestational age (GA), present in 42% of GA of 32 weeks or less, 36% of GA of 33 to 36 weeks, and 32% of GA of 37 weeks or more. Twins of GA of 34 weeks or less were more than two and a half times as likely to be concordant as those of GA of 35 weeks or more (odds ratio (OR) = 2.66, 95% confidence interval (CI) = 1.42-4.99; p < 0.01). In discordant twins, lower birthweight conferred a high risk of IH; of the 64 sets of twins with 10% or greater difference in weight, the smaller twin had IH in 62.5% (n = 40) of cases, versus 37.5% (n = 24) of cases in which the higher-birthweight twin was affected. Zygosity was reported in 188 twin sets (93%). Of these, 78% were dizygotic and 22% monozygotic. There was no statistically significant difference in rates of concordance between monozygotic twins (43%, 18/42) and dizygotic twins (36%, 52/146) (p = 0.50). In multivariate analysis comparing monozygotic and dizygotic twins, adjusting for effects of birthweight and sex, the likelihood of concordance for monozygotic was not appreciably higher than that for dizygotic twins (OR = 1.14, 95% CI = 0.52-2.49). Female sex also influenced concordance, confirming the effects of female sex on IH risk. The female-to-male ratio was 1.7:1 in the entire cohort and 1.9:1 in those with IH. Of the 61 discordant twin sets with known sex of both twins, 41% were female/female, 43% were female/male, and 16% were male/male. **CONCLUSIONS:** These findings suggest that the origin of IHs is multifactorial and that predisposing factors such as birthweight, sex, and GA may interact with one another such that a threshold is reached for clinical expression.


Cultured cells require the actions of growth factors to enter the cell cycle, but how individual members of a population respond to the same stimulus remains unknown. Here we have employed continuous monitoring by live cell imaging in a dual-reporter cell model to investigate the regulation of short-term growth factor signaling (protein kinase B (PKB/Akt) activity) and longer-term progression through the cell cycle (cyclin-dependent kinase 2 activity). In the total population, insulin-like growth factor-I (IGF-I)-enhanced cell cycle entry by >5-fold compared with serum-free medium (from 13.5 to 78%), but at the single cell level we observed a broad distribution in the timing of G1 exit (4-24 h, mean approximately 12 h) that did not vary with either the amount or duration of IGF-I treatment. Cells that failed to re-enter the cell cycle exhibited similar responses to IGF-I in terms of integrated Akt activity and migration distance compared with those that did. We made similar observations with EGF, PDGF-AA, and PDGF-BB. As potential thresholds of growth factor-mediated cell cycle progression appeared to be heterogeneous within the population, the longer-term proliferative outcomes of individual cells to growth factor stimulation could not be predicted based solely on acute Akt signaling responses, no matter how robust these might be. Thus, although we could define a relationship at the population level between growth factor-induced Akt signaling dynamics and cell cycle progression, we could not predict the fate of individual cells.


Peptide growth factors stimulate cellular responses through activation of their trans-membrane receptors. Multiple intracellular signaling cascades are engaged following growth factor - receptor binding, leading to
short- and long-term biological effects. Each receptor-activated signaling pathway does not act in isolation, but rather interacts at different levels with other pathways to shape signaling networks that are distinctive for each growth factor. To gain insights into the specifics of growth factor-regulated interactions among different signaling cascades, we developed a HeLa cell line stably expressing fluorescent live-cell imaging reporters that are readouts for two major growth factor-stimulated pathways, Ras - Raf - Mek - Erk and PI3-kinase - Akt. Incubation of cells with EGF resulted in rapid, robust, and sustained Erk signaling but shorter-term activation of Akt. In contrast, HGF induced sustained Akt signaling, but weak and short-lived Erk activity, and IGF-I stimulated strong long-term Akt responses, but negligible Erk signaling. To address potential interactions between signaling pathways, we employed specific small molecule inhibitors. In cells incubated with EGF or PDGF-AA, Raf activation and the subsequent stimulation of Erk reduced Akt signaling, while Mek inhibition, which blocked Erk activation, enhanced Akt, and turned transient effects into sustained responses. Our results reveal that individual growth factors initiate signaling cascades that vary markedly in strength and duration, and demonstrate in living cells the dramatic effects of crosstalk from Raf and Mek to PI3-kinase and Akt. Our data further indicate how specific growth factors can encode distinct cellular behaviors by promoting complex interactions among signaling pathways.


CONTEXT:: Health care professionals must continually identify collaborative ways to combat antibiotic resistance while improving community health and health care delivery. Clinical Laboratory Improvement Amendments of 1988 (CLIA)-waived point-of-care (POC) testing (POCT) services for infectious disease conducted in community pharmacies provide a means for pharmacists to collaborate with prescribers and/or public health officials combating antibiotic resistance while improving community health and health care delivery. OBJECTIVE:: To provide a comprehensive literature review that explores the potential for pharmacists to collaborate with public health professionals and prescribers using pharmacy-based CLIA-waived POCT services for infectious diseases. DESIGN:: Comprehensive literature review. SETTING:: PubMed and Google Scholar were searched for manuscripts and meeting abstracts for the following key words: infectious disease, community pharmacy, rapid diagnostic tests, rapid assay, and POC tests. INTERVENTION:: All relevant manuscripts and meeting abstracts utilizing POCT in community pharmacies for infectious disease were reviewed. OUTCOME MEASURE:: Information regarding the most contemporary evidence regarding CLIA-waived POC infectious diseases tests for infectious diseases and their use in community pharmacies was synthesized to highlight and identify opportunities to develop future collaborations using community pharmacy-based models for such services. RESULTS:: Evidence demonstrates that pharmacists in collaboration with other health care professionals can leverage their knowledge and accessibility to provide CLIA-waived POCT services for infectious diseases. Testing for influenza may augment health departments’ surveillance efforts, help promote rationale antiviral use, and avoid unnecessary antimicrobial therapy. Services for human immunodeficiency virus infection raise infection status awareness, increase access to health care, and facilitate linkage to appropriate care. Testing for group A streptococcal pharyngitis may curb inappropriate outpatient antibiotic prescribing. However, variance in pharmacy practice statues and the application of CLIA across states stifle collaboration. CONCLUSION:: CLIA-waived POCT services for infectious diseases are a means for pharmacists, public health professionals, and prescribers to collaboratively combat antibiotic resistance and improve community health. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.


Transforming Growth Factor-beta (TGF-beta) signaling in cancer has been termed the "TGF-beta paradox", acting as both a tumor suppressor and promoter. The complexity of TGF-beta signaling within the tumor is context dependent, and greatly impacted by cellular crosstalk between TGF-beta responsive cells in the microenvironment including adjacent epithelial, endothelial, mesenchymal, and hematopoietic cells. Here we utilize normal, weaning-induced mammary gland involution as a tissue microenvironment model to study the complexity of TGF-beta function. This article reviews facets of mammary gland involution that are TGF-beta regulated, namely mammary epithelial cell death, immune activation, and extracellular matrix remodeling. We outline how distinct cellular responses and crosstalk between cell types during physiologically normal mammary gland involution contribute to simultaneous tumor suppressive and promotional microenvironments. We also highlight alternatives to direct TGF-beta blocking anti-cancer therapies with an emphasis on eliciting concerted microenvironmental-mediated tumor suppression.


Despite long-standing hypotheses that intimate partner violence (IPV) may undermine children's ability to form secure attachment representations, few studies have empirically investigated this association. Particularly lacking is research that examines IPV and attachment during middle childhood, a time when the way that children understand, represent, and process the behavior of others becomes particularly important. Using data from a sample of African American children living in rural, low-income communities (N=98), the current study sought to address this gap by examining the association between physical IPV occurring early in children's lives and their attachment security during the first grade. Results indicate that, even after controlling for child- and family-level covariates, physical IPV was associated with a greater likelihood of being rated insecurely attached. This effect was above and beyond the influence of maternal parenting behaviors, demonstrating a unique effect of physical IPV on children's attachment representations during middle childhood. © National Council on Family Relations, 2016.


Red blood cell (RBC) destruction can be secondary to intrinsic disorders of the RBC or to extrinsic causes. In the congenital hemolytic anemias, intrinsic RBC enzyme, RBC membrane, and hemoglobin disorders result in hemolysis. The typical clinical presentation is a patient with pallor, anemia, jaundice, and often splenomegaly. The laboratory features include anemia, hyperbilirubinemia, and reticulocytosis. For some congenital hemolytic anemias, splenectomy is curative. However, in other diseases, avoidance of drugs and toxins is the best therapy. Supportive care with transfusions are also mainstays of therapy. Chronic hemolysis often results in the formation of gallstones, and cholecystectomy is often indicated. © 2016 Elsevier Inc.


PROBLEM: The U.S. health care system is undergoing a major transformation. Clinical delivery systems are now being paid according to the value of the care they provide, in accordance with the Triple Aim, which incorporates improving the quality and cost of care and the patient experience. Increasingly, financial risk is being transferred from insurers to clinical delivery systems that become responsible for both episode-based clinical care and the longitudinal care of patients. Thus, these delivery systems need to develop strategies to manage the health of populations. Academic medical centers (AMCs) serve a unique role in many markets yet may be ill prepared for this transformation. APPROACH: In 2013, Oregon Health & Science University (OHSU) partnered with a large health insurer and six other hospitals across the state to form Propel Health, a collaborative partnership designed to deliver the tools, methods, and support necessary for population health management. OHSU also developed new internal structures and transformed its business model to embrace this value-based care model. OUTCOMES: Each Propel Health partner included the employees and dependents enrolled in its employee medical plan, for approximately 55,000 covered individuals initially. By
2017, Propel Health is expected to cover 110,000 individuals. Other outcomes to measure in the future include the quality and cost of care provided under this partnership. NEXT STEPS: Anticipated challenges to overcome include insufficient primary care networks, conflicting incentives, local competition, and the magnitude of the transformation. Still, the time is right for AMCs to commit to improving the health of populations. © 2016 by the Association of American Medical Colleges

Measurement of cortisol in hair provides a chronic index of hypothalamic–pituitary–adrenal (HPA) axis activity and has been applied to assessments of temperament (stable behavioral differences between individuals). However, the extent to which chronically high HPA axis activity relates to a correspondingly high degree of behavioral reactivity is as yet unknown. Therefore, the goal of the present experiment was to assess the relationship between hair cortisol and a reactive temperament. We administered the Human Intruder Test (HIT) twice to 145 (80 male) rhesus macaques (Macaca mulatta) in order to assess behavioral reactivity. The HIT presents monkeys with an unfamiliar experimenter and is composed of a Baseline phase (no intruder) followed by three experimental phases in which the orientation of the intruder changes (Profile, Stare, Back). Behavioral responses to the test were videotaped and behaviors thought to reflect a reactive response to the intruder were scored for duration. Hair samples collected within ±1 month of the first HIT session were analyzed for cortisol by enzyme immunoassay. Subjects were assigned to three groups based on hair cortisol concentration: high, intermediate, and low cortisol phenotypes. Monkeys with the high cortisol phenotype were more reactive to the presence of the intruder than those with the low cortisol phenotype: they were more aggressive, scratched more, and spent more time in the back half of the cage. Males yawned significantly more while females spent more time immobile and in the back of the cage. Overall, monkeys with higher hair cortisol demonstrated an exaggerated response to the presence of the human intruder, supporting a relationship between high levels of chronic HPA axis activity and a reactive temperament. These results indicate that high levels of HPA axis activity, which may result from either genetic variation or environmental stress, correspond with heightened behavioral responses to a stressful experience. Am. J. Primatol. 79:e22526, 2017. © 2016 Wiley Periodicals, Inc.

The purpose of this study was to compare human fibrinogen-thrombin-based liquid dural graft; Beriplast® (Behring, Malburg, Germany) and collagen-based dural graft; Tissudura® (Baxter, Heidelberg, Germany) in terms of efficiency, side effects and complications. Thirty Spraque Dawley rats were used in this experimental study. A burrhole was opened on the left parietal bone of each subject and experimental dural defect was created. While 10 subjects were in sham group without any dural defect repair, dural defect was repaired by Beriplast in 10 subjects, by Tissudura in 10 subjects. After twenty-one day follow-up, edema, gliosis and inflammatory cell infiltration in the parenchyma, foreign body reaction in the bone, fibrosis in the epidural space and dura were evaluated histopathologically. Beriplast caused much more severe inflammation on cortex. When we compared Tissudura group with the sham group in terms of parenchymal edema and gliosis, the difference was not significant. On the other hand, we have found a significant increase in cortical parenchymal edema in Beriplast group. The last generation dural grafts result in different degrees of the tissue reaction. Severe inflammatory reaction can provide more satisfactory results in terms of watertight dural closure but on the other hand, the same reaction can be a disadvantage to the surrounding tissue. © 2015 OMU.

Research on symptom distress experienced by patients with end-stage liver disease at the end of life is limited. The aims of the study were to describe presence, frequency, severity, and distress of symptoms in patients with end-stage liver disease toward the end of life and to describe the variability in psychological and physical symptom distress between and within patients over time. This study used a prospective, longitudinal descriptive design. Data were collected from 20 patients once a month for up to 6 months. Participants completed the Memorial Symptom Assessment Scale, which reports a total score, a Global Distress Index score, and a psychological and a physical distress score. Patients reported lack of energy, pain, difficulty sleeping, and feeling drowsy as the most frequent, severe, and distressing symptoms. Global Distress Index mean scores (measured on a 1-4 scale) ranged from 2.6 to 2.9 across time. There was notable variability in psychological and physical distress scores between and within patients across time. Gaining knowledge about the prevalent symptoms experienced by patients with end-stage liver disease and the trajectory of these symptoms is crucial for designing interventions that optimize well-being in patients with end-stage liver disease as they are approaching death.


BACKGROUND: In the United States, the incidence of hepatocellular carcinoma (HCC) is rising. For those diagnosed with terminal HCC, there is no curative treatment and duration of survival is typically 1 to 2 years. Research on illness and treatment experiences toward the end of life for patients with terminal HCC is limited. OBJECTIVE: The aim of this study was to explore the illness experiences of patients with terminal HCC as they approached the end of life. METHODS: This study used a prospective, longitudinal descriptive design. Interview data were collected from 14 patients once a month for up to 6 months, for a total of 45 interviews. Data were analyzed using conventional content analysis. RESULTS: Three major themes (illness perceptions, decision to start treatment, and navigating treatment over time) and 10 subthemes were identified that were reflected across time in all patient experiences. Patients faced challenges with symptom experiences, treatment decisions, and unmet information needs affecting their quality of life. CONCLUSIONS: Gaining knowledge about the challenges facing patients with HCC is crucial for designing interventions that optimize their quality of life. IMPLICATIONS FOR PRACTICE: Healthcare professionals may improve the quality of life of patients with terminal HCC by eliciting patients’ perceptions of their illness and treatment decisions, symptom experiences, and information needs as the disease progresses and providing symptom management and offering information tailored to their needs. Care for patients with HCC who are approaching the end of life should be multidisciplinary and include timely referral to palliative care.


This study evaluated the utility of the Balance Error Scoring System (BESS) and the Sensory Organization Test (SOT) as tools for the screening and monitoring of Service members (SMs) with mild traumatic brain injury (mTBI) in a deployed setting during the acute and subacute phases of recovery. Patient records (N = 699) were reviewed for a cohort of SMs who sustained a blast-related mTBI while deployed to Afghanistan and were treated at the Concussion Restoration Care Center (CRCC) at Camp Leatherneck. On initial intake into the CRCC, participants completed two assessments of postural control, the BESS, and SOT. SMs with mTBI performed significantly worse on the BESS and SOT when compared with comparative samples. When the SOT data were further examined using sensory ratios, the results indicated that postural instability was primarily a result of vestibular and visual integration dysfunction (r > 0.62). The main finding of this study was that the sensitivity of the SOT composite score (50-58%) during the acute phase was higher than previous sensitivities found in the sports medicine literature for impact-related trauma.

In this feasibility study, we present a novel, wearable prototype of tactile biofeedback to alleviate gait disturbances, such as freezing of gait in Parkinson’s disease. We designed and tested a phase-dependent tactile biofeedback system that can be easily worn on the feet, with a simple switch to turn it on or off. Preliminary validation was performed in 8 subjects with Parkinson’s disease who show freezing during a turning in place test. A metronome, control condition was used to compare effectiveness in alleviating freezing. Promising results were obtained, both in term of acceptability of the device, and improving motor performance. © 2016 IEEE.


Hematopoietic cell transplantation (HCT) survivors are at risk for development of late complications and require lifelong monitoring for screening and prevention of late effects. There is an increasing appreciation of the issues related to healthcare delivery and coverage faced by HCT survivors. The 2016 National Institutes of Health Blood and Marrow Transplant Late Effects Initiative included an international and broadly representative Healthcare Delivery Working Group that was tasked with identifying research gaps pertaining to healthcare delivery and to identify initiatives that may yield a better understanding of the long-term value and costs of care for HCT survivors. There is a paucity of literature in this area. Critical areas in need of research include pilot studies of novel and information technology supported models of care delivery and coverage for HCT survivors along with development and validation of instruments that capture patient-reported outcomes. Investment in infrastructure to support this research, such as linkage of databases including electronic health records and routine inclusion of endpoints that will inform analyses focused around care delivery and coverage, is required. © 2016 The American Society for Blood and Marrow Transplantation.


American Thyroid Association (ATA) leadership asked the ATA Thyroid Nodules and Differentiated Thyroid Cancer Guidelines Task Force to review, comment on and make recommendations related to the suggested new classification of Encapsulated Follicular Variant Papillary Thyroid Carcinoma (eFVPTC) without capsular or vascular invasion to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The task force consists of members from the 2015 guidelines task force with the recusal of three members who were authors on the paper under review. Four pathologists and one endocrinologist were added for this specific review. We assessed the manuscript proposing the new classification and related literature. We recommend that the histopathologic nomenclature for Encapsulated Follicular Variant Papillary Thyroid Carcinoma (eFVPTC) without invasion may be re-classified as a NIFTP given the excellent prognosis of this neoplastic variant. This is a weak recommendation based on moderate-quality evidence. We also note that retrospective studies are needed to validate the observed patient outcomes (and test performance in predicting thyroid cancer outcomes), as well as implications on patients’ psychosocial health and economics.

Numerous observational studies appear to demonstrate an association between packed red blood cell (pRBC) transfusions and necrotizing enterocolitis (NEC). However, the limited numbers of randomized controlled trials (RCTs) do not support a causal relationship between pRBC transfusion and NEC. We sought to determine the quality of the evidence behind transfusion-associated necrotizing enterocolitis (TANEC), and to formulate a GRADE-based recommendation regarding transfusion practices to reduce the risk of TANEC. A systematic search including MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials and clinical trials registries was performed for studies assessing the association between transfusion and NEC. Teams of two paired reviewers independently screened studies for eligibility, assessed risk of bias using the GRADE framework, and collected data from each eligible study. We examined studies for two time points following transfusion: within 48 h if this was available, and otherwise at any time after transfusion. In total, 23 observational studies and three RCTs met inclusion criteria. The average rating for the quality of evidence of individual studies was between very low and low. On pooling studies for GRADE review, we observed an inconsistency of results. This led to a final overall quality of very low for the evidence for an association between transfusions and necrotizing enterocolitis. The pooled outcome of NEC for observational/case control studies was an odds ratio of 1.13 (95% CI: 0.99–1.29) when TANEC was defined as occurring within 48 hours of transfusion. For NEC occurring at any time post-transfusion, the pooled OR was 1.95 (1.60–2.38). Conversely, the pooled outcome of NEC for the RCT data had an odds ratio of 0.6 (0.3, 1.21) with NEC being less frequent in the liberal transfusion group compared to the restrictive transfusion group. The overall quality of the evidence for TANEC is very low, suggesting very little confidence in the effect estimate. RCT data tended toward apparent protection against NEC. The available evidence is not sufficient to support a practice recommendation around pRBC transfusions in the context of preventing the development of NEC. © 2016 Elsevier Inc.

Because of the significant emotional and psychosocial impact of chronic pruritus, it is important to accurately assess and measure itch severity. This study aims to validate and apply clinically meaningful bands to the ItchyQuant, an illustrated self-report numeric rating scale (NRS) for itch severity. A total of 76 adults with chronic pruritus were recruited. Participants rated their itch on the ItchyQuant, on a traditional 11-point NRS, and with verbal categorizations (no, mild, moderate, or severe). There was a significant, high correlation between the ItchyQuant and NRS (>0.92, P < 0.0001), demonstrating concurrent validity. Significantly more patients (47.2%) preferred the ItchyQuant than the NRS (23.6%) or had no preference (29.2%), P = 0.0015. Significantly more patients found the ItchyQuant easier to use (45.8%) than the NRS (20.8%) or had no preference (33.3%), P = 0.008. The set of clinically meaningful bands with the highest weighted kappa coefficient of agreement (κ = 0.69) was as follows: 0 (no itch), 1–3 (mild itch), 4–7 (moderate itch), 8–10 (severe itch). The ItchyQuant is a clinically meaningful measure of itch severity, demonstrating face and concurrent validity, that many patients prefer and find easier to use when compared with a traditional NRS. We suggest that the ItchyQuant can be added to the existing armamentarium of itch severity scales. We plan to investigate the ItchyQuant further in cognitively challenged populations. © 2016 The Authors

The goal of work-up of lower urinary tract symptoms is to establish the severity and cause of lower urinary tract symptoms and to predict with certainty which patients will respond to which treatments. Clinical guidelines exist to guide urologists in decision-making. All patients need a medical history with a validated symptom score, a physical examination, and a urinalysis. Prostate-specific antigen, postvoid urine residual, and peak urine flow rate provide additional information at little cost. For more invasive testing high-level

PURPOSE: To quantify Tofts model (TM) and shutter-speed model (SSM) perfusion parameters in prostate cancer (PCa) and noncancerous peripheral zone (PZ) and to compare the diagnostic performance of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to Prostate Imaging and Reporting and Data System (PI-RADS) classification for the assessment of PCa aggressiveness. MATERIALS AND METHODS: Fifty PCa patients (mean age 60 years old) who underwent MRI at 3.0T followed by prostatectomy were included in this Institutional Review Board-approved retrospective study. DCE-MRI parameters (Ktrans, ve, kep (TM&SSM) and intracellular water molecule lifetime taui (SSM)) were determined in PCa and PZ. Differences in DCE-MRI parameters between PCa and PZ, and between models were assessed using Wilcoxon signed-rank tests. Receiver operating characteristic (ROC) analysis for differentiation between PCa and PZ was performed for individual and combined DCE-MRI parameters. Diagnostic performance of DCE-MRI parameters for identification of aggressive PCa (Gleason >/=8, grade group [GG] >/=3 or pathology stage pT3) was assessed using ROC analysis and compared with PI-RADsv2 scores. RESULTS: DCE-MRI parameters were significantly different between TM and SSM and between PZ and PCa (P < 0.037). Diagnostic performances of TM and SSM for differentiation of PCa from PZ were similar (highest AUC TM: Ktrans +kep 0.76, SSM: taui +kep 0.8). PI-RADS outperformed TM and SSM DCE-MRI for identification of Gleason >/=8 lesions (AUC PI-RADS: 0.91, highest AUC DCE-MRI: Ktrans +taui SSM 0.61, P = 0.002). The diagnostic performance of PI-RADS and DCE-MRI for identification of GG >/=3 and pT3 PCa was not significantly different (P > 0.213). CONCLUSION: SSM DCE-MRI did not increase the diagnostic performance of DCE-MRI for PCa characterization. PI-RADS outperformed both TM and SSM DCE-MRI for identification of aggressive cancer. LEVEL OF EVIDENCE: 3 J. Magn. Reson. Imaging 2017.


Significant delays occur in providing adequate pain relief for patients who present to the emergency department (ED) with extremity fractures. The median time to pain medication administration for patients presenting to our ED with extremity fractures was 72.5 minutes. We used a multidisciplinary approach to implement three improvement cycles with the goal of reducing the median time to pain medication by 15% over an eight month time period. First, we redesigned nursing triage and treatment processes. Second, we improved nursing documentation standardization to ensure accurate tracking of patients who declined pain medication. Third, through consensus building within our physician group, we implemented a department-wide standard of care to provide early pain relief for extremity fractures. Median time to pain medication for patients with an extremity fracture reduced significantly between the pre-and post-intervention periods (p<0.009). The average monthly median time to medication was 72.5 minutes (95% CI: 57.1 to 88.0) before the intervention (Jan 2013-Oct 2014) and 49.8 minutes (95% CI: 42.7 to 56.9) after the intervention (November 2014 to June 2016). In other words, monthly median time was 31% faster (22.7 minute difference) in the post intervention period. Implementing three key interventions reduced the time to pain medication for patients with extremity injuries. Since June 2016 the reductions in median time to medication have continued to improve.


Epigenetic mechanisms have the potential to give rise to lasting changes in cell function that ultimately can affect behavior persistently. This concept is especially interesting with respect to fear reconsolidation and fear memory extinction. These two behavioral approaches are used in the laboratory to investigate how fear memory can be attenuated, which becomes important when searching for therapeutic intervention to treat
anxiety disorders and post-traumatic stress disorder. Here we review the role of several key epigenetic mechanisms in reconsolidation and extinction of learned fear and their potential to persistently alter behavioral responses to conditioned cues. We also briefly discuss how epigenetic mechanisms may establish persistent behaviors that challenge our definitions of extinction and reconsolidation.


PURPOSE: We investigated the use of genome sequencing for preconception carrier testing. Genome sequencing could identify one or more of thousands of X-linked or autosomal recessive conditions that could be disclosed during preconception or prenatal counseling. Therefore, a framework that helps both clinicians and patients understand the possible range of findings is needed to respect patient preferences by ensuring that information about only the desired types of genetic conditions are provided to a given patient.

METHODS: We categorized gene-condition pairs into groups using a previously developed taxonomy of genetic conditions. Patients could elect to receive results from these categories. A Return of Results Committee (RORC) developed inclusion and exclusion criteria for each category. RESULTS: To date, the RORC has categorized 728 gene-condition pairs: 177 are categorized as life span-limiting, 406 are categorized as serious, 93 are categorized as mild, 41 are categorized as unpredictable, and 11 are categorized as adult-onset. An additional 64 gene-condition pairs were excluded from reporting to patients or put on a watch list, generally because evidence that a gene and condition were associated was limited. CONCLUSION: Categorization of gene-condition pairs using our taxonomy simplifies communication regarding patient preferences for carrier information from a genomic test. Genet Med advance online publication 12 January 2017Genetics in Medicine (2017); doi:10.1038/gim.2016.198.


OBJECTIVE: Paroxysmal sympathetic hyperactivity (PSH) is characterized by episodic, hyperadrenergic alterations in vital signs after traumatic brain injury (TBI). We sought to apply an objective scale to the vital sign alterations of PSH in order to determine whether 1 element might be predictive of developing PSH.

SETTING/PARTICIPANTS/DESIGN: We conducted an observational study of consecutive TBI patients (Glasgow Coma Scale score </=12) and monitored the cohort for clinical evidence of PSH. PSH was defined as a paroxysm of 3 or more of the following characteristics: (1) tachycardia, (2) tachypnea, (3) hypertension, (4) fever, (5) dystonia (rigidity or decerebrate posturing), and (6) diaphoresis, with no other obvious causation (ie, alcohol withdrawal, sepsis). MAIN MEASURES: The Modified Clinical Feature Severity Scale (mCFSS) was applied to each participant once daily for the first 5 days of hospitalization. RESULTS: Nineteen (11%) of the 167 patients met criteria for PSH. Patients with PSH had a higher 5-day cumulative mCFSS score than those without PSH (median [interquartile range] = 36 [29-42] vs 29 [22-35], P = .01). Of the 4 components of the mCFSS, elevated temperature appeared to be most predictive of the development of PSH, especially during the first 24 hours (odds ratio = 1.95; 95% confidence interval, 1.12-3.40).

CONCLUSION: Early fever after TBI may signal impending autonomic dysfunction.


PURPOSE: Colon cancer screening is effective. To complete screening in 80% of individuals over age 50 years by 2018 will require adequate colonoscopy capacity throughout the country, including rural areas, where colonoscopy providers may have less specialized training. Our aim was to study the quality of colonoscopy in rural settings. METHODS: The Clinical Outcomes Research Initiative (CORI) and the Oregon Rural Practice-based Research Network (ORPRN) collaborated to recruit Oregon rural practices to submit colonoscopy reports to CORI's National Endoscopic Database (NED). Ten ORPRN sites were compared to non-ORPRN rural (n = 11) and nonrural (n = 43) sites between January 2009 and October 2011. Established colonoscopy quality measures were calculated for all sites. RESULTS: No ORPRN physicians were gastroenterologists compared with 82% of nonrural physicians. ORPRN practices reached the cecum in 87.4% of exams compared with 89.3% of rural sites (P = .0002) and 90.9% of nonrural sites (P < .0001). Resected polyps were less likely to be retrieved (84.7% vs 91.6%; P < .0001) and sent to pathology (77.1% vs 91.3%; P < .0001) at ORPRN practices compared to nonrural sites. The overall polyp detection (39.0% vs 40.3%) was similar (P = .217) between ORPRN and nonrural practices. Of exams with polyps, the rate for largest polyp on exam 6-9 mm was 20.8% at ORPRN sites, compared to 26.8% at nonrural sites (P < .0001), and for polyps >9mm 16.6% vs 18.7% (P = .106). CONCLUSION: ORPRN sites performed well on most colonoscopy quality measures, suggesting that high-quality colonoscopy can be performed in rural settings.


BACKGROUND/PURPOSE: We aim to evaluate the accuracy of the new prehospital notification criteria for patients with potential acute stroke in the prehospital setting. METHODS: We conducted a retrospective observational study from March 2011 to February 2013 of potential acute stroke patients prenotified using the new criteria which were: (1) positive Cincinnati Prehospital Stroke Scale (CPSS); (2) symptom onset within 3 hours; and (3) blood glucose level > 60 mg/dL. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the new criteria were calculated and outcomes of acute stroke patients were reported. Data of all patients with stroke or transient ischemic attack (TIA) transported to the destination hospital were also obtained to evaluate the compliance of emergency medical technicians. RESULTS: There were 2888 patients suspected of stroke by emergency medical technicians and 221 patients prenotified due to meeting the criteria. The PPV, NPV, sensitivity, and specificity of the new criteria were 76.9%, 96.6%, 64.9%, and 98.1%, respectively. Onset time > 3 hours (24/51, 47.1%) and seizure (27.5%) were the two most common conditions leading to false prenotification. Of all prenotified patients, 23.1% (51/221) received thrombolytic therapy. Hemorrhagic stroke or ischemic stroke with hemorrhagic transformation (53.8%) and minor symptoms or rapid recovery (26.9%) were the most common reasons excluding correctly prenotified patients from thrombolytic therapy. CONCLUSION: The accuracy of the new prehospital stroke criteria has higher PPV and specificity compared to previous CPSS validation studies.
Accurate prediction of Alzheimer’s disease (AD) is important for the early diagnosis and treatment of this condition. Mild cognitive impairment (MCI) is an early stage of AD. Therefore, patients with MCI who are at high risk of fully developing AD should be identified to accurately predict AD. However, the relationship between brain images and AD is difficult to construct because of the complex characteristics of neuroimaging data. To address this problem, we present a longitudinal measurement of MCI brain images and a hierarchical classification method for AD prediction. Longitudinal images obtained from individuals with MCI were investigated to acquire important information on the longitudinal changes, which can be used to classify MCI subjects as either MCI conversion (MCInc) or MCI non-conversion (MCInc) individuals. Moreover, a hierarchical framework was introduced to the classifier to manage high feature dimensionality issues and incorporate spatial information for improving the prediction accuracy. The proposed method was evaluated using 131 patients with MCI (70 MCInc and 61 MCInc) based on MRI scans taken at different time points. Results showed that the proposed method achieved 79.4% accuracy for the classification of MCInc versus MCInc, thereby demonstrating very promising performance for AD prediction. © The Author(s) 2017.

This study aims to assess the utility of quantitative dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) parameters in comparison with imaging tumor size for early prediction and evaluation of soft tissue sarcoma response to preoperative chemoradiotherapy. In total, 20 patients with intermediate- to high-grade soft tissue sarcomas received either a phase I trial regimen of sorafenib + chemoradiotherapy (n = 8) or chemoradiotherapy only (n = 12), and underwent DCE-MRI at baseline, after 2 weeks of treatment with sorafenib or after the first chemotherapy cycle, and after therapy completion. MRI tumor size in the longest diameter (LD) was measured according to the RECIST (Response Evaluation Criteria In Solid Tumors) guidelines. Pharmacokinetic analyses of DCE-MRI data were performed using the Shutter-Speed model. After only 2 weeks of treatment with sorafenib or after 1 chemotherapy cycle, Ktrans (rate constant for plasma/interstitium contrast agent transfer) and its percent change were good early predictors of optimal versus suboptimal pathological response with univariate logistic regression C statistics values of 0.90 and 0.80, respectively, whereas RECIST LD percent change was only a fair predictor (C = 0.72). Post-therapy Ktrans, ve (extravascular and extracellular volume fraction), and kep (intravasation rate constant), not RECIST LD, were excellent (C > 0.90) markers of therapy response. Several DCE-MRI parameters before, during, and after therapy showed significant (P < .05) correlations with percent necrosis of resected tumor specimens. In conclusion, absolute values and percent changes of quantitative DCE-MRI parameters provide better early prediction and evaluation of the pathological response of soft tissue sarcoma to preoperative chemoradiotherapy than the conventional measurement of imaging tumor size change.

Problems with sleep and cognitive impairment are common among people with multiple sclerosis (MS). The present study examined the relationship between self-reported sleep and both objective and perceived cognitive impairment in MS. Data were obtained from the baseline assessment of a multi-centre intervention trial (NCT00841321). Participants were 121 individuals with MS. Nearly half (49%) of participants met the criteria for objective cognitive impairment; however, cognitively impaired and unimpaired participants did not differ on any self-reported sleep measures. Nearly two-thirds (65%) of participants met the criteria for ‘poor’ sleep, and poorer sleep was significantly associated with greater levels of perceived cognitive impairment. Moreover, the relationships between self-reported sleep and perceived cognitive impairment were significant beyond the influence of clinical and demographic factors known to influence sleep and cognitive functioning (e.g. age, sex, education level, disability severity, type of MS, disease duration,
depression and fatigue). However, self-reported sleep was not associated with any measures of objective cognitive impairment. Among different types of perceived cognitive impairment, poor self-reported sleep was most commonly related to worse perceived executive function (e.g., planning/organization) and prospective memory. Results from the present study emphasize that self-reported sleep is significantly and independently related to perceived cognitive impairment in MS. In terms of clinical implications, interventions focused on improving sleep may help improve perceived cognitive function and quality of life in this population; however, the impact of improved sleep on objective cognitive function requires further investigation.


The striatum integrates excitatory inputs from the cortex and the thalamus to control diverse functions. Although the striatum is thought to consist of sensorimotor, associative and limbic domains, their precise demarcations and whether additional functional subdivisions exist remain unclear. How striatal inputs are differentially segregated into each domain is also poorly understood. This study presents a comprehensive map of the excitatory inputs to the mouse striatum. The input patterns reveal boundaries between the known striatal domains. The most posterior striatum likely represents the 4th functional subdivision, and the dorsomedial striatum integrates highly heterogeneous, multimodal inputs. The complete thalamo-cortico-striatal loop is also presented, which reveals that the thalamic subregions innervated by the basal ganglia preferentially interconnect with motor-related cortical areas. Optogenetic experiments show the subregion-specific heterogeneity in the synaptic properties of striatal inputs from both the cortex and the thalamus. This projectome will guide functional studies investigating diverse striatal functions. © Hunnicutt et al.


Personality may affect the way adolescents and young adults (AYAs) with cancer report health-related quality of life (HRQoL). Patients aged 15-39 years (n = 165) completed a survey at 12-16 months postdiagnosis. The survey included questions on HRQoL (SF-36), distress Brief Symptom Inventory-18, and personality (NEO-Five-Factor Inventory). Personality traits were not associated with physical HRQoL. The personality trait neuroticism was negatively associated with mental HRQoL (beta = -0.37; p < 0.001) and positively with psychological distress (beta = 0.47; p < 0.001). Hierarchical regression and mediation analyses indicated that psychological distress fully mediated the association between neuroticism and mental HRQoL. Findings emphasize the importance of psychosocial intervention for distress in AYAs with cancer.


Purpose To examine changes in health-related quality of life (HRQoL) and its predictors during the first 2 years after initial cancer diagnosis in adolescent and young adult (AYA) patients with cancer. Patients and Methods A multicenter, longitudinal, prospective study was conducted among a diverse sample of AYA patients with cancer ages 15 to 39 years. One hundred seventy-six patients (75% response) completed a self-report measure of HRQoL (Short Form-36 [SF-36]) within the first 4 months after diagnosis and again 12 and 24 months later. Linear mixed models with random intercepts and slopes estimated changes in QoL. Results Recently diagnosed AYA patients with cancer had significantly worse physical component scale (PCS) scores (38.7 v 52.8; P < .001) and mental component scale (MCS) scores (42.9 v 48.9; P < .001) when compared with population norms. Significant improvements in PCS and MCS scores from baseline to 24-month follow-up were observed; however, these increases were largest during the first 12 months. At the 24-month follow-up, AYA patients still had significantly lower PCS scores (48.0 v 52.8; P < .001) and MCS scores (45.8 v 48.9; P = .002) when compared with population norms. Multivariable analyses revealed that improvements in PCS and
MCS scores were primarily a function of being off-treatment and being involved in school or work. PCS but not MCS scores were worse for AYA patients diagnosed with cancers with poorer prognoses. Conclusion Although HRQoL improved over time, it was still compromised 24 months after primary diagnosis. Given relatively little observed improvement in HRQoL during the 12- to 24-month period after diagnosis, AYA patients may benefit from supportive care interventions administered during the second year after diagnosis.


Cardiorenal syndrome type 1 causes acute kidney injury but is poorly understood; animal models and diagnostic aids are lacking. Robust noninvasive measurements of glomerular filtration rate are required for injury models and clinical use. Several have been described but are untested in translational models and suffer from biologic interference. We developed a mouse model of cardiorenal syndrome and tested the novel near-infrared fluorophore, ZW800-1, to assess renal and cardiac function. We performed murine cardiac arrest and cardiopulmonary resuscitation followed by transthoracic echocardiography, 2- and 24h later. Transcutaneous fluorescence of ZW800-1 bolus dispersion and clearance was assessed with whole-animal imaging and compared with glomerular filtration rate (GFR, inulin clearance), tubular cell death (using unbiased stereology), and serum creatinine, and urine protein creatinine ratio. Correlation, Bland-Altman, and polar analysis were used to compare GFR with ZW800-1 clearance. Cardiac arrest and cardiopulmonary resuscitation caused reversible cardiac failure, halving fractional shortening of the left ventricle (n=12, p=0.03). Acute kidney injury resulted with near-zero GFR and six-fold increase in serum creatinine 24h later (n=16, p<0.01). ZW800-1 biodistribution and clearance was exclusively renal. ZW800-1 t1/2 and clearance correlated with GFR (r=0.92, n=31, p<0.0001). ZW800-1 fluorescence was reduced in cardiac arrest and cardiopulmonary resuscitation-treated mice compared to sham animals 8-10s after injection (p<0.01) and bolus time-dispersion curves demonstrated that ZW800-1 fluorescence dispersion correlated with left ventricular function (r=0.74, p<0.01). Cardiac arrest and cardiopulmonary resuscitation leads to experimental cardiorenal syndrome type 1. ZW800-1, a small near-infrared fluorophore being developed for clinical intraoperative imaging is favorable for evaluating cardiac and renal function noninvasively.


Background: Proton irradiation poses a potential hazard to astronauts during and following a mission, with post-mitotic cells at most risk because they cannot dilute resultant epigenetic changes via cell division. Persistent epigenetic changes that result from environmental exposures include gains or losses of DNA methylation of cytosine, which can impact gene expression. In the present study, we compared the long-term epigenetic effects of whole body proton irradiation in the mouse hippocampus and left ventricle. We used an unbiased genome-wide DNA methylation study, involving ChIP-seq with antibodies to 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) to identify DNA regions in which methylation levels have changed 22 weeks after a single exposure to proton irradiation. We used DIP-Seq to profile changes in genome-wide DNA methylation and hydroxymethylation following proton irradiation. In addition, we used published RNAseq data to assess whether differentially methylated regions were linked to changes in gene expression. Results: The DNA methylation data showed tissue-dependent effects of proton irradiation and revealed significant major pathway changes in response to irradiation that are related to known pathophysio logic processes. Many regions affected in the ventricle mapped to genes involved in cardiovascular function pathways, whereas many regions affected in the hippocampus mapped to genes involved in neuronal functions. In the ventricle, increases in 5hmC were associated with decreases in 5mC. We also observed spatial overlap for regions where both epigenetic marks decreased in the ventricle. In
hippocampus, increases in 5hmC were most significantly correlated (spatially) with regions that had
increased 5mC, suggesting that deposition of hippocampal 5mC and 5hmC may be mechanistically coupled.
Conclusions: The results demonstrate long-term changes in DNA methylation patterns following a single
proton irradiation, that these changes are tissue specific, and that they map to pathways consistent with
tissue specific responses to proton irradiation. Further, the results suggest novel relationships between
changes in 5mC and 5hmC. © 2016 Impey et al.

biomarkers and changes in clinical/MRI evidence of golimumab-treated patients with ankylosing spondylitis:
Results of the randomized, placebo-controlled GO-RAISE study. Arthritis Research and Therapy, 18(1).

Background: In the present study, we evaluated relationships between serum biomarkers and
clinical/magnetic resonance imaging (MRI) findings in golimumab-treated patients with ankylosing
spondylitis. Methods: In the GO-RAISE study, 356 patients with ankylosing spondylitis randomly received
either placebo (n = 78) or golimumab 50mg or 100mg (n = 278) injections every 4 weeks through week 24
(placebo-controlled); patients continuing GO-RAISE received golimumab through week 252. Up to 139/125
patients had sera collected for biomarkers/serial spine MRI scans (sagittal plane, 1.5-T scanner). Two blinded
readers employed modified ankylosing spondylitis spine magnetic resonance imaging score for activity
(ASspiMRI-a) and ankylosing spondylitis spine magnetic resonance imaging score for chronicity. Spearman
correlations (r s) were assessed between serum biomarkers (n = 73) and Bath Ankylosing Spondylitis Disease
Activity Index (BASDAI), C-reactive protein (CRP)-based Ankylosing Spondylitis Disease Activity Score
(ASDAS), modified Stokes Ankylosing Spondylitis Spine Score (mSASSS), and ASspiMRI scores. Serum
biomarkers predicting postbaseline spinal fatty lesion development and inflammation were analyzed by
logistic regression. Results: Significant, moderately strong correlations were observed between baseline
inflammatory markers interleukin (IL)-6, intracellular adhesion molecule-1, complement component 3 (C3),
CRP, haptoglobin, and serum amyloid-P and baseline ASDAS (r s = 0.39-0.66, p ≤ 0.01). Only baseline leptin
significantly correlated with ASDAS improvement at week 104 (r s = 0.55, p = 0.040), and only baseline IL-6
significantly predicted mSASSS week 104 change (β = 0.236, SE = 0.073, p = 0.002, model R2 = 0.093). By
logistic regression, baseline leptin, C3, and tissue inhibitor of metalloproteinase (TIMP)-1 correlated with new
fatty lesions per spinal MRI at week 14 and week 104 (both p ≤ 0.01). Changes in serum C3 levels at week
4 (r s = 0.55, p = 0.001) and week 14 (r s = 0.49, p = 0.040) significantly correlated with BASDAI improvement
at week 14. Baseline IL-6 and TIMP-1 (r s = 0.63, 0.67; p ≥ 0.05) and reductions at week 4 in IL-6 (r s = 0.61,
p ≤ 0.05) and C3 (r s = 0.72; p ≤ 0.05) significantly correlated with week 14 ASspiMRI-a improvement.
Conclusions: Extensive serum biomarker multiparameter analyses in golimumab-treated patients with
ankylosing spondylitis demonstrated few correlations with disease activity or MRI changes; IL-6 weakly
correlated with radiographic progression. Trial registration: ClinicalTrials.gov identifier: NCT00265083.
Registered on 12 December 2005. © 2016 The Author(s).

About a decade age, loss-of-function mutations in the filaggrin molecule were first implicated in the
pathogenesis of ichthyosis vulgaris and, subsequently, of atopic dermatitis and other atopic diseases. Since
then, intensive study of the role of filaggrin null mutations have led to other milestones in understanding the
pathologic pathways in these diseases, including the initiation, maintenance, and promotion of the disease
processes. The result has been new and emerging clinical and pharmacologic strategies for early

doi:10.1016/j.addbeh.2016.02.037
OBJECTIVES: To examine recent trends in cigarette smoking among older (65 years and above) adults in the United States. METHODS: We used data from the Medicare Health Outcomes Survey dataset to estimate rates of smoking, quitting, and (re)starting from 2005 to 2012. Medicare Advantage enrollees completed mail surveys at baseline and two years later. We included subgroup analyses by sex, race, and self-rated health. RESULTS: Smoking prevalence declined slightly, with most of the decline occurring over the course of a single year (2007-2008). Rates of quitting declined slightly (meaning fewer people were quitting), and (re)starting marginally declined from 2005 to 2012. There were no substantial differences between subgroups. We did not observe any significant changes in prevalence or cessation of smoking among Medicare Advantage participants during this time. CONCLUSIONS: Smoking remains a public health problem for older adults. We did not find evidence of significant changes in smoking prevalence or cessation for older adults during the time period we examined.


Introduction Cooking interventions may improve diet quality. Most cooking interventions are delivered in group settings. Home visiting programs may be an appropriate mechanism for delivering such interventions to low-income families with young children. We conducted a pilot study to test the feasibility of using a cooking intervention delivered by home visitors to improve attitudes and behaviors related to vegetable consumption by low-income parents with children enrolled in a home visiting program. Methods We invited 121 parents with children enrolled in an Early Head Start Home Visiting program in Portland, Oregon, to participate. During 2013-2014, each month for 8 months, home visitors (n = 14) implemented 1 cooking activity plus 1 complementary activity focused on 12 vegetables. We collected pre- and post-intervention data on participants’ cooking confidence and whether they tried and liked the selected vegetables. We also measured fidelity to protocol and home visitors’ perception of intervention usability. Results Of 104 participants, 58 provided pre- and post-intervention data. We observed a significant increase in confidence in baking, roasting or grilling vegetables; cooking 6 of 10 vegetables; and trying 7 of 12 vegetables. Nearly all respondents participated in the monthly cooking activity (96%) and complementary activity (94%). Twelve of 14 home visitors reported that the intervention was acceptable, feasible, and easy to understand, and needed systems supports to implement. Conclusion Cooking interventions may be a feasible approach to improving attitudes and behaviors related to vegetable consumption by low-income families with young children. Additional research is needed to assess the impact of such interventions on vegetable consumption.


Objectives: The purpose of this study was to investigate the influence of insufficient light exposure on the polymerization of conventional and self-adhesive dual-cure resin cements under ceramic restorations. Methods: Two conventional dual-cure resin cements (Rely-X ARC, Duolink) and two self-adhesive resin cements (Rely-X U200, Maxcem Elite) were polymerized under different curing modes (dual-cure or self-cure), curing times (20 and 120 seconds), and thickness of a ceramic overlay (2 and 4 mm). Polymerization kinetics was measured by Fourier transform infrared spectroscopy for the initial 10 minutes and after 24 hours. Data were analyzed using mixed model analysis of variance (ANOVA), one-way ANOVA/Student-
Newman-Keuls post hoc test, and paired t-test (α=0.05). Results: When light-curing time was set to 20 seconds, the presence of the ceramic block significantly affected the degree of conversion (DC) of all resin cements. Especially, the DC of the groups with 20 seconds of light-curing time under 4 mm of ceramic thickness was even lower than that of the self-cured groups at 24 hours after polymerization (p<0.05). However, when light-curing time was set to 120 seconds, a similar DC compared with the group with direct light exposure (p>0.05) was achieved in all dual-cure groups except Maxcem Elite, at 24 hours after polymerization. Conclusions: For both conventional and self-adhesive dual-cure resin cements, insufficient light exposure (20 seconds of light-curing time) through thick ceramic restoration (4 mm thick) resulted in a DC even lower than that of self-curing alone.


Background: Seasonal variation has been reported in diagnosis of eosinophilic oesophagitis (EoE), but results are not consistent across studies and there are no national-level data in the USA. Aim: To determine if there is seasonal variation in diagnosis of oesophageal eosinophilia and EoE in the USA, while accounting for factors such as climate zone and geographic variation. Methods: This was a cross-sectional study using a USA national pathology database. Patients with oesophageal eosinophilia (≥15 eosinophils per high-power field) comprised the primary case definition and were compared to those with normal oesophageal biopsies. We calculated the crude and adjusted odds of oesophageal eosinophilia by season, as well as by day of the year. Sensitivity analyses were performed using more restrictive case definitions of EoE, and after stratification by climate zone. Results: Exactly, 14,524 cases with oesophageal eosinophilia and 90,459 normal controls were analysed. The adjusted odds of oesophageal eosinophilia were higher in the late spring and summer months, with the highest odds in July (aOR: 1.13; 95% CI: 1.03–1.24). These findings persisted with increasing levels of oesophageal eosinophilia, as well as across EoE case definitions. Seasonal variation was strongest in temperate and cold climates, and peak diagnosis varied by climate zone. Conclusions: There is a mild but consistent seasonal variation in the diagnosis of oesophageal eosinophilia and EoE, with cases more frequently diagnosed during summer months. These findings take into account climate and geographic differences, suggesting that aeroallergens may contribute to disease development or flare. © 2015 John Wiley & Sons Ltd


Lutein is the predominant carotenoid in the developing primate brain and retina, and may have important functional roles. However, its bioaccumulation pattern during early development is not understood. In this pilot study, we investigated whether carotenoid supplementation of infant formula enhanced lutein tissue deposition in infant rhesus macaques. Monkeys were initially breastfed; from 1 to 3 months of age they were fed either a formula supplemented with lutein, zeaxanthin, beta-carotene and lycopene, or a control formula with low levels of these carotenoids, for 4 months (n = 2/group). All samples were analyzed by high pressure liquid chromatography (HPLC). Final serum lutein in the supplemented group was 5 times higher than in the unsupplemented group. All brain regions examined showed a selective increase in lutein deposition in the supplemented infants. Lutein differentially accumulated across brain regions, with highest amounts in occipital cortex in both groups, beta-carotene accumulated, but zeaxanthin and lycopene were undetectable in any brain region. Supplemented infants had higher lutein concentrations in peripheral retina but not in macular retina. Among adipose sites, abdominal subcutaneous adipose tissue exhibited the highest lutein level and was 3-fold higher in the supplemented infants. The supplemented formula enhanced carotenoid deposition in several other tissues. In rhesus infants, increased intake of carotenoids from formula enhanced their deposition in serum and numerous tissues and selectively increased lutein in multiple brain regions.

Congenital cataract is both clinically diverse and genetically heterogeneous. To investigate the underlying genetic defect in three-generations of a Chinese family with autosomal dominant congenital cataracts, we recruited family members who underwent comprehensive ophthalmic examinations. A heterozygous missense mutation c.634G > C (p.G212R) substitution was identified in the MIP gene through target region capture sequencing. The prediction results of PolyPhen-2 and SIFT indicated that this mutation was likely to damage the structure and function of MIP. Confocal microscopy images showed that the intensity of the green fluorescent signal revealed much weaker signal from the mutant compared to the wild-type MIP. The expressed G212R-MIP was diminished and almost exclusively cytoplasmic in the HeLa cells; whereas the WT-MIP was stable dispersed throughout the cytoplasm, and it appeared to be in the membrane structure. Western blot analysis indicated that the protein expression level of the mutant form of MIP was remarkably reduced compared with that of the wild type, however, the mRNA levels of the wild-type and mutant cells were comparable. In conclusion, our study presented genetic and functional evidence for a novel MIP mutation of G212R, which leads to congenital progressive cortical punctate with or without Y suture.


Historically, the primary marker of quality for congenital cardiac surgery has been postoperative mortality. The purpose of this study was to determine whether additional markers (10 surgical metrics) independently predict length of stay (LOS), thereby providing specific targets for quality improvement. Ten metrics (unplanned ECMO, unplanned cardiac catheterization, revision of primary repair, delayed closure, mediastinitis, reexploration for bleeding, complete heart block, vocal cord paralysis, diaphragm paralysis, and change in preoperative diagnosis) were defined in 2008 and subsequently collected from 1024 consecutive index congenital cardiac cases, yielding 990 cases. Four patient characteristics and 22 case characteristics were used for risk adjustment. Univariate and multivariable analyses were used to determine independent associations between each metric and postoperative LOS. Increased LOS was independently associated with revision of the primary repair (p = 0.014), postoperative complete heart block requiring a permanent pacemaker (p = 0.001), diaphragm paralysis requiring plication (p < 0.001), and unplanned postoperative cardiac catheterization (p < 0.001). Compared with patients without each metric, LOS was 1.6 (95% CI 1.1-2.2, p = 0.014), 1.7 (95% CI 1.2-2.3, p = 0.001), 1.8 (95% CI 1.4-2.3, p < 0.001), and 2.0 (95% CI 1.7-2.4, p < 0.001) times as long, respectively. These effects equated to an additional 4.5-7.8 days in hospital, depending on the metric. The other 6 metrics were not independently associated with increased LOS. The quality of surgery during repair of congenital heart disease affects outcomes. Reducing the incidence of these 4 specific surgical metrics may significantly decrease LOS in this population.


Objective To compare the pulmonary function, measured at birth and at hospital discharge, of infants whose mothers had been randomized to a single rescue course of antenatal steroids versus those whose mothers had been randomized to placebo. Study design This study involved follow-up at hospital discharge of subjects of a randomized, double-blinded trial. In the original trial, pregnant women at ≥14 days after their initial course of antenatal steroids and 34 weeks’ gestation were randomized to rescue antenatal steroids (44 mothers, 56 infants) or placebo (41 mothers, 57 infants). Passive respiratory compliance (Crs), passive respiratory resistance, and functional residual capacity were measured in all infants at birth and again at discharge to evaluate changes in pulmonary mechanics over time. Statistical analyses were based on intention to treat. Results We previously reported that compared with infants in the placebo group, infants in the rescue antenatal steroids group had a higher mean Crs value measured within 72 hours of birth (1.21 vs 1.01 mL/cm H2O/kg; P < .05). Here we show that the Crs benefit in the antenatal steroids group was
sustained until discharge. Infants in the placebo group demonstrated improvement in Crs such that by discharge, there was no difference in mean Crs between the rescue antenatal steroids and placebo groups (1.18 vs 1.22 mL/cm H2O/kg). Conclusions Rescue antenatal steroids significantly increased Crs measured within 72 hours of birth, and this increase was sustained until hospital discharge. Preterm infants in the placebo group demonstrated a decreased initial Crs compared with the rescue antenatal steroids group, but achieved a comparable Crs by the time of discharge. Trial registration ClinicalTrials.gov: NCT00669383. © 2016 Elsevier Inc.

INTRODUCTION: Recent literature calls for initiatives to improve the quality of education studies and support faculty in approaching educational problems in a scholarly manner. Understanding the emergency medicine (EM) educator workforce is a crucial precursor to developing policies to support educators and promote education scholarship in EM. This study aims to illuminate the current workforce model for the academic EM educator. METHODS: Program leadership at EM training programs completed an online survey consisting of multiple choice, completion, and free-response type items. We calculated and reported descriptive statistics. RESULTS: 112 programs participated. Mean number of core faculty/program: 16.02 +/− 7.83 [14.53-17.5]. Mean number of faculty full-time equivalents (FTEs)/program dedicated to education is 6.92 +/− 4.92 [5.87-7.98], including (mean FTE): Vice chair for education (0.25); director of medical education (0.13); education fellowship director (0.2); residency program director (0.83); associate residency director (0.94); assistant residency director (1.1); medical student clerkship director (0.8); assistant/associate clerkship director (0.28); simulation fellowship director (0.11); simulation director (0.42); director of faculty development (0.13). Mean number of FTEs/program for education administrative support is 2.34 +/− 1.1 [2.13-2.61]. Determination of clinical hours varied; 38.75% of programs had personnel with education research expertise. CONCLUSION: Education faculty represent about 43% of the core faculty workforce. Many programs do not have the full spectrum of education leadership roles and educational faculty divide their time among multiple important academic roles. Clinical requirements vary. Many departments lack personnel with expertise in education research. This information may inform interventions to promote education scholarship.


The purpose of this study was to develop optimal configuration of adhesive ECG patches placement on the torso, which would provide the best agreement with the Frank orthogonal ECGs. Ten seconds of orthogonal ECG followed by 3-5min of ECGs using patches at 5 different locations simultaneously on the torso were recorded in 50 participants at rest in sitting position. Median beat was generated for each ECG and 3 patch ECGs that best correlate with orthogonal ECGs were selected for each participant. For agreement analysis, spatial QRS-T angle, spatial QRS and T vector characteristics, spatial ventricular gradient, roundness, thickness and planarity of vectorcardiographic (VCG) loops were measured. Key VCG parameters showed high agreement in Bland-Altman analysis (spatial QRS-T angle on 3-patch ECG vs. Frank ECG bias 0.3 (95% limits of agreement [-6.23;5.71 degrees]), Lin’s concordance coefficient=0.996). In conclusion, newly developed orthogonal 3-patch ECG can be used for long-term VCG monitoring.


BACKGROUND: Genome-wide association studies (GWAS) have identified 18 loci associated with serous ovarian cancer (SOC) susceptibility but the biological mechanisms driving these findings remain poorly characterised. Germline cancer risk loci may be enriched for target genes of transcription factors (TFs) critical to somatic tumorigenesis. METHODS: All 615 TF-target sets from the Molecular Signatures Database were
evaluated using gene set enrichment analysis (GSEA) and three GWAS for SOC risk: discovery (2196 cases/4396 controls), replication (7035 cases/21 693 controls; independent from discovery), and combined (9627 cases/30 845 controls; including additional individuals). RESULTS: The PAX8-target gene set was ranked 1/615 in the discovery (PGSEA<0.001; FDR=0.21), 7/615 in the replication (PGSEA=0.004; FDR=0.37), and 1/615 in the combined (PGSEA<0.001; FDR=0.21) studies. Adding other genes reported to interact with PAX8 in the literature to the PAX8-target set and applying an alternative to GSEA, interval enrichment, further confirmed this association (P=0.006). Fifteen of the 157 genes from this expanded PAX8 pathway were near eight loci associated with SOC risk at P<10^{-5} (including six with P<5 x 10^{-8}). The pathway was also associated with differential gene expression after shRNA-mediated silencing of PAX8 in HeyA8 (PGSEA=0.025) and IGROV1 (PGSEA=0.004) SOC cells and several PAX8 targets near SOC risk loci demonstrated in vitro transcriptomic perturbation. CONCLUSIONS: Putative PAX8 target genes are enriched for common SOC risk variants. This finding from our agnostic evaluation is of particular interest given that PAX8 is well-established as a specific marker for the cell of origin of SOC.


Health insurance markets in the United States are characterized by imperfect information, complex products, and substantial search frictions. Insurance agents and brokers play a significant role in helping employers navigate these problems. However, little is known about the relations between the structure of the agent/broker market and access and affordability of insurance. This article aims to fill this gap by investigating the influence of agents/brokers on health insurance offering decisions of small firms, which are particularly vulnerable to problems of financing health insurance. Using a unique membership database from the National Association of Health Underwriters together with a nationally representative survey of employers, we find that small firms in more competitive agent/broker markets are more likely to offer health insurance and at lower premiums. Moreover, premiums are less dispersed in more competitive agent/broker markets. © 2016 The Journal of Risk and Insurance.


BACKGROUND: Cardiopulmonary involvement in systemic sclerosis (SSc) is a poor prognostic factor, due to pulmonary hypertension and right ventricular dysfunction. We assessed the echocardiographic parameters of right ventricular (RV) function in SSc and correlated echocardiographic findings to clinical features of the disease. METHODS: Thirty patients with SSc (cases) and 30 healthy, age-matched subjects (controls) were studied. Echocardiography, including tissue Doppler imaging, was used to evaluate cardiac function. RESULTS: Pulmonary hypertension could be documented in only 5 cases by Doppler echo, using Bernoulli principle. RV diastolic function was significantly deranged in cases. RV systolic function and left ventricle (LV) diastolic function were also significantly deranged in the cases. RV thickness was increased in patients with SSc. There were no significant differences in the echocardiographic variables between diffuse and limited subtypes of SSc. Myocardial performance index (MPI) of both ventricles were increased in cases. We could demonstrate RV thickness as the single most important predictor of MPI of both ventricles with sensitivity of 82% and specificity of 72% for RV-MPI and 63% for LV-MPI. Diastolic function was not found to be affected by disease duration or Rodnan skin score. CONCLUSION: Patients with SSc exhibit abnormal RV and LV diastolic functions as well as abnormal RV systolic function. RV wall thickness was found to be simple and the single best predictor of global myocardial performance. RV dysfunction may be a response to intermittent pulmonary arterial hypertension, lung parenchymal involvement, or secondary to LV diastolic dysfunction in SSc.

Population-based carrier screening is limited to well-studied or high-impact genetic conditions for which the benefits may outweigh the associated harms and costs. As the cost of genome sequencing declines and availability increases, the balance of risks and benefits may change for a much larger number of genetic conditions, including medically actionable additional findings. We designed an RCT to evaluate genomic clinical sequencing for women and partners considering a pregnancy. All results are placed into the medical record for use by healthcare providers. Through quantitative and qualitative measures, including baseline and post result disclosure surveys, post result disclosure interviews, 1–2 year follow-up interviews, and team journaling, we are obtaining data about the clinical and personal utility of genomic carrier screening in this population. Key outcomes include the number of reportable carrier and additional findings, and the comparative cost, utilization, and psychosocial impacts of usual care vs. genomic carrier screening. As the study progresses, we will compare the costs of genome sequencing and usual care as well as the cost of screening, pattern of use of genetic or mental health counseling services, number of outpatient visits, and total healthcare costs. This project includes novel investigation into human reactions and responses from would-be parents who are learning information that could both affect a future pregnancy and their own health. © 2016 The Authors


Atrial fibrillation (AF) is the most common arrhythmia encountered by clinicians. Clinical decision-making focuses on reducing ischemic stroke risk in AF patients; however, AF is also associated with an increased risk of acute coronary syndromes (ACS). Patients with ACS and concurrent AF are less likely to receive appropriate therapies and more likely to experience adverse outcomes than ACS patients in sinus rhythm (SR). Clinicians may be able to stratify ACS patients at increased risk of AF development based on clinical characteristics. Evidence supporting specific therapeutic options for prevention of ACS in AF patients or for prevention of AF in ACS patients is limited, however there is some evidence of differing effects among oral anticoagulant regimens in these populations. Investigations of the relationship of AF with the full spectrum of ACS are not well described and should be the focus of future research.


Evidence is accumulating to suggest that mutations in the Ankyrin and SOCS Box-containing protein-10 (ASB10) gene are associated with glaucoma. Since its identification in a large Oregon family with primary open-angle glaucoma (POAG), ASB10 variants have been associated with disease in US, German and Pakistani cohorts. ASB10 is a member of the ASB family of proteins, which have a common structure including a unique N-terminus, a variable number of central ankyrin (ANK) repeat domains and a suppressor of cytokine signaling (SOCS) box at the C-terminus. Mutations in . ASB10 are distributed throughout the entire length of the gene including the two alternatively spliced variants of exon 1. A homozygous mutation in a Pakistani individual with POAG, which lies in the center of the SOCS box, is associated with a particularly severe form of the disease. Like other SOCS box-containing proteins, ASB10 functions in ubiquitin-mediated degradation pathways. The ANK repeats bind to proteins destined for degradation. The SOCS box recruits ubiquitin ligase proteins to form a complex to transfer ubiquitin to a substrate bound to the ANK repeats. The ubiquitin-tagged protein then enters either the proteasomal degradation pathway or the autophagic-lysosomal pathway. The choice of pathway appears to be dependent on which lysine residues are used to build polyubiquitin chains. However, these reciprocal pathways work in tandem to degrade proteins because

OBJECTIVE: This study examined the distribution of opioid prescribing across providers and patients and the extent to which concentrated distribution predicts opioid misuse. METHODS: Using 2013 Oregon Medicaid claims and the National Provider Identifier Registry, this study identified patients who filled at least one opioid prescription and providers who prescribed opioids for those patients (N=61,477 Medicaid


Introduction: Suicide rates and the proportion of alcohol-involved suicides rose during the 2008-2009 recession. Associations between county-level poverty, foreclosures, and unemployment and suicide rates and proportion of alcohol-involved suicides were investigated. Methods: In 2015, National Violent Death Reporting System data from 16 states in 2005-2011 were utilized to calculate suicide rates and a measure of alcohol involvement in suicides at the county level. Panel models with year and state fixed effects included county-level measures of unemployment, foreclosure, and poverty rates. Results: Poverty rates were strongly associated with suicide rates for both genders and all age groups, were positively associated with alcohol involvement in suicides for men aged 45-64 years, and negatively associated for men aged 20-44 years. Foreclosure rates were negatively associated with suicide rates for women and those aged ≥65 years but positively related for those aged 45-64 years. Unemployment rate effects on suicide rates were mediated by poverty rates in all groups. Conclusions: Population risk of suicide was most clearly associated with county-level poverty rates, indicating that programs addressing area poverty should be targeted for reducing suicide risk. Poverty rates were also associated with increased alcohol involvement for men aged 45-64 years, indicating a role for alcohol in suicide for this working-aged group. However, negative associations between economic indicators and alcohol involvement were found for four groups, suggesting that non-economic factors or more general economic effects not captured by these indicators may have played a larger role in alcohol-related suicide increases. © 2016 American Journal of Preventive Medicine.


Mouse CA1 pyramidal neurons express apamin-sensitive SK2-containing channels in the post-synaptic membrane, positioned close to NMDA-type (N-methyl-D-aspartate) glutamate receptors. Activated by synaptically evoked NMDAR-dependent Ca(2+) influx, the synaptic SK2-containing channels modulate excitatory post-synaptic responses and the induction of synaptic plasticity. In addition, their activity- and protein kinase A-dependent trafficking contributes to expression of long-term potentiation (LTP). We have identified a novel synaptic scaffold, MPP2 (membrane palmitoylated protein 2; p55), a member of the membrane-associated guanylate kinase (MAGUK) family that interacts with SK2-containing channels. MPP2 and SK2 co-immunopurified from mouse brain, and co-immunoprecipitated when they were co-expressed in HEK293 cells. MPP2 is highly expressed in the post-synaptic density of dendritic spines on CA1 pyramidal neurons. Knocking down MPP2 expression selectively abolished the SK2-containing channel contribution to synaptic responses and decreased LTP. Thus, MPP2 is a novel synaptic scaffold that is required for proper synaptic localization and function of SK2-containing channels.

Inhibition of one pathway increases degradation via the other pathway. In this publication, we will review the literature that supports identification of ASB10 as a glaucoma-associated gene and the current knowledge of the function of the ASB10 protein. In addition, we present new data that indicates ASB10 expression is up-regulated by the inflammatory cytokines tumor necrosis factor-α and interleukin-1α. Finally, we will describe the emerging role of other SOCS box-containing proteins in protein degradation pathways in ocular cells. © 2016 Elsevier Ltd.
beneficiaries). This study examined the distribution of opioid prescriptions by provider and patient, the extent to which high-volume opioid use was associated with potential opioid misuse, and how this association changed when patients received opioids from providers in the top decile of morphine-equivalent doses (MEQ) prescribed in 2013. This study used four indicators of opioid misuse: doctor and pharmacy shopping for opioid prescriptions, opioid prescription overlap, and opioid and benzodiazepine prescription overlap. RESULTS: Opioid use and prescriptions were heavily concentrated among the top 10% of opioid users and prescribers. Those high-volume opioid users and prescribers accounted for, respectively, 83.2% and 80.8% in MEQ of entire opioids prescribed. Patients' increasing use of opioids (by MEQ) was associated with most measures of opioid misuse. Patients receiving opioids from high-volume prescribers had a higher probability of opioid prescription overlap and opioid and benzodiazepine prescription overlap compared with other patients, but the difference was significant only among patients who received high doses of opioids, and the size of the difference was modest. CONCLUSIONS: Whereas current policies emphasize reducing opioid prescriptions across all patients and providers, study results suggest that focusing policies on high-volume opioid users and prescribers may be more beneficial.


The high rate of emergency department (ED) use by Medicaid patients is not fully understood. The objective of this paper is (1) to provide context for ED service use by comparing Medicaid and commercial patients' differences across ED and non-ED health service use, and (2) to assess the extent to which Medicaid-commercial differences in ED use can be explained by observable factors in administrative data. Statistical decomposition methods were applied to ED, mental health, and inpatient care using 2011-2013 Medicaid and commercial insurance claims from the Oregon All-Payer All Claims database. Demographics, comorbidities, health services use, and neighborhood characteristics accounted for 44% of the Medicaid-commercial difference in ED use, compared to 83% for mental health care and 75% for inpatient care. This suggests that relative to mental health and inpatient care, a large portion of ED use cannot be explained by administrative data. Models that further accounted for patient access to different primary care physicians explained an additional 8% of the Medicaid-commercial difference in ED use, suggesting that the quality of primary care may influence ED use. The remaining unexplained difference suggests that appropriately reducing ED use remains a credible target for policy makers, although success may require knowledge about patients' perceptions and behaviors as well as social determinants of health.


Objective: The written history and physical examination (H&P) is an underutilized source of medical trainee assessment. The authors describe development and validity evidence for the Pediatric History and Physical Exam Evaluation (P-HAPEE) rubric: a novel tool for evaluating written H&Ps. Methods: Using an iterative process, the authors drafted, revised, and implemented the 10-item rubric at 3 academic institutions in 2014. Eighteen attending physicians and 5 senior residents each scored 10 third-year medical student H&Ps. Interrater reliability (IRR) was determined using intraclass correlation coefficients. Cronbach α was used to report consistency and Spearman rank-order correlations to determine relationships between rubric items. Raters provided a global assessment, recorded time to review and score each H&P, and completed a rubric utility survey. Results: Overall intraclass correlation was 0.85, indicating adequate IRR. Global assessment IRR was 0.89. IRR for low- and high-quality H&Ps was significantly greater than for medium-quality ones but did not differ on the basis of rater category (attending physician vs. senior resident), note format (electronic health record vs nonelectronic), or student diagnostic accuracy. Cronbach α was 0.93. The highest correlation between an individual item and total score was for assessments was 0.84; the highest interitem correlation was between assessment and differential diagnosis (0.78). Mean time to review and score an H&P was 16.3 minutes; residents took significantly longer than attending physicians. All raters described rubric utility as “good” or “very good” and endorsed continued use. Conclusions: The P-HAPEE rubric offers a novel, practical,

**BACKGROUND/OBJECTIVE:** Intake of high-energy foods and maternal nutrient overload increases the risk of metabolic diseases in the progeny such as obesity and diabetes. We hypothesized that maternal and postnatal intake of chocolate and soft drink will affect leptin sensitivity and hypothalamic astrocyte morphology in adult rat offspring. **METHODS:** Pregnant Sprague-Dawley rats were fed ad libitum chow diet only (C) or with chocolate and high sucrose soft drink supplement (S). At birth, litter size was adjusted into 10 male offspring per mother. After weaning, offspring from both dietary groups were assigned to either S or C diet, giving four groups until the end of the experiment at 26 weeks of age. **RESULTS:** As expected, adult offspring fed the S diet post weaning became obese (body weight: P<0.01, %body fat per kg: P<0.001) and this was due to the reduced energy expenditure (P<0.05) and hypothalamic astrogliosis (P<0.001) irrespective of maternal diet. Interestingly, offspring born to S-diet-fed mothers and fed the S diet throughout postnatal life became obese despite lower energy intake than controls (P<0.05). These SS offspring showed increased feed efficiency (P<0.001) and reduced fasting pSTAT3 activity (P<0.05) in arcuate nucleus (ARC) compared with other groups. The findings indicated that the combination of the maternal and postnatal S-diet exposure induced persistent changes in leptin signalling, hence affecting energy balance. Thus, appetite regulation was more sensitive to the effect of leptin than energy expenditure, suggesting differential programming of leptin sensitivity in ARC in SS offspring. Effects of the maternal S diet were normalized when offspring were fed a chow diet after weaning. **CONCLUSIONS:** Maternal intake of chocolate and soft drink had long-term consequences for the metabolic phenotype in the offspring if they continued on the S diet in postnatal life. These offspring displayed obesity despite lowered energy intake associated with alterations in hypothalamic leptin signalling.


**INTRODUCTION:** Palliative care is an approach to caring for patients and families affected by serious illnesses that focuses on the relief of suffering through the management of medical symptoms, psychosocial issues, advance care planning and spiritual wellbeing. Over the past decade there has been an emerging clinical and research interest in the application of palliative care approaches to Parkinson's disease (PD) and outpatient palliative care services are now offered by several movement disorders centers. **METHODS:** An International Working Group Meeting on PD and Palliative Care supported by the Parkinson's Disease Foundation was held in October 2015 to review the current state of the evidence and to make recommendations for clinical research and practice. **RESULTS:** Topics included: 1) Defining palliative care for PD; 2) Lessons from palliative care for heart failure and other chronic illnesses; 3) Patient and caregiver Needs; 4) Needs assessment tools; 5) Intervention strategies; 6) Predicting prognosis and hospice referrals; 7) Choice of appropriate outcome measures; 8) Implementation, dissemination and education research; and 9) Need for research collaborations. We provide an overview of these discussions, summarize current evidence and practices, highlight gaps in our knowledge and make recommendations for future research. **CONCLUSIONS:** Palliative Care for PD is a rapidly growing area which holds great promise for improving outcomes for PD patients and their caregivers. While clinical research in this area can build from lessons learned in other diseases, there is a need for observational, methodological and interventional research to address the unique needs of PD patients and caregivers.

The objectives of this study were to: 1) Assess and analyze the knowledge and attitudes of caregivers towards dental care for older adults in long-term care facilities; and 2) Train administrators, medical staff, and caregivers in the oral health competencies necessary to provide daily oral health care for residents of Assisted Living Communities in Oregon. Our results indicate that although the majority of caregivers felt comfortable with regard to their oral health background and daily activities, they expressed a need for additional training in several areas. Caregivers who participated in the training recognized the poor oral health of their residents and felt the training curriculum provided them with competencies needed to improve their daily oral health services. This innovative training demonstrates that oral health can be integrated into daily routines which could improve oral and systemic health and reduce inequities in oral health care for older adults.


BACKGROUND AND AIMS: HIV-infected persons with substance use disorders are least likely to benefit from advances in HIV treatment. Integration of extended-release naltrexone (XR-NTX) into HIV clinics may increase engagement in the HIV care continuum by decreasing substance use. We aimed to compare 1) XR-NTX treatment initiation, 2) retention, and 3) safety of XR-NTX versus treatment as usual (TAU) for treating opioid use disorder (OUD) and/or alcohol use disorder (AUD) in HIV clinics. DESIGN: Non-blinded randomized trial of XR-NTX versus pharmacotherapy TAU SETTING: HIV primary care clinics in Vancouver, BC, Canada and Chicago, IL, USA. PARTICIPANTS: 51 HIV-infected patients seeking treatment for OUD (n = 16), AUD (n = 27) or both OUD and AUD (n = 8). MEASUREMENTS: Primary outcomes were XR-NTX initiation (receipt of first injection within 4 weeks of randomization) and retention at 16 weeks. Secondary outcomes generated point estimates for change in substance use, HIV viral suppression (HIV RNA pcr < 200 copies/mL), and safety. FINDINGS: Two-thirds (68%) of participants assigned to XR-NTX initiated treatment, and 88% of these were retained on XR-NTX at 16 weeks. In comparison, 96% of TAU participants initiated treatment, but only 50% were retained on medication at 16 weeks. Mean days of opioid use in past 30 days decreased from 19 to 10 for TAU (n = 12) and from 18 to 13 for XR-NTX (n = 10). Mean heavy drinking days decreased from 18 to 7 for TAU (n = 11) and 13 to 6 for XR-NTX (n = 12). Among those with OUD, HIV suppression improved from 67% to 80% for XR-NTX and 58% to 75% for TAU. XR-NTX was well-tolerated, with no precipitated withdrawals and 1 serious injection site reaction. CONCLUSIONS: Extended-release naltrexone (XR-NTX) is feasible and safe for treatment of opioid use disorder and alcohol use disorder in HIV clinics. Treatment initiation appears to be lower and retention greater for XR-NTX compared with treatment as usual. (clinicaltrials.gov NCT01908062).


Background: The gap between publishing and implementing guidelines differs based on practice setting, clustering, and distribution pattern shed by the American College of Obstetricians and Gynecologists (ACOG) recommended against the routine use of episiotomy and urged clinicians to make judicious decisions to restrict the use of the procedure. Objective: This study investigated changes in trends of episiotomy use before and after the ACOG Practice Guideline was issued in 2006, focusing on differences by hospital geographic location (rural/urban) and teaching status. Methods: In a retrospective analysis of discharge data from the Nationwide Inpatient Sample (NIS) - a 20% sample of US hospitals - 5,779,781 hospital-based births from 2002 to 2011 (weighted N = 28,067,939) were analyzed using multivariable logistic regression analysis to measure odds of episiotomy and trends in
episiotomy use in vaginal deliveries. Results: The overall episiotomy rate decreased from 20.3% in 2002 to 9.4% in 2011. Across all settings, a comparatively larger decline in episiotomy rates preceded the issuance of the ACOG Practice Guideline (34.0% decline), rather than following it (23.9% decline). The episiotomy rate discrepancies between rural, urban teaching, and urban nonteaching hospitals remained steady prior to the guideline’s release; however, differences between urban nonteaching and urban teaching hospitals narrowed between 2007 and 2011 after the guideline was issued. Conclusion: Teaching status was a strong predictor of odds of episiotomy, with urban nonteaching hospitals having the highest rates of noncompliance with evidence-based practice. Issuance of clinical guidelines precipitated a narrowing of this discrepancy. © 2016 The Joint Commission. Published by Elsevier Inc. All rights reserved.


Background Steroid-induced sleep disturbance is a common and highly distressing morbidity for children receiving steroid chemotherapy for the treatment of pediatric acute lymphoblastic leukemia (ALL). Sleep disturbance can negatively impact overall quality of life, neurodevelopment, memory consolidation, and wound healing. Hypothalamic orexin neurons are influential wake-promoting neurons, and disturbances in orexin signaling leads to abnormal sleep behavior. A new class of drug, the orexin receptor antagonists, could be an intriguing option for sleep disorders caused by increased orexinergic output. Our aim was to examine the impact of ALL treatment doses of corticosteroids on the orexin system in rodents and in children undergoing treatment for childhood ALL. Methods We administered repeated injections of dexamethasone to rodents and measured responsive orexin neural activity compared to controls. In children with newly diagnosed standard risk B-cell ALL receiving dexamethasone therapy per Children’s Oncology Group (COG) induction therapy from 2014-2016, we collected pre- and during-steroids matched CSF samples and measured the impact of steroids on CSF orexin concentration. Results In both rodents, all markers orexin signaling, including orexin neural output and orexin receptor expression, were preserved in the setting of dexamethasone. Additionally, we did not detect a difference in pre- and during-dexamethasone CSF orexin concentrations in children receiving dexamethasone. Conclusions Our results demonstrate that rodent and human orexin physiology is largely preserved in the setting of high dose dexamethasone. The data obtained in our experimental model fail to demonstrate a causative role for disruption of the orexin pathway in steroid-induced sleep disturbance. © 2016 Kram et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.


Synaptic transmission is mediated by ionotropic and metabotropic receptors that together regulate the rate and pattern of action potential firing. Metabotropic receptors can activate ion channels and modulate other receptors and channels. The present paper examines the interaction between group 1 mGluR-mediated calcium release from stores and GABAB/D2-mediated GIRK currents in rat dopamine neurons of the Substantia Nigra. Transient activation of mGluRs decreased the GIRK current evoked by GABAB and D2 receptors, although less efficaciously for D2. The mGluR-induced inhibition of GIRK current peaked in 1 s and recovered to baseline after 5 s. The inhibition was dependent on release of calcium from stores, was larger for transient than for tonic currents, and was unaffected by inhibitors of PLC, PKC, PLA2, or calmodulin. This inhibition of GABAB IPSCs through release of calcium from stores is a postsynaptic mechanism that may broadly reduce GIRK-dependent inhibition of many central neurons. © 2016 The Author(s)


Characterization of proteins that mediate mechanotransduction by hair cells, the sensory cells of the inner ear, is hampered by the scarcity of these cells and their sensory organelle, the hair bundle. Mass
spectrometry, with its high sensitivity and identification precision, is the ideal method for determining which proteins are present in bundles and what proteins they interact with. We describe here the isolation of mouse hair bundles, as well as preparation of bundle protein samples for mass spectrometry. We also describe protocols for data-dependent (shotgun) and parallel reaction monitoring (targeted) mass spectrometry that allow us to identify and quantify proteins of the hair bundle. These sensitive methods are particularly useful for comparing proteomes of wild-type mice and mice with deafness mutations affecting hair-bundle proteins.


Essential characteristics of cellular signaling networks include a complex interconnected architecture and temporal dynamics of protein activity. The latter can be monitored by Förster resonance energy transfer (FRET) biosensors at a single-live-cell level with high temporal resolution. However, these experiments are typically limited to the use of a couple of FRET biosensors. Here, we describe a FRET-based multi-parameter imaging platform (FMIP) that allows simultaneous high-throughput monitoring of multiple signaling pathways. We apply FMIP to monitor the crosstalk between epidermal growth factor receptor (EGFR) and insulin-like growth factor-1 receptor signaling, signaling perturbations caused by pathophysiologically relevant EGFR mutations, and the effects of a clinically important MEK inhibitor (selumetinib) on the EGFR network. We expect that in the future the platform will be applied to develop comprehensive models of signaling networks and will help to investigate the mechanism of action as well as side effects of therapeutic treatments. © 2016 The Authors


INTRODUCTION: Achieving profound pulpal anesthesia can be difficult in patients with symptomatic irreversible pulpitis. This study provides a systematic review and meta-analysis to address the population, intervention, comparison, outcome (PICO) question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and incidence of adverse events? METHODS: A protocol was prepared and registered on PROSPERO. Electronic searches were conducted in MEDLINE, Scopus, Cochrane Library, and ClinicalTrials.gov by using strict inclusion and exclusion criteria. Two independent reviewers assessed eligibility for inclusion and quality. Weighted anesthesia success rates and 95% confidence intervals (CIs) were estimated and compared by using a random-effects model. RESULTS: Two hundred seventy-five studies were initially identified from the search; 10 double-blind, randomized clinical trials met the inclusion criteria. For combined studies, articaine was more likely than lidocaine to achieve successful anesthesia (odds ratio [OR], 2.21; 95% CI, 1.41-3.47; P = .0006; I(2) = 40%). Maxillary infiltration subgroup analysis showed no significant difference between articaine and lidocaine (OR, 3.99; 95% CI, 0.50-31.62; P = .19; I(2) = 59%). For combined mandibular anesthesia studies articaine was superior to lidocaine (OR, 2.20; 95% CI, 1.40-3.44; P = .0006; I(2) = 30%), with further subgroup analysis showing no difference for mandibular block anesthesia (OR, 1.44; 95% CI, 0.87-2.38; P = .16; I(2) = 0%). When used for supplemental infiltration after successful mandibular block anesthesia, articaine was significantly more effective than lidocaine (OR, 3.55; 95% CI, 1.97-6.39; P < .0001; I(2) = 9%). There were no reports of adverse events. CONCLUSIONS: This systematic review of double-blind, randomized clinical trials provides level 1 evidence to support the use of articaine for patients with symptomatic irreversible pulpitis. There is a significant advantage to using articaine over lidocaine for supplementary infiltration after mandibular block anesthesia but no advantage when used for mandibular block anesthesia alone or for maxillary infiltration.

OBJECTIVE: To evaluate maternal outcomes before and after implementation of an institutional delayed cord clamping (DCC) protocol. STUDY DESIGN: We performed a secondary analysis of a retrospective cohort study of deliveries occurring at <34 weeks at a tertiary care center in 2013-2014. 139 women who underwent early cord clamping were compared to 130 women delivered after DCC protocol implementation. Maternal estimated blood loss (EBL) was the primary outcome of interest. Operative times, post-Cesarean decrease in hemoglobin (Hgb), and rates of postpartum hemorrhage and transfusion were also examined in bivariate and multivariable analyses. RESULTS: 75% of post-guideline deliveries had actual DCC. In regression analyses only Cesarean delivery and multifetal gestation increased EBL. No trends were identified in EBL over time. In post-hoc analysis the study had over 80% power to detect a difference in postpartum hemorrhage rates of 20%. CONCLUSION: An institutional DCC protocol for deliveries <34 weeks was not associated with an identifiable increase in adverse maternal outcomes.


Scholars have voiced concerns about the potential dark side of Organizational Citizenship Behavior (OCB), arguing that OCB consumes energy, which contributes to a depletion of personal resources and results in poorer well-being. Drawing from research on the meaningfulness of work, we propose a pattern opposite to depletion: that OCB enhances energy, which contributes to an enrichment of personal resources and results in better well-being. This idea was tested over the course of a workweek with 224 day-level ratings from 67 employees and 30 managers working in a service management firm. Three-level hierarchical linear modeling indicated that supervisor-rated daily OCB was positively associated with employees’ vigor at the end of the workday, and multilevel structural equation modeling analyses showed that this relationship was mediated by meaningfulness of work. Moreover, we found that the association between OCB and work meaningfulness was stronger for employees with greater role ambiguity. Exploratory analyses revealed that daily in-role performance and daily OCB interacted to predict meaningfulness of work, such that the association between daily OCB and meaningfulness of work was more prominent among those who exhibited high levels of daily in-role performance. We discuss implications of these findings, limitations, and directions for future research.


We present an unusual pediatric case of invasive upper tract urothelial carcinoma with an associated genetic predisposition. A 14-year-old female presented with intermittent right flank pain, and was found to have a poorly functioning hydronephrotic right kidney. Laparoscopic nephrectomy was performed. Pathology demonstrated upper tract urothelial carcinoma, and she subsequently underwent completion ureterectomy. Genetic studies demonstrated a double-hit constitutional deletion of a DNA mismatch repair protein, revealing a rare Lynch syndrome variant known as Constitutional Mismatch Repair Deficiency Syndrome. This disease places her at high risk for multiple malignancies, including upper tract urothelial carcinoma. © 2016 Elsevier Inc.


As health care rapidly evolves to promote person-centered care, evidence-based practice, and team-structured environments, nurses must lead interprofessional (IP) teams to collaborate for optimal health of the populations and more cost-effective health care. Four professions—nursing, medicine, social work, and pharmacy—formed a teaching team to address fall prevention among older adults in Oregon using an IP approach. The teaching team developed training sessions that included interactive, evidence-based sessions, followed by individualized team coaching. This article describes how the IP teaching team came together to use a unique cross-training approach to teach each other. They then taught and coached IP teams from a variety of community practice settings to foster their integration of team-based falls-prevention strategies into practice. After coaching 25 teams for a year each, the authors present the lessons learned from the teaching team's formation and experiences, as well as feedback from practice team participants that can provide direction for other IP teams. © SLACK Incorporated.


**Background:** We hypothesized hepato-pancreato-biliary (HPB) surgery patients are more likely to be hypercoagulable than hypocoagulable, and that bleeding risks from VTE chemoprophylaxis are low. This study sought to use thromboelastography (TEG) to compare coagulation profiles with bleeding/thrombotic events in HPB patients receiving standardized perioperative chemoprophylaxis. Methods: Consecutive patients undergoing HPB resections by three surgeons at one institution (January 2014-December 2015) received preoperative and early postoperative VTE chemoprophylaxis and were evaluated with TEGs. Coagulation profiles were compared to bleeding/thrombotic events. Results: Of 87 total patients, 83 (95.4%) received preoperative chemoprophylaxis and 100% received it postoperatively. Median estimated blood loss was 190 ml. Only 2 (2.3%) patients received intraoperative transfusions. None required transfusions at 72-hours. Only 2 were transfused within 30 days. There was 1 (1.1%) 30-day VTE event. Of 83 preoperative TEGs, 29 (34.9%) were hypercoagulable and only 8 (9.6%) were hypocoagulable/fibrinolytic. Of 73 postoperative TEGs, 34 (46.6%) were hypercoagulable and just 8 (11.0%) were hypocoagulable/fibrinolytic. Conclusion: With routine perioperative chemoprophylaxis, both VTE and bleeding events were negligible. Perioperative TEG revealed a considerable proportion (46.6%) of HPB patients were hypercoagulable. HPB patients can receive standardized preoperative/early postoperative VTE chemoprophylaxis with effective results and minimal concern for perioperative hemorrhage. © 2016 International Hepato-Pancreato-Biliary Association Inc.


**BACKGROUND AND OBJECTIVE:** The structural and functional integrity of bone-periodontal ligament (PDL)-cementum complex stems from the load-bearing attachment sites (entheses) between soft (PDL) and hard (bone, cementum) tissues. These attachment sites are responsible for the maintenance of a bone-PDL-cementum complex biomechanical function. The objective was to investigate changes in spatiotemporal expression of key biomolecules in developing and functionally active entheses. **MATERIAL AND METHODS:** Multilabeling technique was performed on hemimandibles of 3 wk and 3 mo-old scleraxis-GFP transgenic mice for CD146, CD31, NG2, osterix and bone sialoprotein. Regions of dominant stretch within the PDL were evaluated by identifying directionality of collagen fibrils, PDL fibroblasts and PDL cell cytoskeleton. **RESULTS:** CD146+ cells adjacent to CD31+ vasculature were identified at PDL-bone enthesis. NG2+ cells were located at coronal bone-PDL and apical cementum-PDL entheses in the 3-wk-old group, but at 3 mo, NG2 was positive at the entheses of the apical region and alveolar crest. NG2 and osterix were colocalized at the osteoid and cementoid regions of the PDL-bone and PDL-cementum entheses. Bone sialoprotein was
prominent at the apical region of 3-wk-old mice. The directionality of collagen fibers, fibroblasts and their cytoskeleton overlapped, except in the apical region of 3 wk. CONCLUSION: Colocalization of biomolecules at zones of the PDL adjacent to attachment sites may be essential for the formation of precementum and osteoid interfaces at a load-bearing bone-PDL-tooth fibrous joint. Biophysical cues resulting from development and function can regulate recruitment and differentiation of stem cells potentially from a vascular origin toward osteo- and cemento-blastic lineages at the PDL-bone and PDL-cementum entheses. Investigating the coupled effect of biophysical and biochemical stimuli leading to cell differentiation at the functional attachment sites is critical for developing regeneration strategies to enable functional reconstruction of the periodontal complex.


OBJECTIVES: To examine the effects of a workplace flexibility/support intervention on employees' sleep quantity and quality during nights and days and whether the effects differ by employee age. DESIGN: Cluster-randomized controlled trial. SETTING: Information technology industry workplaces. PARTICIPANTS: US employees (Mage = 46.9 years) at an information technology firm who provided actigraphy at baseline and a 12-month follow-up (N = 396; n = 195 intervention, n = 201 control). INTERVENTION: The Work, Family, and Health Study intervention aimed to increase workplace flexibility and support. The intervention consisted of facilitated discussions to help employees increase control over when and where they work as well as manager-specific training sessions to increase manager support for employees' work-family issues.

MEASUREMENTS: Nighttime sleep duration, wake after sleep onset (WASO), and nap duration were measured with wrist actigraphy. Day-to-day variability in these variables (min2) was also estimated. RESULTS: Intervention employees increased nighttime sleep duration at 12 months, by 9 minutes per day, relative to control employees. There were interaction effects between the intervention and age on daytime nap duration and day-to-day variability in WASO. Older employees (56-70 years) in the intervention condition decreased nap duration at 12 months relative to older employees in the control condition. Older employees in the intervention condition also exhibited a greater decrease in day-to-day variability of WASO at 12 months compared with their baseline. CONCLUSIONS: The workplace flexibility/support intervention was effective in enhancing employees' sleep health by increasing nighttime sleep duration. Furthermore, the intervention was particularly effective for older employees in decreasing their daytime nap duration and day-to-day variability in WASO.


BACKGROUND: Heparin-induced thrombocytopenia (HIT) results in platelet consumption and a virulent thrombotic state, which generally responds to cessation of heparin and initiation of anticoagulation. Rarely, delayed HIT can occur and/or persist after heparin is discontinued. STUDY DESIGN AND METHODS: A 47-year-old male developed delayed HIT with severe thrombocytopenia and thrombosis after cardiac surgery. Thrombocytopenia developed and persisted after heparin cessation and did not improve despite sequential use of argatroban followed by bivalirudin. Treatment with intravenous immunoglobulin (IVIg) was well tolerated and resulted in rapid resolution of thrombocytopenia. RESULTS: There are few case reports on the management of delayed HIT with severe and prolonged thrombocytopenia. The risk for thrombosis and bleeding in the setting of an undefined time course increases uncertainty in management. CONCLUSION: This case, along with others accumulating in the literature, suggest that IVIg may be effective in treating delayed HIT with persistent thrombocytopenia. © 2016 AABB.

Background: Hematologic malignancies arising in the setting of established germ cell tumors have been previously described and have a dismal prognosis. Identification of targetable mutations and pathway dysregulation through massively parallel sequencing and functional assays provides new approaches to disease management. Case Presentation: Herein, we report the case of a 23-year-old male who was diagnosed with a mediastinal germ cell tumor and subsequent acute myeloid leukemia. A shared clonal origin was demonstrated through identification of identical NRAS and TP53 somatic mutations in both malignancies. The patient’s leukemia was refractory to standard therapies with short interval relapse. Functional assays demonstrated the patient’s blasts to be sensitive to the mitogen-activated protein kinase (MEK) inhibitor trametinib, correlating with the activating NRAS mutation. The patient experienced a sustained partial remission while on trametinib therapy but ultimately suffered relapse of the germ cell tumor. The leukemic clone remained stable and sensitive to trametinib at that time. Conclusions: This case highlights the potential power of combining genetic sequencing and in vitro functional assays with targeted therapies in the treatment of rare diseases. © 2016 Leonard et al.


BACKGROUND: Individuals infected with Mycobacterium tuberculosis (Mtb) may develop symptoms and signs of disease (tuberculosis disease) or may have no clinical evidence of disease (latent tuberculosis infection [LTBI]). Tuberculosis disease is a leading cause of infectious disease morbidity and mortality worldwide, yet many questions related to its diagnosis remain. METHODS: A task force supported by the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America searched, selected, and synthesized relevant evidence. The evidence was then used as the basis for recommendations about the diagnosis of tuberculosis disease and LTBI in adults and children. The recommendations were formulated, written, and graded using the Grading, Recommendations, Assessment, Development and Evaluation (GRADE) approach. RESULTS: Twenty-three evidence-based recommendations about diagnostic testing for latent tuberculosis infection, pulmonary tuberculosis, and extrapulmonary tuberculosis are provided. Six of the recommendations are strong, whereas the remaining 17 are conditional. CONCLUSIONS: These guidelines are not intended to impose a standard of care. They provide the basis for rational decisions in the diagnosis of tuberculosis in the context of the existing evidence. No guidelines can take into account all of the often compelling unique individual clinical circumstances.


The rostral ventromedial medulla (RVM) is a relay in the descending pain modulatory system and an important site of endocannabinoid modulation of pain. Endocannabinoids inhibit GABA release in the RVM, but it is not known whether this effect persists in chronic pain states. In the present studies, persistent inflammation induced by complete Freund’s adjuvant (CFA) increased GABAergic miniature IPSCs (mIPSCs). Endocannabinoid activation of cannabinoid (CB1) receptors known to inhibit presynaptic GABA release was significantly reduced in the RVM of CFA-treated rats compared with naive rats. The reduction in CFA-treated rats correlated with decreased CB1 receptor protein expression and function in the RVM. Paradoxically, the nonselective CB1/CB2 receptor agonist WIN55212 inhibited GABAergic mIPSCs in both naive and CFA-treated rats. However, WIN55212 inhibition was reversed by the CB1 receptor antagonist rimonabant in naive rats but not in CFA-treated rats. WIN55212-mediated inhibition in CFA-treated rats was blocked by the CB2 receptor-selective antagonist SR144528, indicating that CB2 receptor function in the RVM is increased during persistent inflammation. Consistent with these results, CB2 receptor agonists AM1241 and GW405833 inhibited GABAergic mIPSC frequency only in CFA-treated rats, and the inhibition was reversed with
SR144528. When administered alone, SR144528 and another CB2 receptor-selective antagonist AM630 increased mIPSC frequency in the RVM of CFA-treated rats, indicating that CB2 receptors are tonically activated by endocannabinoids. Our data provide evidence that CB2 receptor function emerges in the RVM in persistent inflammation and that selective CB2 receptor agonists may be useful for treatment of persistent inflammatory pain. SIGNIFICANCE STATEMENT: These studies demonstrate that endocannabinoid signaling to CB1 and CB2 receptors in adult rostral ventromedial medulla is altered in persistent inflammation. The emergence of CB2 receptor function in the rostral ventromedial medulla provides additional rationale for the development of CB2 receptor-selective agonists as useful therapeutics for chronic inflammatory pain.


Vestibulodynia is a form of provoked vulvodynia characterized by profound tenderness, hyperinnervation, and frequently inflammation within well-defined areas of the human vestibule. Prior experiments in animal models show that inflammatory hypersensitivity and hyperinnervation occur in concert with establishment of a local renin-angiotensin system (RAS). Moreover, mechanical hypersensitivity and sensory axon sprouting are prevented by blocking effects of angiotensin II on AT2 receptors. This case-control study assessed whether a RAS contributes to hyperinnervation observed in human vestibulodynia. Vestibular biopsies from asymptomatic controls or patients' nontender areas showed moderate innervation and small numbers of inflammatory cells. In women with vestibulodynia, tender areas contained increased numbers of mechanoreceptive nociceptor axons, T-cells, macrophages and B-cells, while mast cells were unchanged. RAS proteins were increased due to greater numbers of T-cells and B-cells expressing angiotensinogen, and increased renin-expressing T-cells and macrophages. Chymase, which converts angiotensin I to angiotensin II, was present in constant numbers of mast cells. To determine if tender vestibular tissue generates angiotensin II that promotes axon sprouting, we conditioned culture medium with vestibular tissue. Rat sensory neurons cultured in control-conditioned medium showed normal axon outgrowth, while those in tender tissue-conditioned medium showed enhanced sprouting that was prevented by adding an AT2 antagonist or angiotensin II neutralizing antibody. Hypersensitivity in provoked vestibulodynia is therefore characterized by abnormal mechano-nociceptor axon proliferation, which is attributable to inflammatory cell-derived angiotensin II (or a closely related peptide) acting on neuronal AT2 receptors. Accordingly, reducing inflammation or blocking AT2 represent rational strategies to mitigate this common pain syndrome. PERSPECTIVE: This study provides evidence that local inflammation leads to angiotensin II formation which acts on the angiotensin II receptor type 2 to induce nociceptor axon sprouting in vulvodynia. Preventing inflammation and blocking AT2 therefore present potential pharmacological strategies for reducing vestibular pain.


Objectives: To describe the epidemiology, morbidity, and mortality of new or progressive multiple organ dysfunction syndrome in children with severe sepsis. Design: Secondary analysis of a prospective, cross-sectional, point prevalence study. Setting: International, multicenter PICUs. Patients: Pediatric patients with severe sepsis identified on five separate days over a 1-year period. Interventions: None. Measurements and Main Results: Of 567 patients from 128 PICUs in 26 countries enrolled, 384 (68%) developed multiple organ dysfunction syndrome within 7 days of severe sepsis recognition. Three hundred twenty-seven had multiple organ dysfunction syndrome on the day of sepsis recognition. Ninety-one of these patients developed progressive multiple organ dysfunction syndrome, whereas an additional 57 patients subsequently developed new multiple organ dysfunction syndrome, yielding a total proportion with severe sepsis-
associated new or progressive multiple organ dysfunction syndrome of 26%. Hospital mortality in patients with progressive multiple organ dysfunction syndrome was 51% compared with patients with new multiple organ dysfunction syndrome (28%) and those with single-organ dysfunction without multiple organ dysfunction syndrome (10%) (p < 0.001). Survivors of new or progressive multiple organ dysfunction syndrome also had a higher frequency of moderate to severe disability defined as a Pediatric Overall Performance Category score of greater than or equal to 3 and an increase of greater than or equal to 1 from baseline: 22% versus 29% versus 11% for progressive, new, and no multiple organ dysfunction syndrome, respectively (p < 0.001). Conclusions: Development of new or progressive multiple organ dysfunction syndrome is common (26%) in severe sepsis and is associated with a higher risk of morbidity and mortality than severe sepsis without new or progressive multiple organ dysfunction syndrome. Our data support the use of new or progressive multiple organ dysfunction syndrome as an important outcome in trials of pediatric severe sepsis although efforts are needed to validate whether reducing new or progressive multiple organ dysfunction syndrome leads to improvements in more definitive morbidity and mortality endpoints.

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INTRODUCTION: The purpose of this study was to assess the perceptions, referral trends, and practice patterns of practicing endodontists in the United States and any effect the recent economy may have had on these. METHODS: A 24-question survey was formulated and sent via www.surveymonkey.com to 3255 active members of the American Association of Endodontists. Overall, 875 participants completed the survey, a response rate of 26.9%. RESULTS: The average number of treatment cases per day was 5.7. Average work hours per week were 34.3 for men and 30.7 for women (P < .05). Among all treatment cases, 46% were nonsurgical retreatment, and 7.2% were apical surgical procedures. Procedural misadventure accounted for 10.8% of all treatment cases, with the most common referral reason being unable to locate canals (75.0%) followed by separated instruments (15.3%). Of all respondents, 49.9% performed regenerative endodontic procedures, and 7.7% placed implants. Among endodontists who practice in urban areas, 69.7% believed there were too many endodontists, and 50% have delayed their retirement plans because of recent economic impact, compared with their suburban and rural counterparts at 66.1% and 38%, 25.9% and 33.1%, respectively (P < .05). Fifty-nine percent of respondents were optimistic about the future of endodontics as a specialty, but those who have practiced more than 20 years were more pessimistic than those with less experience (P < .05). CONCLUSIONS: Recent economic impacts appear to have had an effect on the perceptions of active endodontists regarding practice success, the future of the specialty, and their retirement plans. Those who have been in practice longest (>20 years), practice in urban settings, and practice in a solo environment are most significantly affected.


This article is the fourth in a series, Supporting Family Caregivers: No Longer Home Alone, published in collaboration with the AARP Public Policy Institute. Results of focus groups conducted as part of the AARP Public Policy Institute's No Longer Home Alone video project supported evidence that family caregivers aren’t being given the information they need to manage the complex care regimens of their family members. This series of articles and accompanying videos aims to help nurses provide caregivers with the tools they need to manage their family member’s medications. Each article explains the principles nurses should consider and reinforce with caregivers and is accompanied by a video for the caregiver to watch. The fourth video can be accessed at http://links.lww.com/AJN/A78.

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Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for patients with chronic myelomonocytic leukemia (CMML), however, few data exist regarding prognostic factors and transplant outcomes. We performed this retrospective study to identify prognostic factors for post-transplant outcomes. The CMML-specific prognostic scoring system (CPSS) has been validated in subjects receiving non-transplant therapy and was included in our study. From 2001-2012, there were 209 adult subjects who received HCT for CMML reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The median age at transplant was 57 years (range 23-74). Median follow up was 51 months (range, 3-122). On multivariate analyses, CPSS scores, Karnofsky performance status (KPS), and graft source were significant predictors of survival (p=0.004, p=0.01, p=0.01, respectively). Higher CPSS scores were not associated with disease-free survival, relapse, or transplant-related mortality. In a restricted analysis of subjects with relapse following HCT, those with intermediate-2/high risk had a nearly two-fold increased risk of death after relapse compared to those with low/intermediate-1 CPSS scores. Respective 1, 3 and 5-year survival rates for low/intermediate-1 risk subjects were 61% (95% confidence interval [CI], 52%-72%), 48% (95% CI, 37%-59%), and 44% (95% CI, 33%-55%), and for intermediate-2/high risk subjects were 38% (95% CI, 28%-49%), 32% (95% CI, 21% - 42%), and 19% (95% CI,8%-29%). We conclude that higher CPSS score at time of transplant, lower KPS, and a bone marrow (BM) graft are associated with inferior survival after HCT. Further investigation of CMML disease-related biology may provide insights into other risk factors predictive of post-transplant outcomes.


We have modified the mitral repair technique in infants and small children by using autologous pericardial strips to treat mitral regurgitation resulting from a dilated mitral annulus. Our results demonstrate that this technique maintains stability and flexibility of the mitral annulus and decreases the risk of mitral stenosis. © 2016 Wiley Periodicals, Inc.


PURPOSE: Chemical exchange saturation transfer (CEST) is a contrast mechanism enhancing low-concentration molecules through saturation transfer from their exchangeable protons to bulk water. Often many scans are acquired to form a Z-spectrum, making the CEST method time-consuming. Here, an ultrafast localized CEST-spectroscopy with PRESS (UCEPR) is proposed to obtain the entire Z-spectrum of a voxel using only two scans, significantly accelerating CEST. THEORY AND METHODS: The approach combines ultrafast nonlocalized CEST spectroscopy with localization using PRESS. A field gradient is applied concurrently with the saturation pulse producing simultaneous saturation of all Z-spectrum frequencies that are also spatially encoded. A readout gradient during data acquisition resolves the spatial dependence of the CEST responses into frequency. UCEPR was tested on a 3T scanner both in phantoms and in vivo. RESULTS: In phantoms, a fast Z-spectroscopy acquisition of multiple pH-variant iopamidol samples was achieved with

Increasing amounts of pathogen replication usually lead to a proportionate increase in size and effector differentiation of the CD8+ T cell response, which is attributed to increased Ag and inflammation. Using a murine CMV that is highly sensitive to the antiviral drug famciclovir to modulate virus replication, we found that increased virus replication drove increased effector CD8+ T cell differentiation, as expected. Paradoxically, however, increased virus replication dramatically decreased the size of the CD8+ T cell response to two immunodominant epitopes. The decreased response was due to type I IFN-dependent depletion of conventional dendritic cells and could be reproduced by specific depletion of dendritic cells from day 2 postinfection or by sterile induction of type I IFN. Increased virus replication and type I IFN specifically inhibited the response to two immunodominant epitopes that are known to be dependent on Ag cross-presented by DCs, but they did not inhibit the response to “inflationary” epitopes whose responses can be sustained by infected nonhematopoietic cells. Our results show that type I IFN can suppress CD8+ T cell responses to cross-presented Ag by depleting cross-presenting conventional dendritic cells. Copyright © 2016 by The American Association of Immunologists, Inc.


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Youth with chronic illnesses have the greatest risk for a decline in their health management during transition-age. Because of this demonstrated and well-known issue, research has focused on how to improve the transition of care process. Despite the increasing number of technological devices on the market and the advances in telemedicine modalities available to patients with type 1 diabetes (T1D), the utilization of technology is still suboptimal among patients of transition-age (ages 13-25). This article reviews the available resources, patterns of use in transition-age youth, and explores opportunities to advance technology use in transitioning patients with T1D from pediatric to adult care. © Diabetes Technology Society.


Hemodynamic-based brain imaging techniques are typically incapable of monitoring brain activity with both high spatial and high temporal resolutions. In this study, we have used intrinsic signal optical imaging (ISOI), a relatively high spatial resolution imaging technique, to examine the temporal resolution of the hemodynamic signal. We imaged V1 responses in anesthetized monkey to a moving light spot. Movies of
cortical responses clearly revealed a focus of hemodynamic response traveling across the cortical surface. Importantly, at different locations along the cortical trajectory, response timecourses maintained a similar tri-phasic shape and shifted sequentially across cortex with a predictable delay. We calculated the time between distinguishable timecourses and found that the temporal resolution of the signal at which two events can be reliably distinguished is about 80 milliseconds. These results suggest that hemodynamic-based imaging is suitable for detecting ongoing cortical events at high spatial resolution and with temporal resolution relevant for behavioral studies.


BACKGROUND: The minimum recommended treatment duration for i.v. N-acetylcysteine (NAC) after an acute, single acetaminophen (APAP) overdose is 21 h. Some have questioned whether shorter courses may be sufficient in carefully selected cases. OBJECTIVE: We sought to describe the incidence of hepatotoxicity in a cohort of acute APAP overdose patients who received <21 h of i.v. NAC for any reason. METHODS: We performed a secondary analysis of a large multicenter retrospective cohort of patients hospitalized for APAP poisoning. We selected patients with a potentially toxic serum APAP concentration measured between 4 and 24 h post ingestion, in whom i.v. NAC was initiated but discontinued before completing the full 21-h course. We further characterized outcomes in these patients as a function of two novel risk-prediction tools, the psi (ψ) parameter and APAP x aminotransferase (AT) product. The psi parameter is an estimate of the cellular burden of injury based on the area under the concentration-time curve before treatment, and calculated with respect to the APAP concentration and time to initiation of NAC. RESULTS: Fifty-nine patients met inclusion criteria. Intravenous NAC was initiated a median of 11.3 h post ingestion and administered for a median of 11.0 h. Hepatotoxicity (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 1,000 IU/L) occurred in one patient (1.7%; 95% confidence interval 0.04-9.1), and eight additional patients developed hepatic injury (AST or ALT > 100 IU/L). No fatalities occurred. A multiplication product of APAP and AT (APAP x AT) that falls below 10,000 mumol/L/ IU-L, or pretreatment ψ < 5 mmol/L-h suggested a low risk of hepatic injury. CONCLUSIONS: In this retrospective analysis of patients treated with < 21 h of i.v. NAC for acute APAP overdose, the incidence of hepatotoxicity and coagulopathy was low, despite delays to NAC treatment.


Oocyte defects lie at the heart of some forms of infertility and could potentially be addressed therapeutically by alternative routes for oocyte formation. Here, we describe the generation of functional human oocytes following nuclear transfer of first polar body (PB1) genomes from metaphase II (MII) oocytes into enucleated donor MII cytoplasm (PBNT). The reconstructed oocytes supported the formation of de novo meiotic spindles and, after fertilization with sperm, meiosis completion and formation of normal diploid zygotes. While PBNT zygotes developed to blastocysts less frequently (42%) than controls (75%), genome-wide genetic, epigenetic, and transcriptional analyses of PBNT and control ESCs indicated comparable numbers of structural variations and markedly similar DNA methylation and transcriptome profiles. We conclude that rescue of PB1 genetic material via introduction into donor cytoplasm may offer a source of oocytes for infertility treatment or mitochondrial replacement therapy for mtDNA disease. © 2017 Elsevier Inc.

OBJECTIVE: To compare the rates of alloimmunization with the use of cell-free DNA (cfDNA) screening to target antenatal rhesus immune globulin (RhIG) prenatally, versus routine administration of RhIG in rhesus D (RhD)-negative pregnant women in a theoretic cohort using a decision-analytic model. METHODS: A decision-analytic model compared cfDNA testing to routine antenatal RhIG administration. The primary outcome was maternal sensitization to RhD antigen. Sensitivity and specificity of cfDNA testing were assumed to be 99.8% and 95.3%, respectively. Univariate and bivariate sensitivity analyses, Monte Carlo simulation, and threshold analyses were performed. RESULTS: In a cohort of 10,000 RhD-negative women, 22.6 sensitizations would occur with utilization of cfDNA, while 20 sensitizations would occur with routine RhIG. Only when the sensitivity of the cfDNA test reached 100%, the rate of sensitization was equal for both cfDNA and RhIG. Otherwise, routine RhIG minimized the rate of sensitization, especially given RhIG is readily available in the United States. CONCLUSIONS: Adoption of cfDNA testing would result in a 13.0% increase in sensitization among RhD-negative women in a theoretical cohort taking into account the ethnic diversity of the United States' population.


PURPOSE: Established metrics reward academic faculty for clinical productivity. Few data have analyzed a bonus model to measure and reward academic productivity. This study's objective was to describe development and use of a departmental academic bonus system for incenting faculty scholarly and educational productivity. METHOD: This cross-sectional study analyzed a departmental bonus system among emergency medicine academic faculty at Oregon Health & Science University, including growth from 2005 to 2015. All faculty members with a primary appointment were eligible for participation. Each activity was awarded points based on a predetermined education or scholarly point scale. Faculty members accumulated points based on their activity (numerator), and the cumulative points of all faculty were the denominator. Variables were individual faculty member (deidentified), academic year, bonus system points, bonus amounts awarded, and measures of academic productivity. Data were analyzed using descriptive statistics, including measures of variance. RESULTS: The total annual financial bonus pool ranged from $211,622 to $274,706. The median annual per faculty academic bonus remained fairly constant over time ($3,980 in 2005-2006 vs. $4,293 in 2014-2015), with most change at the upper quartile of academic bonus (max bonus $16,920 in 2005-2006 vs. $39,207 in 2014-2015). Bonuses rose linearly among faculty in the bottom three quartiles of academic productivity, but increased exponentially in the 75th to 100th percentile. CONCLUSIONS: Faculty academic productivity can be measured and financially rewarded according to an objective academic bonus system. The “academic point” used to measure productivity functions as an “academic relative value unit.”


Since the sample size of a typical neuroimaging study lacks sufficient statistical power to explore unknown genomic associations with brain phenotypes, several international genetic imaging consortia have been organized in recent years to pool data across sites. The challenges and achievements of these consortia are considered here with the goal of leveraging these resources to study addiction. The authors of this review have joined together to form an Addiction working group within the framework of the ENIGMA project, a meta-analytic approach to multisite genetic imaging data. Collectively, the Addiction working group possesses neuroimaging and genomic data obtained from over 10,000 subjects. The deadline for contributing data to the first round of analyses occurred at the beginning of May 2015. The studies performed on this data should significantly impact our understanding of the genetic and neurobiological basis of addiction.

Freezing of gait (FoG) in people with Parkinson’s disease (PD) is an environmentally sensitive, intermittent problem that occurs most often during turning. FoG is difficult for clinicians to evaluate and treat because it can be difficult to elicit during a clinical visit. Here, we aimed to develop a clinically valid objective measure of freezing severity during a 2-min 360-degree turning-in-place. Twenty-eight subjects with PD (16 freezers, FoG+, and 12 non-freezers, FoG–) in the “off” state and 14 healthy control subjects were tested. Subjects wore three inertial sensors (one on each shin and one on the waist) while (1) turning in place for 2 min (alternating 360 degrees to the right with 360 degrees to the left) and (2) performing an Instrumented 7-m Timed Up and Go test (ITUG). Performance was videotaped, and clinical severity of FoG was independently rated by two movement disorders specialists (co-authors). Turning in place consistently resulted in FoG (13 out of 16 subjects with PD) while FoG was clinically observed in only two subjects with PD during the ITUG.
The Freezing Ratio during the turning test was significantly correlated with the clinical ratings ($\rho = 0.7$, $p = 0.003$) and with score on the new FoG questionnaire ($\rho = 0.5$, $p = 0.03$). After correcting for symptom severity (UPDRS-III), out of the four objective measures of the turning test (total number of turns, average turn peak speed and average turn smoothness), only the Freezing Ratio was significantly different across groups ($p = 0.04$). Freezing can be well quantified with body-worn inertial sensors during a 2-min turning-in-place protocol. © 2016 IBRO


Missing covariate data hamper variable selection in multilevel regression settings. Current variable selection techniques for multiply-imputed data commonly address missingness in the predictors through list-wise deletion and stepwise-selection methods that are problematic. Moreover, most variable selection methods are developed for independent linear regression models and do not accommodate multilevel mixed effects regression models with incomplete covariate data. We develop a novel methodology that is able to perform covariate selection across multiply-imputed data for multilevel random effects models when missing data are present. Specifically, we propose to stack the multiply-imputed data sets from a multiple imputation procedure and to apply a group variable selection procedure through group lasso regularization to assess the overall impact of each predictor on the outcome across the imputed data sets. Simulations confirm the advantageous performance of the proposed method compared with the competing methods. We applied the method to reanalyse the Healthy Directions-Small Business cancer prevention study, which evaluated a behavioural intervention programme targeting multiple risk-related behaviours in a working-class, multi-ethnic population. © 2017 John Wiley & Sons, Ltd.


Although there is substantial support for the validity of the diagnosis of ADHD, there is considerable disagreement about how to best capture developmental changes in the expression of ADHD symptomatology. The current paper examines the associations among the 18 individual ADHD symptoms using a novel network analysis approach, from preschool to adulthood. The 1,420 participants were grouped into four age brackets: Preschool (age 3-6, n = 109), childhood (age 6-12, n = 548), adolescence (age 13-17, n = 357), and young adulthood (age 18-36, n = 406). All participants completed a multi-stage, multi-informant diagnostic process, and self and informant symptom ratings were obtained. Network analysis indicated ADHD symptom structure became more differentiated over development. Two symptoms Often easily distracted and Difficulty sustaining attention appeared as central, or core, symptoms across all age groups. Thus, a small number of core symptoms may warrant extra weighting in future diagnostic systems.


Sibley, Coxe, and Molina provide a thoughtful discussion of the implications of our study and highlight important future directions in this line of work. They helpfully amplify several themes that space did not allow discussion of in our article. In particular, they correctly emphasize the importance of theoretical as well as statistical considerations in model selection. We also agree that clinical tests of sensitivity and specificity, taking into account different base rates and types of samples, are essential before a final algorithm would be ready for dissemination. However, we are not convinced that such tests should be limited to populations of individuals with attention-deficit/hyperactivity disorder (ADHD). Rather, they should include those with and without diagnosed ADHD in order to provide comprehensive tests of reporter sensitivity and specificity across the entire continuum of ADHD symptomatology and in relation to different populations, including other disorders and typically developing populations.
Patients with functional pain disorders often complain of generalized sensory hypersensitivity, finding sounds, smells, or even everyday light aversive. The neural basis for this aversion is unknown, but it cannot be attributed to a general increase in cortical sensory processing. Here, we quantified the threshold for aversion to light in patients with fibromyalgia, a pain disorder thought to reflect dysregulation of pain-modulating systems in the brain. These individuals expressed discomfort at light levels substantially lower than that of healthy control subjects. Complementary studies in lightly anesthetized rat demonstrated that a subset of identified pain-modulating neurons in the rostral ventromedial medulla unexpectedly responds to light. Approximately half of the pain-facilitating “ON-cells” and pain-inhibiting “OFF-cells” sampled exhibited a change in firing with light exposure, shifting the system to a pronociceptive state with the activation of ON-cells and suppression of OFF-cell firing. The change in neuronal firing did not require a trigeminal or posterior thalamic relay, but it was blocked by the inactivation of the olivary pretectal nucleus. Light exposure also resulted in a measurable but modest decrease in the threshold for heat-evoked paw withdrawal, as would be expected with engagement of this pain-modulating circuitry. These data demonstrate integration of information about light intensity with somatic input at the level of single pain-modulating neurons in the brain stem of the rat under basal conditions. Taken together, our findings in rodents and humans provide a novel mechanism for abnormal photosensitivity and suggest that light has the potential to engage pain-modulating systems such that normally innocuous inputs are perceived as aversive or even painful.


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KATP channels are metabolic sensors that couple cell energetics to membrane excitability. In pancreatic beta-cells, channels formed by SUR1 and Kir6.2 regulate insulin secretion and are the targets of antidiabetic sulfonylureas. Here, we used cryo-EM to elucidate structural basis of channel assembly and gating. The structure, determined in the presence of ATP and the sulfonylurea glibenclamide, at ~6Å resolution reveals a closed Kir6.2 tetrameric core with four peripheral SUR1s each anchored to a Kir6.2 by its N-terminal transmembrane domain (TMD0). Intricate interactions between TMD0, the loop following TMD0, and Kir6.2 near the proposed PIP2 binding site, and where ATP density is observed, suggest SUR1 may contribute to ATP and PIP2 binding to enhance Kir6.2 sensitivity to both. The SUR1-ABC core is found in an unusual inward-facing conformation whereby the two nucleotide binding domains are misaligned along a two-fold symmetry axis, revealing a possible mechanism by which glibenclamide inhibits channel activity.


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Background Results of the randomised, double-blind, placebo-controlled Bangkok Tenofovir Study (BTS) showed that taking tenofovir daily as pre-exposure prophylaxis (PrEP) can reduce the risk of HIV infection by 49% in people who inject drugs. In an extension to the trial, participants were offered 1 year of open-label tenofovir. We aimed to examine the demographic characteristics, drug use, and risk behaviours associated with participants’ uptake of and adherence to PrEP. Methods In this observational, open-label extension of the BTS (NCT00119106), non-pregnant, non-breastfeeding, HIV-negative BTS participants, all of whom were current or previous injecting drug users at the time of enrolment in the BTS, were offered daily oral tenofovir (300 mg) for 1 year at 17 Bangkok Metropolitan Administration drug-treatment clinics. Participant

OBJECTIVE: The purpose of this study was to test the efficacy of a tailored motivational interviewing (MI) intervention versus usual care for improving HF self-care behaviors, physical HF symptoms and quality of life. METHODS: This is a single-center, randomized controlled trial. Participants were enrolled in the hospital. Immediately after discharge, those in the intervention group received a single home visit and 3-4 follow-up phone calls by a nurse over 90 days. RESULTS: A total of 67 participants completed the study (mean age 62 +/- 12.8 years), of which 54% were African American, 30% were female, 84% had class III/IV symptoms, and 63% were educated at a high school level or less. There were no differences between the groups in self-care maintenance, self-care confidence, physical HF symptoms, or quality of life at 90 days. CONCLUSION: Patients who received the MI intervention had significant and clinically meaningful improvements in HF self-care maintenance over 90 days that exceeded that of usual care. PRACTICE IMPLICATIONS: These data


Ebola viruses pose significant public health problems due to their high lethality, unpredictable emergence, and localization to the poorest areas of the world. In addition to implementation of standard public health control procedures, a number of experimental human vaccines are being explored as a further means for outbreak control. Recombinant cytomegalovirus (CMV)-based vectors are a novel vaccine platform that have been shown to induce substantial levels of durable, but primarily T-cell-biased responses against the encoded heterologous target antigen. Herein, we demonstrate the ability of rhesus CMV (RhCMV) expressing Ebola virus (EBOV) glycoprotein (GP) to provide protective immunity to rhesus macaques against lethal EBOV challenge. Surprisingly, vaccination was associated with high levels of GP-specific antibodies, but with no detectable GP-directed cellular immunity.


OBJECTIVE: The purpose of this study was to test the efficacy of a tailored motivational interviewing (MI) intervention versus usual care for improving HF self-care behaviors, physical HF symptoms and quality of life. METHODS: This is a single-center, randomized controlled trial. Participants were enrolled in the hospital. Immediately after discharge, those in the intervention group received a single home visit and 3-4 follow-up phone calls by a nurse over 90 days. RESULTS: A total of 67 participants completed the study (mean age 62 +/- 12.8 years), of which 54% were African American, 30% were female, 84% had class III/IV symptoms, and 63% were educated at a high school level or less. There were no differences between the groups in self-care maintenance, self-care confidence, physical HF symptoms, or quality of life at 90 days. CONCLUSION: Patients who received the MI intervention had significant and clinically meaningful improvements in HF self-care maintenance over 90 days that exceeded that of usual care. PRACTICE IMPLICATIONS: These data
support the use of a nurse-led MI intervention for improving HF self-care. Identifying methods to improve HF self-care may lead to improved clinical outcomes.


AIMS: To evaluate the efficacy and safety of insulin glargine 300U/mL (Gla-300) versus glargine 100U/mL (Gla-100) in adults with type 1 diabetes in Japan over 12months. METHODS: EDITION JP 1 was a multicentre, randomised, open-label phase 3 study. Following a 6-month on-treatment period, participants continued to receive Gla-300 or Gla-100 once daily, plus mealtime insulin, over a 6-month open-label extension phase. HbA1c, glycaemic control, cases based on history of tamoxifen use. Patien...
we used a novel transglutaminase probe, Rhod-A14, to identify a subpopulation of platelets with a cross-linked protein coat, and compared this with other platelet subpopulations using a panel of functional assays. Platelet stimulation with convulxin/thrombin resulted in initial integrin alpha(IIb)beta3 activation, the appearance of a platelet population with high fibrinogen binding, (independently of active integrins, but dependent on the presence of thrombin) followed by phosphatidylserine exposure and binding of coagulation factors Va and Xa. A subpopulation of phosphatidylserine-exposing platelets bound Rhod-A14 both in suspension and in thrombi generated on a collagen surface. In suspension, high fibrinogen and Rhod-A14 binding were antagonized by combined inhibition of transglutaminase activity and integrin alpha(IIb)beta3 Markedly, in thrombi from mice deficient in transglutaminase factor XIII, platelet-driven fibrin formation and Rhod-A14 binding were abolished by blockage of integrin alpha(IIb)beta3. Vice versa, star-like fibrin formation from platelets of a patient with deficiency in alpha(IIb)beta3(Glanzmann thrombasthenia) was abolished upon blockage of transglutaminase activity. We conclude that coated platelets, with initial alpha(IIb)beta3 activation and high fibrinogen binding, form a subpopulation of phosphatidylserine-exposing platelets, and function in platelet-dependent star-like fibrin fiber formation via transglutaminase factor XIII and integrin alpha(IIb)beta3.


Patients with prior invasive fungal infection (IFI) increasingly proceed to allogeneic hematopoietic cell transplantation (HSCT). However, little is known about the impact of prior IFI on survival. Patients with pre-transplant IFI (cases; n=825) were compared with controls (n=10247). A subset analysis assessed outcomes in leukemia patients pre- and post 2001. Cases were older with lower performance status (KPS), more advanced disease, higher likelihood of AML and having received cord blood, reduced intensity conditioning, mold-active fungal prophylaxis and more recently transplanted. Aspergillus spp. and Candida spp. were the most commonly identified pathogens. 68% of patients had primarily pulmonary involvement. Univariate and multivariable analysis demonstrated inferior PFS and overall survival (OS) for cases. At 2 years, cases had higher mortality and shorter PFS with significant increases in non-relapse mortality (NRM) but no difference in relapse. One year probability of post-HSCT IFI was 24% (cases) and 17% (control, P<0.001). The predominant cause of death was underlying malignancy; infectious death was higher in cases (13% vs 9%). In the subset analysis, patients transplanted before 2001 had increased NRM with inferior OS and PFS compared with later cases. Pre-transplant IFI is associated with lower PFS and OS after allogeneic HSCT but significant survivorship was observed. Consequently, pre-transplant IFI should not be a contraindication to allogeneic HSCT in otherwise suitable candidates. Documented pre-transplant IFI is associated with lower PFS and OS after allogeneic HSCT. However, mortality post transplant is more influenced by advanced disease status than previous IFI. Pre-transplant IFI does not appear to be a contraindication to allogeneic HSCT. Bone Marrow Transplantation advance online publication, 19 December 2016; doi:10.1038/bmt.2016.259. © 2016 Macmillan Publishers Limited, part of Springer Nature.


INTRODUCTION: We hypothesized that serum neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios may predict pathologic complete response to neoadjuvant chemoradiotherapy in esophageal cancer patients. The ability to predict favorable treatment response to therapy may aid in determining optimal treatment regimens. MATERIALS AND METHODS: A retrospective review of a prospective esophageal disease registry was conducted. Neutrophil-to-lymphocyte ratio was defined as the pre-chemoradiotherapy serum neutrophil count divided by lymphocyte count. Platelet-to-lymphocyte ratio was similarly defined. Logistic regression was applied to analyze these ratios and their effect on pathologic complete response. A Cox proportional-hazards model was used to analyze survival. RESULTS: Sixty patients were included. Elevated neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were both negative predictors of pathologic complete response (odds ratio: 0.62; 95% confidence interval: 0.37-0.89, P = 0.037 and odds ratio:
0.91; 95% confidence interval: 0.82-0.98, P = 0.028, respectively). Only platelet-to-lymphocyte ratio was predictive of decreased overall survival (hazard ratio: 1.05, 95% confidence interval: 0.94-1.16, P = 0.40).

CONCLUSION: Elevated neutrophil and platelet-to-lymphocyte ratios were significant predictors of a poor treatment response to neoadjuvant therapy. Only elevated platelet-to-lymphocyte ratio was predictive of worse overall survival. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios may offer a simple serum test to assess the likelihood of a pathologic complete response after neoadjuvant therapy in esophageal cancer.


Prostate cancer is the most commonly diagnosed malignancy and second leading cause of cancer death among men in the United States. In recent years, several new agents, including cancer immunotherapies, have been approved or are currently being investigated in late-stage clinical trials for the management of advanced prostate cancer. Therefore, the Society for Immunotherapy of Cancer (SITC) convened a multidisciplinary panel, including physicians, nurses, and patient advocates, to develop consensus recommendations for the clinical application of immunotherapy for prostate cancer patients. To do so, a systematic literature search was performed to identify high-impact papers from 2006 until 2014 and was further supplemented with literature provided by the panel. Results from the consensus panel voting and discussion as well as the literature review were used to rate supporting evidence and generate recommendations for the use of immunotherapy in prostate cancer patients. Sipuleucel-T, an autologous dendritic cell vaccine, is the first and currently only immunotherapeutic agent approved for the clinical management of metastatic castrate resistant prostate cancer (mCRPC). The consensus panel utilized this model to discuss immunotherapy in the treatment of prostate cancer, issues related to patient selection, monitoring of patients during and post treatment, and sequence/combination with other anti-cancer treatments. Potential immunotherapies emerging from late-stage clinical trials are also discussed. As immunotherapy evolves as a therapeutic option for the treatment of prostate cancer, these recommendations will be updated accordingly. © 2016 The Author(s).


The nonheme iron complex, [Fe(NO)(N3PyS)]BF4, is a rare example of an (FeNO)(7) species that exhibits spin-crossover behavior. The comparison of X-ray crystallographic studies at low and high temperatures and variable-temperature magnetic susceptibility measurements show that a low-spin S = 1/2 ground state is populated at 0-150 K, while both low-spin S = 1/2 and high-spin S = 3/2 states are populated at T > 150 K. These results explain the observation of two N-O vibrational modes at 1737 and 1649 cm(-1) in CD3CN for [Fe(NO)(N3PyS)]BF4 at room temperature. This (FeNO)(7) complex reacts with dioxygen upon photoirradiation with visible light in acetonitrile to generate a thiolate-ligated, nonheme iron(III)-nitro complex, [Fe(III)(NO2)(N3PyS)](+), which was characterized by EPR, FTIR, UV-vis, and CSI-MS. Isotope labeling studies, coupled with FTIR and CSI-MS, show that one O atom from O2 is incorporated in the Fe(III)-NO2 product. The O2 reactivity of [Fe(NO)(N3PyS)]BF4 in methanol is dramatically different from CH3CN, leading exclusively to sulfur-based oxidation, as opposed to NO oxidation. A mechanism is proposed for the NO oxidation reaction that involves formation of both Fe(III)-superoxo and Fe(III)-peroxynitrite intermediates and takes into account the experimental observations. The stability of the Fe(III)-nitrite complex is limited, and decay of [Fe(III)(NO2)(N3PyS)](+ ) leads to (FeNO)(7) species and sulfur oxygenated products. This work demonstrates that a single mononuclear, thiolate-ligated nonheme (FeNO)(7) complex can exhibit reactivity related to both nitric oxide dioxygenase (NOD) and nitrite reductase (NiR) activity. The presence of the thiolate donor is critical to both pathways, and mechanistic insights into these biologically relevant processes are presented.

High-throughput genetic sequencing produces the ultimate "big data": a human genome sequence contains more than 3B base pairs, and more and more characteristics, or annotations, are being recorded at the base-pair level. Locating areas of interest within the genome is a challenge for researchers, limiting their investigations. We describe our vision of adapting "big data" ranked search to the problem of searching the genome. Our goal is to make searching for data as easy for scientists as searching the Internet.


Inferior vena cava (IVC) filter use is widespread in patients with venous thromboembolism (VTE) and temporary contraindication to anticoagulation, though timely removal is often not performed. We report the case of an expectoration of an IVC filter strut. Review of the patient's prior imaging confirmed an infrarenal Bard G2 filter with an absent strut, which was visualised in the left lung base. The strut was presumed to have embolised to a pulmonary artery branch and eroded into an adjacent bronchus. Subsequent fluoroscopically guided filter retrieval was successful. The incidence of IVC filter fractures increases with longer dwell times. Filter fragment embolisation has resulted in major adverse events, including sudden death and cardiac tamponade. Recent evidence has suggested that retrieval of IVC filters with prolonged dwell times is feasible and safe. This report brings awareness to the range of complications with indwelling IVC filters, and highlights the importance of timely removal. © 2016 BMJ Publishing Group Ltd.


Background: The ability to turn while walking is essential for daily living activities. Turning is slower and more steps are required to complete a turn in people with Parkinson's disease (PD) compared to control subjects but it is unclear whether this altered strategy is pathological or compensatory. The aim of our study is to characterize the dynamics of postural stability during continuous series of turns while walking at various speeds in subjects with PD compared to control subjects. We hypothesize that people with PD slow their turns to compensate for impaired postural stability. Method: Motion analysis was used to compare gait kinematics between 12 subjects with PD in their ON state and 19 control subjects while walking continuously on a route composed of short, straight paths interspersed with eleven right and left turns between 30 and 180°. We asked subjects to perform the route at three different speeds: preferred, faster, and slower. Features describing gait spatio-temporal parameters and turning characteristics were extracted from marker trajectories. In addition, to quantify dynamic stability during turns we calculated the distance between the lateral edge of the base of support and the body center of mass, as well as the extrapolated body center of mass. Results: Subjects with PD had slower turns and did not widen the distance between their feet for turning, compared to control subjects. Subjects with PD tended to cut short their turns compared to control subjects, resulting in a shorter walking path. Dynamic stability was smaller in the PD, compared to the healthy group, particularly for fast turning angles of 90°. Conclusions: The slower turning speeds and larger turning angles in people with PD might reflect a compensatory strategy to prevent dynamic postural instability given their narrow base of support. © 2016 Mellone et al.


Background: The benefits of pay-for-performance (P4P) programs are uncertain. Purpose: To update and expand a prior review examining the effects of P4P programs targeted at the physician, group, managerial, or institutional level on process-of-care and patient outcomes in ambulatory and inpatient settings. Data Sources: PubMed from June 2007 to October 2016; MEDLINE, PsycINFO, CINAHL, Business Economics and
Theory, Business Source Elite, Scopus, Faculty of 1000, and Gartner Research from June 2007 to February 2016. Study Selection: Trials and observational studies in ambulatory and inpatient settings reporting process-of-care, health, or utilization outcomes. Data Extraction: Two investigators extracted data, assessed study quality, and graded the strength of the evidence. Data Synthesis: Among 69 studies, 58 were in ambulatory settings, 52 reported process-of-care outcomes, and 38 reported patient outcomes. Low-strength evidence suggested that P4P programs in ambulatory settings may improve process-of-care outcomes over the short term (2 to 3 years), whereas data on longer-term effects were limited. Many of the positive studies were conducted in the United Kingdom, where incentives were larger than in the United States. The largest improvements were seen in areas where baseline performance was poor. There was no consistent effect of P4P on intermediate health outcomes (low-strength evidence) and insufficient evidence to characterize any effect on patient health outcomes. In the hospital setting, there was low-strength evidence that P4P had little or no effect on patient health outcomes and a positive effect on reducing hospital readmissions. Limitation: Few methodologically rigorous studies; heterogeneous population and program characteristics and incentive targets. Conclusion: Pay-for-performance programs may be associated with improved processes of care in ambulatory settings, but consistently positive associations with improved health outcomes have not been demonstrated in any setting. Primary Funding Source: U.S. Department of Veterans Affairs.


Empathy is a phenomenon often considered dependent on higher-order emotional control and an ability to relate to the emotional state of others. It is, by many, attributed only to species having well-developed cortical circuits capable of performing such complex tasks. However, over the years, a wealth of data has been accumulated showing that rodents are capable not only of sharing emotional states of their conspecifics, but also of prosocial behavior driven by such shared experiences. The study of rodent empathic behaviors is only now becoming an independent research field. Relevant animal models allow precise manipulation of neural networks, thereby offering insight into the foundations of empathy in the mammalian brains. Here we review the data on empathic behaviors in rat and mouse models, their neurobiological and neurophysiological correlates, and the factors influencing these behaviors. We discuss how simple rodent models of empathy enhance our understanding of how brain controls empathic behaviors. © 2016 Elsevier Ltd.


Macrophage migration inhibitory factor (MIF) is a key cytokine in autoimmune and inflammatory diseases that attracts and then retains activated immune cells from the periphery to the tissues. MIF exists as a homotrimer and its effects are mediated through its primary receptor, CD74 (the class II invariant chain that exhibits a highly structured trimerization domain), present on class II expressing cells. Although a number of binding residues have been identified between MIF and CD74 trimers, their spatial orientation has not been established. Using a docking program in silico, we have modeled binding interactions between CD74 and MIF as well as CD74 and a competitive MIF inhibitor, RTL1000, a partial MHC class II construct that is currently in clinical trials for multiple sclerosis. These analyses revealed 3 binding sites on the MIF trimer that each were predicted to bind one CD74 trimer through interactions with two distinct 5 amino acid determinants. Surprisingly, predicted binding of one CD74 trimer to a single RTL1000 antagonist utilized the same two 5 residue determinants, providing strong suggestive evidence in support of the MIF binding regions on CD74. Taken together, our structural modeling predicts a new MIF(CD74)3 dodecamer that may provide the basis for increased MIF potency and the requirement for ~3-fold excess RTL1000 to achieve full antagonism.

Although cardiac malformations at birth are typically associated with genetic anomalies, blood flow dynamics also play a crucial role in heart formation. However, the relationship between blood flow patterns in the early embryo and later cardiovascular malformation has not been determined. We used the chicken embryo model to quantify the extent to which anomalous blood flow patterns predict cardiac defects that resemble those in humans, and found that restricting either the inflow to the heart or the outflow led to reproducible abnormalities with a dose-response type relationship between blood flow stimuli and the expression of cardiac phenotypes. Constricting the outflow tract by 10-35% led predominantly to ventricular septal defects whereas constricting by 35-60%, most often led to double outlet right ventricle. Ligation of the vitelline vein caused mostly pharyngeal arch artery malformations. We show that both cardiac inflow reduction and graded outflow constriction strongly influence the development of specific and persistent abnormal cardiac structure and function. Moreover, the hemodynamic-associated cardiac defects recapitulate those caused by genetic disorders. Thus, our data demonstrate the importance of investigating embryonic blood flow conditions to understand the root causes of congenital heart disease as a prerequisite to future prevention and treatment.


The patient-centered medical home (PCMH) is a promising framework for the redesign of primary care and more recently specialty care. As defined by the Agency for Healthcare Research and Quality, the PCMH framework has 5 attributes: comprehensive care, patient-centered care, coordinated care, accessible services, and quality and safety. Evidence increasingly demonstrates that for the PCMH to best achieve the Triple Aim (improved outcomes, decreased cost, and enhanced patient experience), treatment for behavioral health (including mental health, substance use, and life stressors) must be integrated as a central tenet. However, challenges to implementing the PCMH framework are compounded for real-world practitioners because payment reform rarely happens concurrently. Nowhere is this more evident than in attempts to integrate behavioral health clinicians into primary care. As behavioral health clinicians find opportunities to work in integrated settings, a comprehensive understanding of payment models is integral to the dialogue. This article describes alternatives to the traditional fee for service (FFS) model, including modified FFS, pay for performance, bundled payments, and global payments (i.e., capitation). We suggest that global payment structures provide the best fit to enable and sustain integrated behavioral health clinicians in ways that align with the Triple Aim. Finally, we present recommendations that offer specific, actionable steps to achieve payment reform, complement PCMH, and support integration efforts through policy. (PsycINFO Database Record


Purpose/Objectives: To use dyadic analyses to identify determinants of patients’ and family members’ perceptions of the positive and negative aspects of the decision-making process in families living with lung cancer. Design: Cross-sectional study. Setting: Community setting in Greater Portland, Oregon. Sample: 109 family care dyads (patient and family member) recruited from a statewide cancer registry. Methods: Surveys were completed in-person, separately, and privately by each member of the family care dyad. Secondary analysis was completed using multilevel modeling. Main Research Variables: Negative and positive aspects of the decision process. Findings: Level 1 data revealed significant variability across care dyads’ positive or negative perceptions of the decision-making process. Level 2 results for negative perceptions of decision making indicated that patient and family member perceptions were significantly associated with their own depressive symptoms and feelings of not being listened to by others. Level 2 results for positive perceptions of decision making indicated that patient and family member perceptions were significantly inversely associated with their own feelings of not being listened to and being in nonspousal relationships. In addition, family members’ perceptions were more positive when the patients were older. Conclusions: This study highlighted the complexity of the decision-making process in families with lung cancer, and underscored the importance of the care dyad feeling listened to by family members in the context of life-
threatening illnesses. Implications for Nursing: Nurses assisting families with decisions about lung cancer should be aware of the dynamics of the care dyad and how the decision process is perceived by patients and their family members.


This paper reviews empirical findings concerning the decision-making process of persons with dementia and their family carers, with a particular focus on the extent and determinants of involvement of persons with dementia in the decision-making process. To be included in this review, studies needed to be published in peer-reviewed journals between 1999 and 2014, report empirical data from participants with dementia and/or their family carers, and pertain to the involvement of persons with dementia and their family carers in decisions about everyday care, medical care and treatment, or long-term care. A total of 36 studies were included. Results indicated that not all persons with dementia are excluded from participating in the decision-making process, but there is a broad spectrum of what constitutes shared decision-making in dementia. Studies concerning the determinants of shared decision-making mostly focused on non-modifiable factors. Future research is needed to better promote shared decision-making among persons with dementia and their family carers.


Exposure to estrous ewe urine stimulates investigation and mounting activity in sexually active but not sexually inactive rams. It was hypothesized sexual indifference may result from an inability to detect olfactory cues or an interruption of the pathway from detection of the olfactory stimulus to the motor response.

Sexually active (n = 4) and inactive (n = 3) rams were exposed to urine from estrous ewes. An additional group of sexually active rams (n = 3) were exposed to urine from ovariectomized ewes. Rams were exsanguinated following 1 h of exposure to stimulus. Neural activity was determined in tissues of interest by the presence of fos and fos-related proteins detected by immunohistochemistry procedures. Sexually active rams exposed to urine from ovariectomized ewes had more (P ≤ 0.05) fos-positive cells in the olfactory bulb, but fewer (P = 0.03) fos-positive cells in the cortical amygdala compared to sexually active rams exposed to urine from estrous ewes. Sexually inactive rams had similar (P ≥ 0.13) numbers of fos positive neurons in the olfactory bulb and medial amygdala but fewer (P ≤ 0.04) in the central amygdala, bed nucleus of the stria terminalis and the medial preoptic area compared to sexually active rams exposed to urine from estrous ewes. Sexual inactivity was not associated with decreased hypothalamic function since fos activity was similar (P ≥ 0.14) among groups in the suprachiasmatic and ventral medial nucleus. Sexual inactivity is not likely due to an impaired ability to detect or process olfactory stimuli by the main olfactory bulb and medial-cortical amygdala. Sexually inactive rams may have reduced attentiveness to sexual stimuli and/or decreased responsiveness of regions in the brain which regulate reproductive behaviors. © 2015 Elsevier B.V.


PURPOSE: To identify any temporal trends in the diagnosis of plus disease in retinopathy of prematurity (ROP) by experts. DESIGN: Reliability analysis. METHODS: ROP experts were recruited in 2007 and 2016 to classify 34 wide-field fundus images of ROP as plus, pre-plus, or normal, coded as “3,” “2,” and “1” respectively in the database. The main outcome was the average calculated score for each image in each cohort. Secondary outcomes included correlation on the relative ordering of the images in 2016 versus 2007,

The transcriptional events that lead to the cessation of neural proliferation, and therefore enable the production of proper numbers of differentiated neurons and glia, are still largely uncharacterized. Here, we report that the transcription factor Insulinoma-associated 1 (INSM1) forms complexes with RE1 Silencing Transcription factor (REST) corepressors RCOR1 and RCOR2 in progenitors in embryonic mouse brain. Mice lacking both RCOR1 and RCOR2 in developing brain die perinatally and generate an abnormally high number of neural progenitors at the expense of differentiated neurons and oligodendrocyte precursor cells. In addition, Rcor1/2 deletion detrimentally affects complex morphological processes such as closure of the interganglionic sulcus. We find that INSM1, a transcription factor that induces cell-cycle arrest, is coexpressed with RCOR1/2 in a subset of neural progenitors and forms complexes with RCOR1/2 in embryonic brain. Further, the Insm1−/− mouse phenocopies predominant brain phenotypes of the Rcor1/2 knockout. A large number of genes are concordantly misregulated in both knockout genotypes, and a majority of the down-regulated genes are targets of REST. Rest transcripts are up-regulated in both knockouts, and reducing transcripts to control levels in the Rcor1/2 knockout partially rescues the defect in interganglionic sulcus closure. Our findings indicate that an INSM1/RCOR1/2 complex controls the balance of proliferation and differentiation during brain development.


PURPOSE: To assess the performance of the deformable image registration algorithm used for MRI-guided adaptive radiation therapy using image feature analysis. METHODS: MR images were collected from five patients treated on the MRIdian (ViewRay, Inc., Oakwood Village, OH), a three head Cobalt–60 therapy machine with an 0.35 T MR system. The images were acquired immediately prior to treatment with a uniform 1.5 mm resolution. Treatment sites were as follows: head/neck, lung, breast, stomach, and bladder. Deformable image registration was performed using the ViewRay software between the first fraction MRI and the final fraction MRI, and the DICE similarity coefficient (DSC) for the skin contours was reported. The SIFT and Harris feature detection and matching algorithms identified point features in each image separately, then found matching features in the other image. The target registration error (TRE) was defined as the vector distance between matched features on the two image sets. Each deformation was evaluated based on comparison of average TRE and DSC. RESULTS: Image feature analysis produced between 2000-9500 points for evaluation on the patient images. The average (+/- standard deviation) TRE for all patients was 3.3 mm (+/- 3.1 mm), and the passing rate of TRE<3 mm was 60% on the images. The head/neck patient had the best average TRE (1.9 mm +/- 2.3 mm) and the best passing rate (80%). The lung patient had the worst average TRE (4.8 mm +/- 3.3 mm) and the worst passing rate (37.2%). DSC was not significantly correlated with either TRE (p=0.63) or passing rate (p=0.55). CONCLUSIONS: Feature matching provides a quantitative assessment of deformable image registration, with a large number of data points for analysis. The TRE of matched features can be used to evaluate the registration of many objects throughout the
volume, whereas DSC mainly provides a measure of gross overlap. We have a research agreement with ViewRay Inc.


**Background:** Extracardiac total cavopulmonary connection (E-TCPC) is widely performed for single ventricle palliation, yet there is little experience with catheter ablation in this population. Objectives: We hypothesized that atrial tachycardia substrates after primary E-TCPC would be similar to those in other forms of congenital heart disease and that catheter ablation could be performed effectively using a primarily transconduit approach. Methods: Catheter ablation characteristics of patients with E-TCPC from 9 centers were collected. Acute procedural success was defined as elimination of all sustained supraventricular tachyarrhythmias. Procedural complications, acute success, and recurrences were assessed. Results: Forty-six catheter ablation procedures were performed in 36 patients. Access to the atrium was by transconduit puncture in 29 procedures (63%). The most common supraventricular tachyarrhythmia mechanism was intra-atrial reentrant tachycardia (IART) in 21 patients (58%); and for all patients with primary E-TCPC and IART, an isthmus between the atroventricular valve annulus and the oversewn inferior vena cava was critical for maintenance of tachycardia. Overall, acute success was achieved in 38 procedures (83%). There were 8 complications, with only 1 requiring intervention (epicardial pacemaker) and none related to conduit puncture. Recurrence after the final procedure occurred in 6 patients (17%) over a median follow-up duration of 0.4 years (interquartile range 0.1-1.5 years). Conclusion: Catheter ablation could be performed effectively in this group of patients with E-TCPC, and the underlying IART substrate after primary E-TCPC appears to be reproducible. Catheter ablation may be a reasonable alternative to long-term antiarrhythmic therapy in this patient group. © 2016.


**BACKGROUND:** Urine drug testing (UDT) is recommended for all patients who initiate chronic opioid therapy (COT) for the treatment of chronic pain; however, it is infrequently utilized. Some prior research has identified factors that may predict UDT, but studies have been limited. The purpose of this study is to examine the rate and predictors of UDT among a national sample of patients with chronic pain who had new initiations of COT. **METHODS:** Administrative data were examined for all veterans receiving medical care at Department of Veterans Affairs medical facilities who had new initiations of chronic opioid therapy (COT) during fiscal year 2011. **RESULTS:** Nineteen percent of patients who had new initiations of COT for chronic noncancer pain received UDT within 90 days of starting opioids. In adjusted analyses, patient-level factors that predicted increased likelihood of UDT included male gender (risk ratio [RR] = 1.23, 95% confidence interval [CI] = 1.02-1.49), Black race (RR = 1.20, 95% CI = 1.06-1.37), divorced/separated marital status (RR = 1.13, 95% CI = 1.02-1.25), higher pain intensity (RR = 1.03, 95% CI = 1.01-1.05), comorbid substance use disorder (RR = 1.42, 95% CI = 1.27-1.60), posttraumatic stress disorder (PTSD) (RR = 1.14, 95% CI = 1.01-1.29), bipolar disorder or schizophrenia (RR = 1.29, 95% CI = 1.08-1.53), having received UDT prior to initiating opioid therapy (RR = 1.43, 95% CI = 1.26-1.62), and a higher baseline opioid dose (RR = 1.38-1.81, 95% CIs = 1.20-1.58, 1.57-2.09). Age was also associated with UDT, in a nonlinear manner. Several factors were associated with lower likelihood of UDT, including living in a highly rural setting (RR = 0.62, 95% CI = 0.29-0.99), having a VA service-connected disability (RR = 0.85-0.89, 95% CIs = 0.75-0.97, 0.79-0.99), and having a nurse practitioner or physician assistant as one’s primary care clinician (RR = 0.72, 95% CI = 0.61-0.85). **CONCLUSIONS:** Urine drug testing was conducted with 19% of patients who had new initiations of COT. Factors that predicted UDT were multifaceted and included patient and clinician variables. Multidimensional system-level interventions may be needed to facilitate widespread implementation of UDT.

We investigated the predictors of time from metastatic castration-resistant prostate cancer (mCRPC) to all-cause mortality among patients treated at Veteran Affairs hospitals. We found that age, more remote year of mCRPC, greater number of bone metastasis, higher prostate-specific antigen levels, and shorter prostate-specific antigen doubling time at mCRPC diagnosis were associated with shorter overall survival. A nomogram was generated yielding good concordance and calibration. © 2016 Elsevier Inc.


Carbapenem-resistant Enterobacteriaceae (CRE) are an urgent public health threat. We evaluated the capacity of the Carba NP test to detect carbapenemase production in 206 isolates: 143 Enterobacteriaceae identified by Oregon’s CRE surveillance program in 2013 and 63 known carbapenemase-positive organisms. Overall, test sensitivity and specificity were 89% (59/66 isolates; 95% confidence interval [CI], 81 to 97%) and 100% (140/140 isolates; 95% CI, 98 to 100%), respectively. All KPC, NDM-1, VIM, and IMP producers but no (0/7 isolates) OXA-48-like strains were Carba NP positive prior to a post hoc protocol modification. We subsequently incorporated Carba NP into Oregon’s CRE screening algorithm. Copyright © 2016 American Society for Microbiology. All Rights Reserved.


**PURPOSE.** We determine if several hours of controlled elevation of IOP (CEI) will produce the optic nerve head (ONH) gene expression changes and optic nerve (ON) damage pattern associated with early experimental glaucoma in rats. **METHODS.** The anterior chambers of anesthetized rats were cannulated and connected to a reservoir to elevate IOP. Physiologic parameters were monitored. Following CEI at various recovery times, ON cross-sections were graded for axonal injury. Anterior ONHs were collected at 0 hours to 10 days following CEI and RNA extracted for quantitative PCR measurement of selected messages. The functional impact of CEI was assessed by electroretinography (ERG). **RESULTS.** During CEI, mean arterial pressure (99 ± 6 mm Hg) and other physiologic parameters remained stable. An 8-hour CEI at 60 mm Hg produced significant focal axonal degeneration 10 days after exposure, with superior lesions in 83% of ON. Message analysis in CEI ONH demonstrated expression responses previously identified in minimally injured ONH following chronic IOP elevation, as well as their sequential patterns. Anesthesia with cannulation at 20 mm Hg did not alter these message levels. Electroretinographic A- and B-waves, following a significant reduction at 2 days after CEI, were fully recovered at 2 weeks, while peak scotopic threshold response (pSTR) remained mildly but significantly depressed. **CONCLUSIONS.** A single CEI reproduces ONH message changes and patterns of ON injury previously observed with chronic IOP elevation. Controlled elevation of IOP can allow detailed determination of ONH cellular and functional responses to an injurious IOP insult and provide a platform for developing future therapeutic interventions. © 2016, Association for Research in Vision and Ophthalmology Inc. All rights reserved.


Background The role of Troponin (Tn) levels in the management of patients post out-of-hospital cardiac arrest (OHCA) is unclear. Methods All OHCA patients enrolled in the Resuscitation Outcomes Consortium Prehospital Resuscitation using an IMPedance valve and Early versus Delayed analysis trial and admitted to hospital with a Tn level and a 12-lead electrocardiogram were stratified by ST elevation (STE) or no STE in a regression model for survival to discharge adjusted for Utstein predictors and site. Results Of the 15,617
enrolled OHCA patients, 4118 (26%) survived to admission to hospital; 17% (693) were STE and 77% (3188) were no STE with 6% unknown; 83% (3460) had at least one Tn level. Reperfusion rates were higher when Tn level >2 ng/ml (p > 0.1 ng/ml) improved with a diagnostic cardiac catheterization (p < 0.001). Conclusions Elevated Tn levels >2 ng/ml were associated with improved survival to discharge in patients post OHCA with STE. Survival in patients with no STE and Tn values >0.1 ng/ml was higher when associated with diagnostic cardiac catheterization or treated with reperfusion or revascularization. © 2016 Elsevier Ireland Ltd


Oxidative stress, mainly contributed by reactive oxygen species (ROS), has been implicated in pathogenesis of several diseases. We review two primary examples: fibrosis and cancer. In fibrosis, ROS promote activation and proliferation of fibroblasts and myofibroblasts, activating TGF-β pathway in an autocrine manner. In cancer, ROS account for its genomic instability, resistance to apoptosis, proliferation, and angiogenesis. Importantly, ROS trigger cancer cell invasion through invadopodia formation as well as extravasation into a distant metastasis site. Use of antioxidant supplements, enzymes, and inhibitors for ROS-generating NADPH oxidases (NOX) is a logical therapeutic intervention for fibrosis and cancer. We review such attempts, progress, and challenges. Lastly, we review how nanoparticles with inherent antioxidant activity can also be a promising therapeutic option, considering their additional feature as a delivery platform for drugs, genes, and imaging agents. © 2016


Significant progress has been made in characterizing the biological changes occurring in preclinical Alzheimer's disease (AD). Cognitive dysfunction has been viewed, however, as a late-stage phenomenon, despite increasing evidence that changes may be detected in the decades preceding dementia. In the absence of comprehensive evidence-based guidelines for preclinical cognitive assessment, longitudinal cohort and neuroimaging studies have been reviewed to determine the temporal order and brain biomarker correlates of specific cognitive functions. Episodic memory decline was observed to be the most salient cognitive function, correlating with high levels of amyloid deposition and hypoconnectivity across large-scale brain networks. Prospective studies point to early decline in both episodic and semantic memory processing as well as executive functions in the predementia period. The cognitive tests have, however, been principally those used to diagnose dementia. New procedures are required which target more finely the medial temporal lobe subregions first affected by clinically silent AD pathology. © 2016 The Alzheimer's Association.


BACKGROUND: People with multiple sclerosis (MS) have identified "wellness" and associated behaviors as a high priority based on "social media listening" undertaken by the National MS Society (i.e. the Society).

OBJECTIVE: The Society recently convened a group that consisted of researchers with experience in MS and wellness-related research, Society staff members, and an individual with MS for developing recommendations regarding a wellness research agenda.

METHOD: The members of the group engaged in focal reviews and discussions involving the state of science within three approaches for promoting wellness in MS, namely diet, exercise, and emotional wellness.

RESULTS: That process informed a group-mediated activity for developing and prioritizing research goals for wellness in MS. This served as a background for articulating the mission and objectives of the Society’s Wellness Research Working Group.

CONCLUSION: The primary mission of the Wellness Research Working Group is the provision of scientific evidence supporting the application of lifestyle, behavioral, and psychosocial approaches for promoting optimal
health of mind, body, and spirit (i.e. wellness) in people with MS as well as managing the disease and its consequences.


Objectives: We hypothesized that microvascular retention of phosphatidylserine-containing microbubbles (MB-PS) would allow detection of recent but resolved myocardial ischemia with myocardial contrast echocardiographic (MCE) molecular imaging. Background: Techniques for ischemic memory imaging which can detect and spatially assess resolved myocardial ischemia are being developed for rapid evaluation of patients with chest pain. Methods: MCE molecular imaging with MB-PS was performed 1.5 h, 3.0 h, and 6.0 h after brief (10 min) myocardial ischemia in mice; data were compared to selectin-targeted microbubbles. MCE molecular imaging with Sonazoid (GE Healthcare, Amersham, United Kingdom), a commercially produced phosphatidylserine (PS) - containing agent, was performed in separate mice at 1.5 h and 3.0 h after ischemia-reperfusion; and in dogs undergoing 135 min of ischemia and 60 min of reflow as well as in closed-chest nonischemic control dogs. The mechanism for MB-PS attachment was assessed by intravital microscopy of post-ischemic muscle and by flow cytometry analysis of cell-MB interactions. Results: In mice undergoing ischemia-reperfusion without infarction, signal enhancement in the risk area for MB-PS and p-selectin glycoprotein ligand-1-targeted microbubbles was similar at reflow times of 1.5 h (23.3 ± 7.3 IU vs. 30.7 ± 4.1 IU), 3.0 h (42.2 ± 6.2 IU vs. 33.9 ± 7.4 IU), and 6.0 h (24.1 ± 4.3 IU vs. 25.5 ± 4.7 IU). For both agents, signal in the risk area was significantly (p < 0.05) higher than remote region at all reflow times.

Sonazoid also produced strong risk area enhancement at 1.5 h (34.7 ± 5.0 IU) and 3.0 h (52.5 ± 4.5 IU) which was approximately 3-fold greater than in the control region, and which correlated spatially with the microsphere-derived risk area. In dogs, Sonazoid signal in the risk area was >5-fold higher in closed-chest control myocardium (42.2 ± 8.1 IU vs. 7.9 ± 3.3 IU; p < 0.001). Mechanistic studies indicated that MB-PS attached directly to venular endothelium and adherent leukocytes which was dependent on serum complement components C1q and C3. Conclusions: Ischemic memory imaging with MCE is possible using MB-PS which may obviate the need for ligand-directed targeting. © 2016 American College of Cardiology Foundation.


Background: Neurocysticercosis is a common helminthic infection of the central nervous system and an important cause of adult-onset epilepsy in endemic countries. However, few studies have examined associations between neurologic symptoms, serology and radiographic findings on a community-level. Methodology: We conducted a population-based study of resident’s ≥2 years old in a highly endemic village in Peru (pop. 454). We applied a 14 -question neurologic screening tool and evaluated serum for antibodies against Taenia solium cysticercosis using enzyme-linked immunoelctrotransfer blot (LLGP-EITB). We invited all residents ≥18 years old to have non-contrast computerized tomography (CT) of the head. Principal findings: Of the 385 residents who provided serum samples, 142 (36.9%) were seropositive. Of the 256 residents who underwent CT scan, 48 (18.8%) had brain calcifications consistent with NCC; 8/48 (17.0%) reported a history of headache and/or seizures. Exposure to T. solium is very common in this endemic community where 1 out of 5 residents had brain calcifications. However, the vast majority of people with calcifications were asymptomatic. Conclusion: This study reports a high prevalence of NCC infection in an endemic community in Peru and confirms that a large proportion of apparently asymptomatic residents have brain calcifications that could provoke seizures in the future. © 2016 Moyano et al.

UNLABELLED: In the transition from childhood to adolescence, attention-deficit/hyperactivity disorder (ADHD) developmental trajectories diverge. Family environment, as indexed by parental expressed emotion, may moderate these trajectories. 388 children with ADHD and 127 controls were assessed using multi-informant, multimethod diagnostic procedures at up to 3 time points 1 year apart in an accelerated longitudinal design spanning ages 7-13 years. Latent-class growth analysis was used to identify developmental trajectories for parent- and teacher-rated ADHD and oppositional-defiant disorder (ODD) symptoms within the ADHD sample. Parental expressed emotion, criticism, and emotional overinvolvement were coded from a 5-min speech sample at 2 time points, 1 year apart, for 208 of these children and compared among ADHD trajectory groups. RESULTS: Parent-rated hyperactivity yielded a 4-class trajectory solution in latent-class growth analysis; teacher-rated inattention yielded a 3-trajectory solution. Teacher-rated ODD also yielded 3-trajectory solution. A parent-rated high persistent hyperactive group was more likely than the other ADHD groups to have parents with stable high criticism (34.6%, p < .001), with ODD symptoms controlled. A teacher-identified high ODD-worsening group was more likely to experience high criticism, particularly the initial time point; (87.5%, p < .001), with hyperactivity controlled. Parental criticism, an index of the family environment, is uniquely associated with divergent developmental trajectories among children with ADHD in addition to those associated with ODD symptoms. Lay summary: For many children, ADHD symptoms decrease as they transition to adolescence. Family environmental factors, such as parental criticism, may help explain for whom symptom remission is less likely.


Children with attention deficit/hyperactivity disorder (ADHD) display alterations in both emotion reactivity and regulation. One mechanism underlying such alternations may be reduced coherence among emotion systems (i.e., autonomic, facial affect). The present study sought to examine this. One hundred children (50 with ADHD combined presentation), 7-11 years of age (62% male, 78% White), completed an emotion induction and suppression task. This task was coded for facial affect behavior across both negative and positive emotion eliciting task conditions. Electrocardiogram and impedance cardiography data were acquired throughout the task. Time-linked coherence of facial affect behavior and autonomic reactivity and regulation were examined during the induction conditions using hierarchical linear modeling. Although ADHD and typically developing children did not differ with respect to rates of facial affect behavior displayed (all Fs < 2.09, ps > .29), the ADHD group exhibited reduced coherence between facial affect behavior and an index of parasympathetic functioning (i.e., respiratory sinus arrhythmia), gamma10 = -0.03, SE = 0.02, t(138) = -1.96, p = .05. In contrast, children in the control group displayed a significant, positive, gamma10 = 0.06, SE = 0.01, t(138) = 4.07, p < .001, association between facial affect behavior and respiratory sinus arrhythmia. Children with ADHD may receive conflicting emotional signals at the levels of facial affective behavior and parasympathetic functioning when compared to typically developing youth. Weakened coherence among these emotion systems may be an underlying mechanism of emotion dysregulation in ADHD. Implications for etiology and treatment are discussed.


Background: High maternal prepregnancy body mass index (BMI) has been associated with increased risk of offspring attention-deficit/hyperactivity disorder (ADHD). However, whether this effect is attributable to maternal or familial level confounds has been little examined. Methods: The present study sought to examine these associations, utilizing data from the medical records of a health care system which treats

BACKGROUND: Cerebral edema is a major cause of mortality following cardiac arrest (CA) and cardiopulmonary resuscitation (CPR). Arginine vasopressin (AVP) and water channel aquaporin-4 (AQP4) have been implicated in the pathogenesis of CA-evoked cerebral edema. In this study, we examined if conivaptan, a V1a and V2 antagonist, attenuates cerebral edema following CA/CPR in wild type (WT) mice as well as mice with targeted disruption of the gene encoding alpha-syntrophin (alpha-syn(-/-)) that demonstrate diminished perivascular AQP4 pool. METHODS: Isoflurane-anesthetized adult male WT C57Bl/6 and alpha-syn(-/-) mice were subjected to 8 min CA/CPR and treated with either bolus IV injection (0.15 or 0.3 mg/kg) followed by continuous infusion of conivaptan (0.15 mg/kg/day or 0.3 mg/kg/day), or vehicle infusion for 48 h. Serum osmolality, regional brain water content, and blood-brain barrier (BBB) disruption were determined at the end of the experiment. Sham-operated mice in both strains served as controls. RESULTS: Treatment with conivaptan elevated serum osmolality in a dose-dependent manner. In WT mice, conivaptan at 0.3 mg dose significantly attenuated regional water content in the caudoputamen (81.0 +/- 0.5 vs. 82.5 +/- 0.4% in controls; mean +/- SEM) and cortex (78.8 +/- 0.2 vs. 79.4 +/- 0.2% in controls), while conivaptan at 0.15 mg was not effective. In alpha-syn(-/-) mice, conivaptan at 0.3 mg dose did not attenuate water content compared with controls. Conivaptan (0.3 mg/kg/day) attenuated post-CA BBB disruption at 48 h in WT mice but not in alpha-syn(-/-) mice. CONCLUSIONS: Continuous IV infusion of conivaptan attenuates cerebral edema and BBB disruption following CA. These effects of conivaptan that are dependent on the presence of perivascular pool of AQP4 appear be mediated via its dual effect on V1 and V2 receptors.

BACKGROUND: Neovascularization, a distinguishing trait of high-grade glioma, is a target for anti-angiogenic treatment with bevacizumab (BEV). This study sought to use ferumoxytol-based dynamic susceptibility contrast magnetic resonance imaging (MRI) to clarify perfusion and relative blood volume (rCBV) changes in glioma treated with BEV and to determine potential impact on clinical management.

METHODS: 16 high grade glioma patients who received BEV following post-chemoradiation radiographic or clinical progression were included. Ferumoxytol-based MRI perfusion measurements were taken before and after BEV. Lesions were defined at each timepoint by gadolinium-based contrast agent (GBCA)-enhancing area. Lesion volume and rCBV were compared pre and post-BEV in the lesion and rCBV “hot spot” (mean of the highest rCBV in a 1.08 cm2 area in the enhancing volume), as well as hypoperfused and hyperperfused subvolumes within the GBCA-enhancing lesion. RESULTS: GBCA-enhancing lesion volumes decreased 39% (P = 0.01) after BEV. Mean rCBV in post-BEV GBCA-enhancing area did not decrease significantly (P = 0.227) but significantly decreased in the hot spot (P = 0.046). Mean and hot spot rCBV decreased (P = 0.039 and 0.007) when post-BEV rCBV was calculated over the pre-BEV GBCA-enhancing area. Hypoperfused pixel count increased from 24% to 38 (P = 0.007) and hyperperfused decreased from 39 to 28% (P = 0.017). Mean rCBV decreased in 7/16 (44%) patients from >1.75 to <1.75, the cutoff for pseudoprogression diagnosis. CONCLUSIONS: Decreased perfusion after BEV significantly alters rCBV measurements when using ferumoxytol. BEV treatment response hinders efforts to differentiate true progression from pseudoprogression using blood volume measurements in malignant glioma, potentially impacting patient diagnosis and management.


BACKGROUND: Misleading early blood volume measurements in malignant glioma, potentially impacting patient diagnosis and management. OBJECTIVES: This study aimed to identify patient and operational characteristics associated with patient satisfaction scores. METHODS: This was a retrospective analysis of data from Press Ganey patient satisfaction surveys of pediatric patients (<18 years) and their families, discharged from the ED of a single, academic, pediatric ED from December 2009 to May 2013. A linear mixed-effects regression model was used to identify significant associations while taking the clustering within patients and physicians into account. Outcome variables included scores for overall experience (0-10), wait time to be seen by a provider (0-100), and likelihood to recommend (0-100). The ED characteristics considered included daily census, proportion of left

BACKGROUND: Self-regulation (SR) is central to developmental psychopathology, but progress has been impeded by varying terminology and meanings across fields and literatures. METHODS: The present review attempts to move that discussion forward by noting key sources of prior confusion such as measurement-concept confounding, and then arguing the following major points. RESULTS: First, the field needs a domain-general construct of SR that encompasses SR of action, emotion, and cognition and involves both top-down and bottom-up regulatory processes. This does not assume a shared core process across emotion, action, and cognition, but is intended to provide clarity on the extent of various claims about kinds of SR. Second, top-down aspects of SR need to be integrated. These include (a) basic processes that develop early and address immediate conflict signals, such as cognitive control and effortful control (EC), and (b) complex cognition and strategies for addressing future conflict, represented by the regulatory application of complex aspects of executive functioning. Executive function (EF) and cognitive control are not identical to SR because they can be used for other activities, but account for top-down aspects of SR at the cognitive level. Third, impulsivity, risk-taking, and disinhibition are distinct although overlapping; a taxonomy of the kinds of breakdowns of SR associated with psychopathology requires their differentiation. Fourth, different aspects of the SR universe can be organized hierarchically in relation to granularity, development, and time. Low-level components assemble into high-level components. This hierarchical perspective is consistent across literatures. CONCLUSIONS: It is hoped that the framework outlined here will facilitate integration and cross-talk among investigators working from different perspectives, and facilitate individual differences research on how SR relates to developmental psychopathology.


Although attention-deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental condition, there is also considerable scientific and public interest in environmental modulators of its etiology. Exposure to neurotoxins is one potential source of perturbation of neural, and hence psychological, development. Exposure to lead in particular has been widely investigated and is correlated with neurodevelopmental outcomes, including ADHD. To investigate whether this effect is likely to be causal, we used a Mendelian randomization design with a functional gene variant. In a case-control study, we examined the association between ADHD symptoms in children and blood lead level as moderated by variants in the hemochromatosis (HFE) gene. The HFE gene regulates iron uptake and secondarily modulates lead metabolism. Statistical moderation was observed: The magnitude of the association of blood lead with symptoms of ADHD was altered by functional HFE genotype, which is consistent with a causal hypothesis.

**MOTIVATION:** In recent years, vast advances in biomedical technologies and comprehensive sequencing have revealed the genomic landscape of common forms of human cancer in unprecedented detail. The broad heterogeneity of the disease calls for rapid development of personalized therapies. Translating the readily available genomic data into useful knowledge that can be applied in the clinic remains a challenge. Computational methods are needed to aid these efforts by robustly analyzing genome-scale data from distinct experimental platforms for prioritization of targets and treatments. **RESULTS:** We propose a novel, biologically-motivated, Bayesian multitask approach, which explicitly models gene-centric dependencies across multiple and distinct genomic platforms. We introduce a genewise prior and present a fully Bayesian formulation of a group factor analysis model. In supervised prediction applications, our multitask approach leverages similarities in response profiles of groups of drugs that are more likely to be related to true biological signal, which leads to more robust performance and improved generalization ability. We evaluate the performance of our method on molecularly characterized collections of cell lines profiled against two compound panels, namely the Cancer Cell Line Encyclopedia and the Cancer Therapeutics Response Portal. We demonstrate that accounting for the gene-centric dependencies enables leveraging information from multi-omic input data and improves prediction and feature selection performance. We further demonstrate the applicability of our method in an unsupervised dimensionality reduction application by inferring genes essential to tumorigenesis in the pancreatic ductal adenocarcinoma and lung adenocarcinoma patient cohorts from The Cancer Genome Atlas. **AVAILABILITY:** The code for this work is available at https://github.com/olganikolova/gbgfa CONTACT: nikolova@ohsu.edu,margolin@ohsu.edu.


Liquid nicotine used in electronic cigarette devices is highly concentrated, unreliably packaged, and poorly regulated. We present a case report of a 6-year-old female who developed severe toxicity and required intubation after an unintentional oral ingestion of approximately 703 mg (35 mg/kg) of liquid nicotine, with accompanying serum and urine concentrations of nicotine and its metabolites. Analysis of the ingested liquid suggests a nicotine concentration of 140.6 mg/mL in the purchased commercial product, or 234% of its labeled concentration. Clinicians should be aware of these products and the potential severity of toxicity they may incur. © 2016 American College of Emergency Physicians.


Exposure of infant animals, including non-human primates (NHPs), to anaesthetic drugs causes apoptotic death of neurons and oligodendrocytes (oligos) and results in long-term neurodevelopmental impairment (NDI). Moreover, retrospective clinical studies document an association between anaesthesia exposure of human infants and significant increase in NDI. These findings pose a potentially serious dilemma because millions of human infants are exposed to anaesthetic drugs every year as part of routine medical care. Lithium (Li) at clinically established doses is neuroprotective in various cerebral injury models. We therefore investigated whether Li also protects against anaesthesia neurotoxicity in infant NHPs. On postnatal day 6 NHPs were anaesthetized with the widely used anaesthetic isoflurane (ISO) for 5 h employing the same standards as in a human pediatric surgery setting. Co-administration of Li completely prevented the acute ISO-induced neuroapoptosis and significantly reduced ISO-induced apoptosis of oligodendroglia. Our findings are highly encouraging as they suggest that a relatively simple pharmacological manipulation might protect the developing primate brain against the neurotoxic action of anaesthetic drugs while not interfering with the beneficial actions of these drugs. Further research is needed to determine Li’s potential to prevent long-term NDI resulting from ISO anaesthesia, and to establish its safety in human infants.


Dissolved Mn (dMnT) is thought to be dominated by metastable Mn(II) in the presence of oxygen, as the stable form is insoluble Mn(IV). We show, for the first time, that Mn(III) is also stable as a soluble species in the oxygenated water column, when stabilized by organic ligands as Mn(III)–L complexes. We measured Mn(III)–L complexes in the oxygenated waters of a coastal fjord and a hemipelagic system where they make up to 86% of the dMnT. Although Mn(III) forms similar complexes to Fe(III), unlike most of the analogous Fe(III)–L complexes, the Mn(III)–L complexes are not colloidal, as they pass through both 0.20 μm and 0.02 μm filters. Depending on the kinetic stability of the Mn(III) complexes and the microbial community of a given system, these Mn(III)–L complexes are capable of donating or accepting electrons and may therefore serve as both reductants or oxidants, can be biologically available, and can thus participate in a multitude of redox reactions and biogeochemical processes. Furthermore, sample acidification experiments revealed that Mn(III) binding to humic ligands is responsible for up to 100% of this complexation, which can influence the formation of other metal complexes including Fe(III) and thus impact nutrient availability and uptake. Hence, humic ligands may play a greater role in dissolved Mn transport from coastal areas to the ocean than previously thought. © 2016 Elsevier Ltd


Objective: To evaluate the influence of phenyl-propanedione on yellowing and chemical-mechanical properties of experimental resin-based materials photoactivated using different light curing units (LCUs).

Material and Methods: Experimental resin-based materials with the same organic matrix (60:40 wt% BisGMA:TEGDMA) were mechanically blended using a centrifugal mixing device. To this blend, different photoinitiator systems were added in equimolar concentrations with aliphatic amine doubled by wt%: 0.4 wt% CQ; 0.38 wt% PPD; or 0.2 wt% CQ and 0.19 wt% PPD. The degree of conversion (DC), flexural strength (FS), Young’s modulus (YM), Knoop hardness (KNH), crosslinking density (CLD), and yellowing (Y) were evaluated (n=10). All samples were light cured with the following LCUs: a halogen lamp (XL 2500), a monowave LED (Radii), or a polywave LED (Valo) with 16 J/cm². The results were analysed by two-way ANOVA and Tukey’s test (alpha=0.05). Results: No statistical differences were found between the different photoinitiator systems to KNH, CLS, FS, and YM properties (p>/=0.05). PPD/CQ association showed the higher DC values compared with CQ and PPD isolated systems when photoactivated by a polywave LED (p</=0.05). Y values were highest for the CQ compared with the PPD systems (p</=0.05). Conclusion: PPD isolated system promoted similar chemical and mechanical properties and less yellowing compared with the CQ isolated system, regardless of the LCU used.


OBJECTIVE: The objectives of the study were to describe a sample of truck drivers, identify clusters of drivers with similar patterns in behaviors affecting energy balance (sleep, diet, and exercise), and test for cluster differences in health safety, and psychosocial factors. METHODS: Participants’ (n = 452, body mass index M = 37.2, 86.4% male) self-reported behaviors were dichotomized prior to hierarchical cluster analysis, which identified groups with similar behavior covariation. Cluster differences were tested with generalized estimating equations. RESULTS: Five behavioral clusters were identified that differed significantly in age,
smoking status, diabetes prevalence, lost work days, stress, and social support, but not in body mass index. Cluster 2, characterized by the best sleep quality, had significantly lower lost workdays and stress than other clusters. CONCLUSIONS: Weight management interventions for drivers should explicitly address sleep, and may be maximally effective after establishing socially supportive work environments that reduce stress exposures.


An image-based skeletal dosimetry model for internal electron sources was created for the ICRP-defined reference adult female. Many previous skeletal dosimetry models, which are still employed in commonly used internal dosimetry software, do not properly account for electron escape from trabecular spongiosa, electron cross-fire from cortical bone, and the impact of marrow cellularity on active marrow self-irradiation. Furthermore, these existing models do not employ the current ICRP definition of a 50 m bone endosteum (or shallow marrow). Each of these limitations was addressed in the present study. Electron transport was completed to determine specific absorbed fractions to both active and shallow marrow of the skeletal regions of the University of Florida reference adult female. The skeletal macrostructure and microstructure were modeled separately. The bone macrostructure was based on the whole-body hybrid computational phantom of the UF series of reference models, while the bone microstructure was derived from microCT images of skeletal region samples taken from a 45 years-old female cadaver. The active and shallow marrow are typically adopted as surrogate tissue regions for the hematopoietic stem cells and osteoprogenitor cells, respectively. Source tissues included active marrow, inactive marrow, trabecular bone volume, trabecular bone surfaces, cortical bone volume, and cortical bone surfaces. Marrow cellularity was varied from 10 to 100 percent for active marrow self-irradiation. All other sources were run at the defined ICRP Publication 70 cellularity for each bone site. A total of 33 discrete electron energies, ranging from 1 keV to 10 MeV, were either simulated or analytically modeled. The method of combining skeletal macrostructure and microstructure absorbed fractions assessed using MCNPX electron transport was found to yield results similar to those determined with the PIRT model applied to the UF adult male skeletal dosimetry model. Calculated skeletal averaged absorbed fractions for each source-target combination were found to follow similar trends of more recent dosimetry models (image-based models) but did not follow results from skeletal models based upon assumptions of an infinite expanse of trabecular spongiosa. © 2016 Institute of Physics and Engineering in Medicine.


Background: Intracranial pressure (ICP) monitoring is not routinely used during complex spinal deformity correction surgery. The authors report a 66-year-old male who during thoracolumbar deformity surgery required the placement of an ICP monitor due to the underlying history of a superior vena cava syndrome (e.g., s/p right jugular stent). Case Description: A 66-year-old male with multiple prior lumbar spinal procedures presented with lower back and bilateral lower extremity pain, paresthesias, and weakness. He had a history of chronic left internal jugular and brachiocephalic venous occlusion (e.g., he had a right internal jugular stent). During deformity surgery, a frontal intraparenchymal ICP monitor was placed. During the early portion of the operation, bed adjustments (increasing reverse trendelenburg position) were required to compensate for ICP elevations as high as 30 mm Hg. A subsequent inadvertent durotomy during decompression lowered the ICP to <5 mm Hg; no further ICP spikes occurred. His postoperative course was uneventful, and 14-month later, he was dramatically improved. Conclusion: ICP monitoring may be a useful adjunct for patient safety in selected patients who are at risk for developing intracranial hypertension during extensive spinal deformity surgery. © 2016 Surgical Neurology International | Published by Wolters Kluwer-Medknow.

**INTRODUCTION:** The objective of this study was to determine whether serum vitamin D [25(OH)D] levels are associated with disease progression in amyotrophic lateral sclerosis (ALS). **METHODS:** 25(OH)D was measured in subjects enrolled in a multicenter study for validation of ALS biomarkers. Baseline 25(OH)D levels were correlated with baseline ALSFRS-R scores. Average 25(OH)D levels from Baseline and Month 6 visits (seasonally asynchronous) were used to predict subsequent rate of change in ALSFRS-R from Month 6 to Month 18. **RESULTS:** Most subjects had either insufficient or deficient 25(OH)D levels. Lower 25(OH)D was associated with lower ALSFRS-R gross motor scores, but not lower ALSFRS-R total scores at baseline. Levels of 25(OH)D were not predictive of disease progression over the following 12 months. **DISCUSSION:** 25(OH)D was associated with baseline gross motor ALSFRS-R scores but did not predict the rate of disease progression. Vitamin D levels may reflect poor mobility in people with ALS. This article is protected by copyright. All rights reserved.


**INTRODUCTION:** The close functional relationship between areas 3b and 1 of the somatosensory cortex is based on their reciprocal connections indicating that tactile sensation depends on the interaction of these two areas. **AIM:** The aim of the authors was to explore this neuronal circuit at the level of the distal finger pad representation. **METHOD:** The study was made by bidirectional tract tracing aided by neurophysiological mapping in squirrel monkeys (Saimiri sciureus). **RESULTS:** Inter-areal connections between the two areas preferred the homologues representations. However, intra-areal connections were formed between the neighboring finger pad representations supporting the physiological observations. Interestingly, the size of the local input area of the injected cortical micro-region, which differed in the two areas, represented the same skin area. **CONCLUSIONS:** The authors propose that intra-areal connections are important in integrating information across fingers, while inter-areal connections are important in maintaining input localization during hand movement. *Orv. Hetil.*, 2016, 157(33), 1320-1325.


**Purpose:** We aimed: (1) to establish endothelial expression of ubiquitin carboxyl-terminal esterase L1 (UCHL1) in human choroid and retina and; (2) to investigate a role for UCHL1 in basic processes involved in intraocular neovascularization. **Design:** Controlled translational experimental study. **Methods:** Ethanol-fixed human choroid and retina (n = 3 eyes) were indirectly immunostained with rabbit anti-human UCHL1 antibody. Endothelial proliferation and migration assays were performed using cultured human choroidal and retinal endothelial cells (n = 6 isolates/assay). Cells were transfected with UCHL1-targeted or non-targeted small interfering (si)RNA and a commercially available transfection system, and used 48 hours later in experiments. Cell proliferation was evaluated using an assay in which cellular DNA was fluorescently tagged for quantification by microplate reader. Cell migration was examined in an assay that involved counting the number of endothelial cells moving across a perforated membrane. Transcript silencing was verified by Western blot for all assays. **Results:** Immunohistochemistry confirmed expression of UCHL1 by endothelium in human choroid and retina in vivo. UCHL1-specific knockdown resulted in significantly less proliferation (p < 0.0001) for 3 human choroidal endothelial isolates and 3 human retinal endothelial isolates, and significantly less migration (p ≤ 0.016) for 2 of 3 human choroidal endothelial isolates and 1 of 3 human retinal endothelial isolates. **Conclusions:** Our results suggest that UCHL1 may be involved in choroidal and retinal endothelial proliferation in most persons, and endothelial migration in some persons. UCHL1 may be a suitable target for a new treatment of intraocular neovascularisation. © 2015 Asia Pacific Academy of Ophthalmology.
Zika virus (ZIKV) is a mosquito-borne and sexually transmitted flavivirus currently spreading throughout the Pacific and Western Hemisphere. ZIKV infection is often either asymptomatic or causes a self-limiting illness with symptoms such as rash, fever, myalgia, arthralgia, headache, or conjunctivitis. Rarely, ZIKV infection has been associated with conditions such as severe thrombocytopenia, microcephaly and other developmental abnormalities, acute polynuropathy/Guillain–Barré syndrome, myelitis, meningoencephalitis, transient encephalopathy, provoked seizures, and various ophthalmologic conditions. Optimal treatment of these ZIKV-associated conditions is currently unclear and is largely guided by expert opinion or case reports/series. Further studies are needed to establish best treatment practices. This review concentrates on caring by neurointensivists for the patient affected with Zika virus—expected to flare up again in the summer. © 2016 Springer Science+Business Media New York


BACKGROUND: Identification of strategies to improve organ donor use remains imperative. Despite the association between hospital volume and outcomes for many common disease processes, there have been no studies that assess the impact of organ donor hospital volume on organ yield. STUDY DESIGN: A prospective observational study of all deceased organ donors managed by 10 organ procurement organizations across United Network for Organ Sharing regions 4, 5, and 6 was conducted from February 2012 to June 2015. To study the impact of hospital volume on organ yield, each donor was placed into a hospital-volume quartile based on the number of donors managed by their hospital. Stepwise logistic regression was used to identify the independent effect of hospital volume on the primary outcomes measure of having >/=4 organs transplanted per donor. RESULTS: Data from 4,427 donors across 384 hospitals were collected and hospitals were assigned quartiles based on their volume of deceased donors. Hospitals managed a mean +/- SD of 3.3 +/- 5.2 donors per hospital per year. After adjusting for age, ethnicity, donor type, blood type, BMI, creatinine, and organ procurement organization/donor service area, being managed in hospitals within the highest volume quartile remained a positive independent predictor of >/=4 organs transplanted per donor (odds ratio = 1.52; 95% CI, 1.29 to 1.79; p < 0.001). CONCLUSIONS: Deceased organ donor hospital volume impacts organ yield, with the highest-volume centers being 52% more likely to achieve >/=4 organs transplanted per donor. Efforts should be made to share practices from these higher-volume centers and consideration should be given to centralization of donor care.


Context: Direct oral anticoagulants (DOACs) may be as effective as, and at times safer than, warfarin. Because DOACs do not require regular serum level monitoring, patients’ interaction with the health care system may be reduced. To the authors’ knowledge, although studies have evaluated warfarin adherence, few studies have evaluated the real-world adherence to DOACs. Objective: To evaluate whether a difference exists between medication adherence of patients taking DOACs vs patients taking warfarin. Methods: The electronic medical records of the Anticoagulation Clinic database at Mayo Clinic in Scottsdale, Arizona, were reviewed. Inclusion criteria were adults taking DOACs and a matching cohort taking warfarin between January 1, 2011, and December 30, 2013. The Morisky Medication Adherence Scale–8 item, a validated medication adherence tool, was used to evaluate adherence in both cohorts, and the qualitative covariates were analyzed using ordinal logistic regression. Results: Of 324 surveys that were sent, 110 patients (34.0%) responded. Most patients took DOACs for atrial fibrillation, and few took DOACs for venous thromboembolism. Overall, 60 of 66 patients (90.9%) in the DOAC group and 42 of 44 patients (95.5%) in the warfarin group reported medium or high adherence. Difference in adherence scores between the 2 groups was not statistically significant (P=.8). Conclusion: Similar adherence was noted between DOACs and warfarin regardless of the frequency of serum level monitoring. © 2017 American Osteopathic Association.
Permanent contraception is a highly desired and commonly used contraceptive option for women around the world who desire never to become pregnant. Current methods of female permanent contraception require surgery. Postpartum tubal ligation and interval surgical tubal ligation are safe and effective, do not interfere with menstrual cycles, and require no ongoing cost or medical checkups. Hysteroscopic tubal occlusion offers a less invasive surgical approach, but requires an imaging study for verification of correct placement. However, not all women have access to a surgeon trained to provide permanent contraception, or they may face other prohibitive logistic or financial burdens. The development of novel permanent contraception methods that are immediately effective and/or nonsurgical could help improve access to and acceptability of permanent contraception. The expansion of permanent contraception options could help women achieve their family planning goals and reduce unintended pregnancies.

Inducing sustained, robust CD8(+) T cell responses is necessary for therapeutic intervention in chronic infectious diseases and cancer. Unfortunately, most adjuvant formulations fail to induce substantial cellular immunity in humans. Attenuated acute infectious agents induce strong CD8(+) T cell immunity, and are thought to therefore represent a good road map for guiding the development of subunit vaccines capable of inducing the same. However, recent evidence suggests that this assumption may need reconsideration. Here we provide an overview of subunit vaccine history as it pertains to instigating T cell responses. We argue that in light of evidence demonstrating that T cell responses to vaccination differ from those induced by infectious challenge, research in pursuit of cellular immunity-inducing vaccine adjuvants should no longer follow only the infection paradigm.

Objective In rheumatoid arthritis (RA), MRI provides earlier detection of structural damage than radiography (X-ray) and more sensitive detection of intra-articular inflammation than clinical examination. This analysis was designed to evaluate the ability of early MRI findings to predict subsequent structural damage by X-ray. Methods Pooled data from four randomised controlled trials (RCTs) involving 1022 RA hands and wrists in...

Background Interventions based around objective measurement of adherence to antiretroviral drugs for HIV have potential to improve adherence and to enable differentiation of care such that clinical visits are reduced in those with high adherence. It would be useful to understand the approximate upper limit of cost that could be considered for such interventions of a given effectiveness in order to be cost effective. Such information can guide whether to implement an intervention in the light of a trial showing a certain effectiveness and cost. Methods An individual-based model, calibrated to Zimbabwe, which incorporates effects of adherence and resistance to antiretroviral therapy, was used to model the potential impact of adherence monitoring-based interventions on viral suppression, death rates, disability adjusted life years and costs. Potential component effects of the intervention were: enhanced average adherence when on ART, reduced risk of ART discontinuation, and reduced risk of resistance acquisition. We considered a situation in which viral load monitoring is not available and one in which it is. In the former case, it was assumed that care would be differentiated based on the adherence level, with fewer clinic visits in those demonstrated to have high adherence. In the latter case, care was assumed to be primarily differentiated according to viral load level. The maximum intervention cost required to be cost effective was calculated based on a cost effectiveness threshold of $500 per DALY averted. Findings In the absence of viral load monitoring, an adherence monitoring-based intervention which results in a durable 6% increase in the proportion of ART experienced people with viral load < 1000 cps/mL was cost effective if it cost up to $50 per person-year on ART, mainly driven by the cost savings of differentiation of care. In the presence of viral load monitoring availability, an intervention with a similar effect on viral load suppression was cost-effective when costing $23-$32 per year, depending on whether the adherence intervention is used to reduce the level of need for viral load measurement. Conclusion The cost thresholds identified suggest that there is clear scope for adherence monitoring-based interventions to provide net population health gain, with potential cost-
Effective use in situations where viral load monitoring is or is not available. Our results guide the implementation of future adherence monitoring interventions found in randomized trials to have health benefit. © 2016 Phillips et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.


Heart failure is characterized by the loss of sympathetic innervation to the ventricles, contributing to impaired cardiac function and arrhythmogenesis. We hypothesized that renal denervation (RDx) would reverse this loss. Male Wistar rats underwent myocardial infarction (MI) or sham surgery and progressed into heart failure for four weeks before receiving bilateral RDx or sham RDx. After a further three weeks, left ventricular (LV) function was assessed and ventricular sympathetic nerve fibre density determined via histology. Post-MI heart failure rats displayed significant reductions in ventricular sympathetic innervation and tissue noradrenaline content (nerve fibre density in the LV of MI+sham RDx hearts was 0.31 +/- 0.05 % vs. 1.00 +/- 0.10 % in sham MI+sham RDx group, P < 0.05) and RDx significantly increased ventricular sympathetic innervation (0.76 +/- 0.14 %, P < 0.05) and tissue noradrenaline content. MI was associated with an increase in fibrosis of the non-infarcted ventricular myocardium which was attenuated by RDx. RDx improved LV ejection fraction and end-systolic and -diastolic areas when compared to pre-RDx levels. This is the first study to show an interaction between renal nerve activity and cardiac sympathetic nerve innervation in heart failure. Our findings show denervating the renal nerves improves cardiac sympathetic innervation and function in the post-MI failing heart.


BACKGROUND: Pegfilgrastim's role in reducing the risk of febrile neutropenia (FN) in patients with colorectal cancer (CRC) receiving chemotherapy plus bevacizumab was not previously evaluated in a prospective study. The present phase III, double-blind trial evaluated the efficacy of pegfilgrastim versus placebo in reducing the incidence of grade 3/4 FN in patients with advanced CRC receiving bevacizumab combined with first-line chemotherapy (FOLFOX [leucovorin, 5-fluorouracil, oxaliplatin] or FOLFIRI [leucovorin, 5-fluorouracil, irinotecan]). PATIENTS AND METHODS: Patients aged >/= 18 years with locally advanced or metastatic CRC were randomized 1:1 to placebo or 6 mg of pegfilgrastim approximately 24 hours after receiving chemotherapy plus bevacizumab every 14 days. The study treatment period included 4 cycles, but patients could continue treatment for </= 60 months. The primary endpoint was incidence of grade 3/4 FN in the first 4 cycles. The secondary endpoints included the objective response rate (ORR), overall survival, and progression-free survival, analyzed at the end of the long-term follow-up period. RESULTS: A total of 845 patients were randomized from November 2009 to January 2012 (422, pegfilgrastim; 423, placebo). Pegfilgrastim significantly reduced the incidence of grade 3/4 FN in the first 4 treatment cycles (pegfilgrastim, 2.4%; 95% confidence interval [CI], 1.1%-4.3%; placebo, 5.7%; 95% CI, 3.7%-8.3%; odds ratio [OR], 0.41; P = .014). No significant differences were observed between the 2 arms in ORR (OR, 1.15; P = .330), overall survival (hazard ratio, 0.94; P = .440), and progression-free survival (hazard ratio, 0.93; P = .300). CONCLUSION: Pegfilgrastim reduced the FN incidence in patients with advanced CRC receiving chemotherapy and bevacizumab. Administration of pegfilgrastim was tolerable and did not negatively affect the tumor response or survival in this patient population.

Objectives: Fractures comprise 3% of all emergency department (ED) visits. Although emergency physicians are often responsible for managing most of the initial care of these patients, many report a lack of proficiency and comfort with these skills. The primary objective was to assess how prepared recent emergency medicine (EM) residency graduates felt managing closed fractures upon completion of residency. Secondary objectives included whether residency training or independent practice contributed most to the current level of comfort with these procedures and which fractures were most commonly reduced without orthopedic consultation. Methods: An anonymous online survey was sent to graduates from seven EM residency programs over a 3-month period to evaluate closed fracture reduction training, practice, and comfort level. Each site primary investigator invited graduates from 2010 to 2014 to participate and followed a set schedule of reminders. Results: The response rate was 287/384 (74.7%) and included 3-year (198/287, 69%) and 4-year (89/287, 31%) programs. Practice in community, academic, and hybrid ED settings was reported by 150/287 (52.3%), 64/287 (22.3%), and 73/287 (25.4%), respectively. It was indicated by 137/287 (47.7%) that they reduce closed fractures without a bedside orthopedic consultation greater than 75% of the time. The majority of graduates felt not at all prepared (35/287, 12.2%) or somewhat prepared (126/287, 43.9%) upon residency graduation. Postresidency independent practice contributed most to the current level of comfort for 156/287 (54.4%). The most common fractures requiring reduction were wrist/distal radius and/or ulna, next finger/hand, and finally, ankle/distal tibia and/or fibula. Conclusions: Although most recent graduates feel at least “somewhat” prepared to manage closed fractures in the ED, most felt that independent practice was a greater contributor to their current level of comfort than residency training. Recent graduates indicate that fracture reduction without orthopedic consultation is common in today’s clinical practice. This survey identifies common fractures requiring reduction which EM residencies may wish to consider prioritizing in their emergency orthopedic curricula to better prepare their residents for independent clinical practice. © 2016 by the Society for Academic Emergency Medicine


Neurodevelopment continues through adolescence, with notable maturation of white matter tracts comprising regional fiber systems progressing at different rates. To identify factors that could contribute to regional differences in white matter microstructure development, large samples of youth spanning adolescence to young adulthood are essential to parse these factors. Recruitment of adequate samples generally relies on multi-site consortia but comes with the challenge of merging data acquired on different platforms. In the current study, diffusion tensor imaging (DTI) data were acquired on GE and Siemens systems through the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), a multi-site study designed to track the trajectories of regional brain development during a time of high risk for initiating alcohol consumption. This cross-sectional analysis reports baseline Tract-Based Spatial Statistic (TBSS) of regional fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (L1), and radial diffusivity (L2) from the five consortium sites on 671 adolescents who met no/low alcohol or drug consumption criteria and 132 adolescents with a history of exceeding consumption criteria. Harmonization of DTI metrics across manufacturers entailed the use of human-phantom data, acquired multiple times on each of three non-NCANDA participants at each site’s MR system, to determine a manufacturer-specific correction factor. Application of the correction factor derived from human phantom data measured on MR systems from different manufacturers reduced the standard deviation of the DTI metrics for FA by almost a half, enabling harmonization of data that would have otherwise carried systematic error. Permutation testing supported the hypothesis of higher FA and lower diffusivity measures in older adolescents and indicated that, overall, the FA, MD, and L1 of the boys were higher than those of the girls, suggesting continued microstructural development notable in the boys. The contribution of demographic and clinical differences to DTI metrics was assessed with General Additive Models (GAM) testing for age, sex, and ethnicity differences in regional skeleton mean values. The results supported the primary study hypothesis that FA skeleton mean values in the no/low-drinking group were highest at different ages. When differences in intracranial volume were covaried, FA skeleton mean reached a maximum at younger ages in girls than boys and varied in magnitude with ethnicity. Our results, however, did not support the hypothesis that youth who exceeded exposure
criteria would have lower FA or higher diffusivity measures than the no/low-drinking group; detecting the effects of excessive alcohol consumption during adolescence on DTI metrics may require longitudinal study.


PURPOSE: This study investigates the effect of eye size and eccentricity on doses to critical tissues by simulating doses in the Plaque Simulator (v. 6.3.1) software. Present OHSU plaque brachytherapy treatment focuses on delivering radiation to the tumor measured with ocular ultrasound plus a small margin and assumes the orbit has the dimensions of a "standard eye." Accurately modeling the dimensions of the orbit requires a high resolution ocular CT. This study quantifies how standard differences in equatorial diameters and eccentricity affect calculated doses to critical structures in order to query the justification of the additional CT scan to the treatment planning process. METHODS: Tumors of 10 mm x 10 mm x 5 mm were modeled at the 12:00:00 hour with a latitude of 45 degrees. Right eyes were modeled at a number of equatorial diameters from 17.5 to 28 mm for each of the standard non-notched COMS plaques with silastic inserts. The COMS plaques were fully loaded with uniform activity, centered on the tumor, and prescribed to a common tumor dose (85 Gy/100 hours). Variations in the calculated doses to normal structures were examined to see if the changes were significant. RESULTS: The calculated dose to normal structures show a marked dependence on eye geometry. This is exemplified by fovea dose which more than doubled in the smaller eyes and nearly halved in the larger model. Additional significant dependence was found in plaque size on the calculated dose in spite of all plaques giving the same dose to the prescription point. CONCLUSION: The variation in dose with eye dimension fully justifies the addition of a high resolution ocular CT to the planning technique. Additional attention must be made to plaque size beyond simply covering the tumor when considering normal tissue dose.


West Nile virus (WNV) is a mosquito-transmitted pathogen with a wide geographical range that can lead to long-term disability and death in some cases. Despite the public health risk posed by WNV, including an estimated 3 million infections in the United States alone, no vaccine is available for use in humans. Here, we present a scaled manufacturing approach for production of a hydrogen peroxide-inactivated whole virion WNV vaccine, termed HydroVax-001 WNV. Vaccination resulted in robust virus-specific neutralizing antibody responses and protection against WNV-associated mortality in mice or viremia in rhesus macaques (RM). A GLP-compliant toxicology study performed in rats demonstrated an excellent safety profile with clinical findings limited to minor and transient irritation at the injection site. An in vitro relative potency (IVRP) assay was developed and shown to correlate with in vivo responses following forced degradation studies. Long-term in vivo potency comparisons between the intended storage condition (2–8 °C) and a thermally stressed condition (40 ± 2 °C) demonstrated no loss in vaccine efficacy or protective immunity over a 6-month span of time. Together, the positive pre-clinical findings regarding immunogenicity, safety, and stability indicate that HydroVax-001 WNV is a promising vaccine candidate. © 2016 Elsevier Ltd


Numerous studies using a variety of imaging techniques have reported age-related differences in neural activity while subjects carry out cognitive tasks. Surprisingly little attention has been paid to the potential impact of age-associated changes in sensory acuity on these findings. Studies in the visual modality frequently report that their subjects had "normal or corrected- to-normal vision." However, in most cases, there is no indication that visual acuity was actually measured, and it is likely that the investigators relied largely on self-reported visual status of subjects, which is often inaccurate. We investigated whether differences in visual acuity influence one of the most commonly observed findings in the event-related
potentials literature on cognitive aging, a reduction in posterior P3b amplitude, which is an index of cognitive decision-making/updating. Well-matched young (n=26) and old adults (n=29) participated in a visual oddball task. Measured visual acuity with corrective lenses was worse in old than young adults. Results demonstrated that the robust age-related decline in P3b amplitude to visual targets disappeared after controlling for visual acuity, but was unaffected by accounting for auditory acuity. Path analysis confirmed that the relationship between age and diminished P3b to visual targets was mediated by visual acuity, suggesting that conveyance of suboptimal sensory data due to peripheral, rather than central, deficits may undermine subsequent neural processing. We conclude that until the relationship between age-associated differences in visual acuity and neural activity during experimental tasks is clearly established, investigators should exercise caution attributing results to differences in cognitive processing.


OBJECTIVES: Acute uncomplicated urinary tract infection (UTI) in women is often treated based on symptoms alone. Urinary tract infection symptoms are highly sensitive but lack specificity and result in overuse of antibiotics. We sought to determine if urine neutrophil gelatinase-associated lipocalin (uNGAL) levels in urine can accurately discriminate between UTI and healthy women. METHODS: We recruited adult women aged 18 to 85 years presenting in the ambulatory setting from November 2014 to January 2016. Cases were defined as women with Centers for Disease Control and Prevention-defined UTI symptoms and a positive urine culture of more than 10 organisms/mL on a midstream catch specimen. Women without UTI symptoms were matched by age and menopausal status as control subjects. Exclusion criteria were no UTIs within 8 weeks, urinary tract anomalies, renal disease, pregnancy, or diabetes. Clean-catch urine samples were obtained for measuring uNGAL, prior to antibiotic treatment of cases. We used Mann-Whitney U test to compare the 2 groups. Receiver operating characteristic curves were plotted to compare the performance of uNGAL to established urinary markers. RESULTS: We enrolled 50 UTI cases and 50 control subjects. Urine NGAL levels were higher in the UTI group than in the control subjects (P < 0.0001). Using a cutoff of 23.9 ng/mL, NGAL achieved 98% sensitivity and 100% specificity. The receiver operating characteristic curve had an area under the curve of 0.97 (95% confidence interval, 0.93-1.00), which was significantly high and
showed that uNGAL can identify UTI. CONCLUSIONS: Urine NGAL has the potential as a biomarker for diagnosing UTIs in adult women.


Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on oral pharmacologic treatment of type 2 diabetes in adults. This guideline serves as an update to the 2012 ACP guideline on the same topic. This guideline is endorsed by the American Academy of Family Physicians. Methods: This guideline is based on a systematic review of randomized, controlled trials and observational studies published through December 2015 on the comparative effectiveness of oral medications for type 2 diabetes. Evaluated interventions included metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Study quality was assessed, data were extracted, and results were summarized qualitatively on the basis of the totality of evidence identified by using several databases. Evaluated outcomes included intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure, and heart rate; all-cause mortality; cardiovascular and cerebrovascular morbidity and mortality; retinopathy, nephropathy, and neuropathy; and harms. This guideline grades the recommendations by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with type 2 diabetes. Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence). Recommendation 2: ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.


As cells progress through carcinogenesis, the associated exponential expansion of genetic and molecular aberrations and resultant heterogeneity make therapeutic success increasingly unattainable. Therapeutic intervention at early stages of carcinogenesis that occurs within the primary organ and in the face of a lower burden of molecular aberrations, constitutes a basic tenet of cancer chemoprevention, and provides a situation that favors a greater degree of therapeutic efficacy compared with that of advanced cancer. A longstanding barrier to chemoprevention relates to the requirement for essentially no systemic toxicity, and the fact that when large numbers of people are treated, the emergence of systemic toxicity is almost universal. A rational means to address this in fact relates to a second basic tenet of the chemopreventive strategy: the focus of therapeutic intervention is to disrupt a process that is in essence localized to a single organ. Based upon this consideration, a strategy which is based upon local delivery of therapeutics to an at-risk organ will achieve therapeutic efficacy while avoiding systemic delivery and its associated toxicity. This article will review the rationale for undertaking such an approach, describe successful clinical achievements based on this strategy, describe ongoing efforts to expand the impact of this approach, and together will highlight the high impact that this approach has already had on the field as well as its extremely high potential for future impact. © 2017 American Association for Cancer Research.


The brain could be exposed to irradiation as part of a nuclear accident, radiological terrorism (dirty bomb scenario) or a medical radiological procedure. In the context of accidents or terrorism, there is considerable interest in compounds that can mitigate radiation-induced injury when treatment is initiated a day or more
after the radiation exposure. As it will be challenging to determine the radiation exposure an individual has received within a relatively short time frame, it is also critical that the mitigating agent does not negatively affect individuals, including emergency workers, who might be treated, but who were not exposed. Alterations in hippocampus-dependent cognition often characterize radiation-induced cognitive injury. The catalytic ROS scavenge EUK-207 is a member of the class of metal-containing salen manganese (Mn) complexes that suppress oxidative stress, including in the mitochondria, and have been shown to mitigate radiation dermatitis, promote wound healing in irradiated skin, and mitigate vascular injuries in irradiated lungs. As the effects of EUK-207 against radiation injury in the brain are not known, we assessed the effects of EUK-207 on sham-irradiated animals and the ability of EUK-207 to mitigate radiation-induced cognitive injury. The day following irradiation or sham-irradiation, the mice started to receive EUK-207 and were cognitively tested 3 months following exposure. Mice irradiated at a dose of 15 Gy showed cognitive impairments in the water maze probe trial. EUK-207 mitigated these impairments while not affecting cognitive performance of sham-irradiated mice in the water maze probe trial. Thus, EUK-207 has attractive properties and should be considered an ideal candidate to mitigate radiation-induced cognitive injury. © 2016 Elsevier B.V.


Proteolytic processing of the Amyloid Precursor Protein (APP) produces beta-amyloid (Aβ) peptide fragments that accumulate in Alzheimer’s Disease (AD), but APP may also regulate multiple aspects of neuronal development, albeit via mechanisms that are not well understood. APP is a member of a family of transmembrane glycoproteins expressed by all higher organisms, including two mammalian orthologs (APLP1 and APLP2) that have complicated investigations into the specific activities of APP. By comparison, insects express only a single APP-related protein (APP-Like, or APPL) that contains the same protein interaction domains identified in APP. However, unlike its mammalian orthologs, APPL is only expressed by neurons, greatly simplifying an analysis of its functions in vivo. Like APP, APPL is processed by secretases to generate a similar array of extracellular and intracellular cleavage fragments, as well as an Aβ-like fragment that can induce neurotoxic responses in the brain. Exploiting the complementary advantages of two insect models (Drosophila melanogaster and Manduca sexta), we have investigated the regulation of APPL trafficking and processing with respect to different aspects of neuronal development. By comparing the behavior of endogenously expressed APPL with fluorescently tagged versions of APPL and APP, we have shown that some full-length protein is consistently trafficked into the most motile regions of developing neurons both in vitro and in vivo. Concurrently, much of the holoprotein is rapidly processed into N- and C-terminal fragments that undergo bi-directional transport within distinct vesicle populations. Unexpectedly, we also discovered that APPL can be transiently sequestered into an amphisome-like compartment in developing neurons, while manipulations targeting APPL cleavage altered their motile behavior in cultured embryos. These data suggest that multiple mechanisms restrict the bioavailability of the holoprotein to regulate APPL-dependent responses within the nervous system. Lastly, targeted expression of our double-tagged constructs (combined with time-lapse imaging) revealed that APP family proteins are subject to complex patterns of trafficking and processing that vary dramatically between different neuronal subtypes. In combination, our results provide a new perspective on how the regulation of APP family proteins can be modulated to accommodate a variety of cell type-specific responses within the embryonic and adult nervous system. © 2016 Ramaker, Cargill, Swanson, Quiirindongo, Cassar, Kretzschmar and Copenhaver.


BACKGROUND: In addition to known concerns regarding antibiotic overuse, recent research indicates that excessive antibiotic use is associated with poorer long-term health. Given that rhinosinusitis is the leading condition accounting for antibiotic prescriptions in the ambulatory setting, we aimed to evaluate characteristics associated with greater antibiotic use in chronic rhinosinusitis (CRS). METHODS: Adult CRS patients enrolled in a prospective, multi-institutional, observational cohort study evaluating treatment
outcomes were included in this analysis. Study participants were asked to report the number of days out of the previous 90 days that systemic antibiotics were taken for sinus disease. Patient demographics, disease characteristics, and measures of disease severity were evaluated. RESULTS: A total of 561 patients from 4 institutions were included in the analysis, with mean antibiotic use of 17.4 ± 22.4 out of the prior 90 days. No differences between antibiotic-use groups were found for objective measures of disease severity (computed tomography [CT], endoscopy, Brief Smell Identification Test [BSIT] scores), however, increased patient-reported symptom burden (22-item Sino-Nasal Outcome Test [SNOT-22], Rhinosinusitis Disability Index [RSDI]) was associated with more antibiotic use. Patients reporting the most antibiotic use were older (p = 0.004) but no ethnic or gender differences were seen. Comorbid diagnoses of allergy, asthma, diabetes, depression, or fibromyalgia were not associated with increased antibiotic use. In accordance with literature recommendations, CRS with nasal polyps (CRSwNP) patients were less likely to have used antibiotics. Endoscopic sinus surgery (ESS) significantly decreased antibiotic use. CONCLUSION: Variability in antibiotic use in CRS appears to be driven by symptom burden, independent of objective measures of disease severity, patient demographics, and presence of comorbid disease. Clear guidelines are essential to define appropriate antibiotic use in CRS.


Aortic root reconstruction in the setting of redo aortic valve procedures or infective endocarditis may be technically challenging, particularly because of variable destruction or distortion of the left ventricular outflow tract. Homograft aortic root replacement is an excellent option for aortic root abscesses but is limited by homograft availability. We describe a simple technique of a bioprosthetic valved conduit constructed on the table using a Dacron (DuPont, Wilmington, DE) skirt below the valve. The use of the Dacron skirt facilitates easy reconstruction of the left ventricular outflow tract. © 2017 The Society of Thoracic Surgeons


BACKGROUND AND PURPOSE: Some patients are at high risk of aneurysm recurrence after endovascular treatment: patients with large aneurysms (Patients Prone to Recurrence After Endovascular Treatment PRET-1) or with aneurysms that have previously recurred after coiling (PRET-2). We aimed to establish whether the use of hydrogel coils improved efficacy outcomes compared with bare platinum coils. MATERIALS AND METHODS: PRET was an investigator-led, pragmatic, multicenter, parallel, randomized (1:1) trial. Randomized allocation was performed separately for patients in PRET-1 and PRET-2, by using a Web-based platform ensuring concealed allocation. The primary outcome was a composite of a residual/recurrent aneurysm, adjudicated by a blinded core laboratory, or retreatment, intracranial bleeding, or mass effect during the 18-month follow-up. Secondary outcomes included adverse events, mortality, and morbidity (mRS > 2). The hypothesis was that hydrogel would decrease the primary outcome from 50% to 30% at 18 months, necessitating 125 patients per group (500 for PRET-1 and PRET-2). RESULTS: The trial was stopped once 250 patients in PRET-1 and 197 in PRET-2 had been recruited because of slow accrual. A poor primary outcome occurred in 44.4% (95% CI, 35.5%-52.3%) of those in PRET-1 allocated to platinum compared with 52.5% (95% CI, 43.4%-61.6%) of patients allocated to hydrogel (OR, 1.387; 95% CI, 0.838-2.295; P = .20) and in 49.0% (95% CI, 38.8%-59.1%) in PRET-2 allocated to platinum compared with 42.1% (95% CI, 32.0%-52.2%) allocated to hydrogel (OR, 0.959; 95% CI, 0.428-1.342; P = .34). Adverse events and morbidity were similar. There were 3.6% deaths (1.4% platinum, 5.9% hydrogel; P = .011). CONCLUSIONS: Coiling of large and recurrent aneurysms is safe but often poorly effective according to angiographic results. Hydrogel coiling was not shown to be better than platinum.

We report here on chronic neurological impairment in three car painters with constant occupational exposure to organic solvents. All had a clinical presentation of Parkinson’s disease and, in all cases, SPECT DaTscan brain imaging, using 123I-FP-CIT, showed bilateral reduction of tracer uptake in the basal ganglia, evidence of dysfunction at the dopaminergic terminal. © 2016 Elsevier Masson SAS

The Artificial Pancreas (AP) is a new technology for helping people with type 1 diabetes to better control their glucose levels through automated delivery of insulin and optionally glucagon in response to sensed glucose levels. In a dual hormone AP, insulin and glucagon are delivered automatically to the body based on glucose sensor measurements using a control algorithm that calculates the amount of hormones to be infused. A dual-hormone MPC may deliver insulin continuously; however, it must avoid continuous delivery of glucagon because nausea can occur from too much glucagon. In this paper, we propose a novel dual-hormone (DH) switching model predictive control and compare it with a single-hormone (SH) MPC. We extended both MPCs by integrating an exercise model and compared performance with and without the exercise model included. Results were obtained on a virtual patient population undergoing a simulated exercise event using a mathematical glucoregulatory model that includes exercise. Time spent in hypoglycemia is significantly less with the DH-MPC than the SH-MPC (p = 0.0022). Additionally, including the exercise model in the DH-MPC can help prevent hypoglycemia (p < 0.001). © 2016 IEEE.

BACKGROUND: Attrition in pediatric weight management negatively impacts treatment outcomes. A potentially modifiable contributor to attrition is unmet family expectations. This study aimed to evaluate the association between adolescent and parent/guardian treatment expectations and attrition. PATIENTS AND METHODS: A prospective, nonrandomized, uncontrolled, single-arm pilot trial was conducted among 12 pediatric weight management programs in the Children’s Hospital Association’s FOCUS on a Fitter Future collaborative. Parents/guardians and adolescents completed an expectations/goals survey at their initial visit, with categories including healthier food/drinks, physical activity/exercise, family support/behavior, and weight management goals. Attrition was assessed at 3 months. RESULTS: From January to August 2013, 405 parents/guardians were recruited and reported about their children (203 adolescents, 202 children < 12 years). Of the 203 adolescents, 160 also self-reported. Attrition rate was 42.2% at 3 months. For adolescents, greater interest in family support/behavior skills was associated with decreased odds of attrition at 3 months [odds ratio (OR) 0.75, 95% confidence interval (CI) 0.57-0.98, p = 0.04]. The more discordant the parent/adolescent dyad responses in this category, the higher the odds of attrition at 3 months (OR 1.36, 95% CI 1.04-1.78, p = 0.02). Weight loss was an important weight management goal for both adolescents and parents. For adolescents with this goal, the median weight-loss goal was 50 pounds. Attrition was associated with adolescent weight-loss goals above the desired median (50% above the median vs. 28% below the median, p = 0.02). CONCLUSIONS: Assessing initial expectations may help tailor treatment to meet families’ needs, especially through focus on family-based change and realistic goal setting. CLINICAL TRIAL REGISTRATION: Clinicaltrials.gov NCT01753063.


Recent evidence suggests that inhibition of protein phosphatase 2A (PP2A) tumor suppressor activity via the SET oncoprotein contributes to the pathogenesis of various cancers. Here we demonstrate that both SET and c-MYC expression are frequently elevated in T-ALL cell lines and primary samples compared to healthy T cells. Treatment of T-ALL cells with the SET antagonist OP449 restored the activity of PP2A and reduced SET interaction with the PP2A catalytic subunit, resulting in a decrease in cell viability and c-MYC expression in a dose-dependent manner. Since a tight balance between phosphatases and kinases is required for the growth of both normal and malignant cells, we sought to identify a kinase inhibitor that would synergize with SET antagonism. We tested various T-ALL cell lines against a small-molecule inhibitor screen of 66 compounds targeting two-thirds of the tyrosine kinase and found that combined treatment of T-ALL cells with dovitinib, an orally active multi-targeted small-molecule receptor tyrosine kinase inhibitor, and OP449 synergistically reduced the viability of all tested T-ALL cell lines. Mechanistically, combined treatment with OP449 and dovitinib decreased total and phospho-c-MYC levels and reduced ERK1/2, AKT, and p70S6 kinase activity in both NOTCH-dependent and independent T-ALL cell lines. Overall, these results suggest that combined targeting of tyrosine kinases and activation of serine/threonine phosphatases may offer novel therapeutic strategies for the treatment of T-ALL.


**BACKGROUND AND OBJECTIVE:** Approximately 1.7 million patients are affected by hospital-acquired infections every year in the United States. The increasing prevalence of multidrug-resistant bacteria associated with these infections prompts the investigation of alternative sterilization and antibacterial therapies. One method currently under investigation is the antibacterial properties of visible light. This study examines the effect of a visible light therapy (VLT) on beta-lactam-resistant Escherichia coli, a common non-skin flora pathogen responsible for a large percentage of indwelling medical device-associated clinical infection. **MATERIALS AND METHODS:** 405 nm light-emitting diodes were used to treat varying concentrations of a common laboratory E. coli K-12 strain transformed with the pCIG mammalian expression vector. This conferred ampicillin resistance via expression of the beta-lactamase gene. Bacteria were grown on sterile polystyrene Petri dishes plated with Luria-Bertani broth. Images of bacterial growth colonies on plates were processed and analyzed using ImageJ. Irradiance levels between 2.89 +/- 0.19 and 9.45 +/- 0.63 mW cm(-2) and radiant exposure levels between 5.60 +/- 0.39 and 136.91 +/- 4.06 J cm(-2) were tested. **RESULTS:** VLT with variable irradiance and constant treatment time (120 minutes) demonstrated significant reduction (P < 0.001) in E. coli between an irradiance of 2.89 mW cm(-2) (81.70%) and 9.37 mW cm(-2) (100.00%). Similar results were found with variable treatment time with constant irradiance. Log10 reduction analysis produced between 1.98 +/- 0.53 (60 minute treatment) and 6.27 +/- 0.54 (250 minute treatment) log10 reduction in bacterial concentration (P < 0.001). **CONCLUSIONS:** We have successfully demonstrated a significant bacterial reduction using high intensity 405 nm light. Illustrating the efficacy of this technology against a beta-lactam-resistant E. coli is especially relevant to the need for novel methods of sterilization in healthcare settings. These results suggest that VLT using 405 nm light could be a suitable clinical option for eradication of beta-lactam-resistant E. coli. Visible light kills statistically significant concentrations of E. coli. Antibiotic-resistant Gram-negative bacteria exhibits sensitivity to 405 nm light. Greater than 6 log10 reduction in beta-lactam-resistant E. coli when treated with visible light therapy.
STUDY OBJECTIVE: To determine if the addition of video coaching to an OBGYN resident laparoscopic simulation curriculum improves acquisition of suturing skills. DESIGN: Randomized controlled trial DESIGN CLASSIFICATION: I SETTING: Academic teaching hospital with a residency program in obstetrics and gynecology PATIENTS: Twenty OBGYN residents undergoing a 4-week laparoscopic simulation curriculum were video-recorded weekly performing a suturing task on a validated vaginal cuff model. INTERVENTIONS: Residents were randomized to standard simulation curriculum or standard curriculum plus weekly video coaching by an expert laparoscopic surgeon. Primary outcome measure was comparison of weekly GOALS+ (Global Operative Assessment of Laparoscopic Skills plus Vaginal Cuff Metrics) scores of the suturing task. MEASUREMENTS AND MAIN RESULTS: Baseline GOALS+ scores did not differ across training groups (p = 0.406), though "Senior" (postgraduate year (PGY) 3 and 4) residents initially had significantly higher GOALS+ scores than "junior" (PGY1 and 2) residents (p <0.001). There were significantly improved GOALS+ scores from week 1 to week 2 in the intervention group compared to the control group (p<0.05). Junior coached residents had significantly higher GOALS+ scores at week 2 (M= 28.06, SD = 3.10) compared to the junior control residents (M = 20.75, SD = 6.38, p<0.04). Over the 4-week period, all residents showed significant improvement (p=0.005), with novice residents improving more than experienced residents (p=0.001). The group that exhibited a significant difference between weeks 1 and 2 was the junior coached residents when compared to the junior residents undergoing the standard curriculum. CONCLUSION: Video coaching during laparoscopic simulation training has the greatest impact early in junior learners' skill acquisition, thus providing another tool for simulation training curricula.


The Horizon 2020/IMI European Prevention of Alzheimer’s Dementia (EPAD) project will undertake large-scale proof-of-concept trials in predementia AD. Within EPAD, the monitoring of cognitive trajectories in the preclinical period will constitute a central outcome measure; however, there are currently no clear guidelines as to how this should be achieved as most measures have been developed for the period around dementia diagnosis. The EPAD Scientific Advisory Group for Clinical and Cognitive Outcomes identified appropriate cognitive measures based on a literature search covering both cognitive correlates of preclinical brain changes from imaging studies and cognitive changes observed over time in nondementia population cohorts developing incident dementia. These measures were evaluated according to the following criteria: validity, coherence with biomarker changes, psychometric properties, cross-cultural suitability, availability of alternative forms, and normative data limited practice effects. The resulting consensus statement provides recommendations for both future drug trials and research into preclinical Alzheimer’s disease. © 2016 the Alzheimer’s Association.


Appropriate imaging modalities for the follow-up of malignant or aggressive musculoskeletal tumors include radiography, MRI, CT, (18)F-2-fluoro-2-deoxy-D-glucose PET/CT, (99m)Tc bone scan, and ultrasound. Clinical scenarios reviewed include evaluation for metastatic disease to the lung in low- and high-risk patients, for osseous metastatic disease in asymptomatic and symptomatic patients, for local recurrence of osseous tumors with and without significant hardware present, and for local recurrence of soft tissue tumors. The timing for follow-up of pulmonary metastasis surveillance is also reviewed. The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every three years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.
The use of the fecal occult blood test (FOBT) for colorectal cancer (CRC) screening is supported by randomized trials demonstrating effectiveness in cancer prevention and widely recommended by guidelines for this purpose. The fecal immunochemical test (FIT), as a direct measure of human hemoglobin in stool, has a number of advantages relative to conventional FOBT and is increasingly used relative to that test. This review summarizes current evidence for FIT in colorectal neoplasm detection and the comparative effectiveness of FIT relative to other commonly used CRC screening modalities. Based on evidence, guidance statements on FIT application were developed and quality metrics for program implementation proposed.


The majority of abortions in Colombia continue to take place outside the formal health system under a range of conditions, with the majority of women obtaining misoprostol from a thriving black market for the drug and self-administering the medication. We conducted a cost analysis to compare the costs to the health system of three approaches to the provision of abortion care in Colombia: post-abortion care for complications of unsafe abortions, and for legal abortions in a health facility, misoprostol-only medical abortion and vacuum aspiration abortion. Hospital billing records from three institutions, two large maternity hospitals and one specialist reproductive health clinic, were analysed for procedure and complication rates, and costs by diagnosis. The majority of visits (94%) were to the two hospitals for post-abortion care; the other 6% were for legal abortions. Only one minor complication was found among the women having legal abortions, a complication rate of less than 1%. Among the women presenting for post-abortion care, 5% had complications during their treatment, mainly from infection or haemorrhage. Legal abortions were associated not only with far fewer complications for women, but also lower costs for the health system than for post-abortion care. We calculated based on our findings that for every 1,000 women receiving post-abortion care instead of a legal abortion within the health system, 16 women experienced avoidable complications, and the health system spent US $48,000 managing them. Increasing women’s access to safe abortion care would not only reduce complications for women, but would also be a cost-saving strategy for the health system.


Over the last few decades there has been an increased concern about the health risks from exposure to metallic trace elements, including arsenic, because of their potential neurotoxic effects on the developing brain. This study assessed whether urinary arsenic (UA) levels are associated with attention performance and Attention-Deficit/Hyperactivity Disorder (ADHD) in children living in an area with high industrial and mining activities in Southwestern Spain. A cross-sectional study was conducted on 261 children aged 6-9 years. Arsenic levels were determined in urine samples. Attention was measured by using 4 independent tools: a) tests from the Behavioral Assessment and Research System (BARS) designed to measure attention function: Simple Reaction Time Test (RTT), Continuous Performance Test (CPT) and Selective Attention Test (SAT); b) AULA Test, a virtual reality (VR)-based test that evaluates children’s response to several stimuli in an environment simulating a classroom; c) Child Behavior Checklist (CBCL), administered to parents; and d) Teacher’s Report Form (TRF), administered to teachers. Multivariate linear and logistic regression models, adjusted for potential confounders, were used to estimate the magnitude of the association between UA levels and attention performance scores. Higher UA levels were associated with an increased latency of
response in RTT (beta = 12.3; 95% confidence interval (CI): 3.5-21.1) and SAT (beta = 3.6; 95% CI: 4.6-8.8) as well as with worse performance on selective and focalized attention in the AULA test (beta for impulsivity = .6; 95% CI: 1.0-1.1; beta for inattention = .5; 95% CI: .03-1.0). A dose-response relationship was observed between UA levels and inattention and impulsivity scores. In contrast, results from the CBCL and TRF tests failed to show a significant association with UA levels. In conclusion, UA levels were associated with impaired attention/cognitive function, even at levels considered safe. These results provide additional evidence that postnatal arsenic exposure impairs neurological function in children.


OBJECTIVE: To evaluate proinflammatory cytokines and leukocyte subpopulations in cerebrospinal spinal fluid (CSF) and blood of NOMID patients post-treatment; and to compare inflammatory cytokines in CSF and blood in 6 patients treated with two IL-1 blockers, anakinra and canakinumab. METHODS: We immunophenotyped CSF on 17 anakinra-treated pediatric NOMID patients during routine follow-up visits between December 2011 and October 2013 and analyzed CSF cytokine levels in baseline and 3-5 years follow-up samples compared to healthy controls. RESULTS: Elevated CSF IL-6, IP-10/CXCL10, IL-18 levels, and monocyte and granulocytes counts significantly decreased with anakinra treatment, but did not normalize to control levels, even in patients fulfilling criteria of “clinical remission” (CR). CSF IL-6 and IL-18 levels significantly correlate with measures of blood brain barrier (BBB) function, specifically CSF protein (r=0.75; r=0.81 respectively); and albumin quotient (r=0.79, r=0.68 respectively). Median CSF WBC levels (10.2 vs. 3.7cells/mm3) and CSF IL-6 levels (150.7 vs. 28.5pg/ml) were significantly higher when patients received canakinumab than anakinra despite similar serum cytokine levels. CONCLUSIONS: CSF leukocyte subpopulations and cytokine levels significantly improve with optimized IL-1 blocking treatment but do not normalize. The correlation of CSF IL-6, IP-10/CXCL10 and IL-18 with clinical-laboratory measures of inflammation and BBB function suggests a role as biomarkers in CNS inflammation. The difference in inhibition of CSF biomarkers between two IL-1 blocking agents, anakinra and canakinumab, suggests differences in efficacy in the intrathecal compartment, with anakinra being more effective. Our data indicate that intrathecal immune responses shape CNS inflammation and should be assessed in addition to blood markers. This article is protected by copyright. All rights reserved.


Summary: Dysregulated rest-activity rhythm (RAR) patterns have been associated with several health conditions in older adults. This study showed that later acrophase was associated with a modestly greater risk of falls but not fractures in elderly men. Associations between dysregulated RAR patterns and osteoporosis risk warrant further investigation. Purpose: The purpose of this study was to investigate the relationship between rest-activity rhythm (RAR) patterns and risk of falls/fractures in older men. We hypothesized that dysregulated RAR would be associated with incident falls/fractures. Methods: We used wrist-worn actigraphy to measure RAR over 4.8 ± 0.8 24-h periods in men (≥67 years) enrolled in the multicenter Outcomes of Sleep Disorders in Men (MrOS Sleep) Study (n = 3001). Men were contacted every 4 months to report occurrence of falls/fractures. RAR parameters included amplitude (difference between peak and nadir activity in counts/minute), mesor (activity counts/minute), acrophase (time of day of peak activity), and pseudo-F statistic (rhythm robustness) and were evaluated as continuous variables with associations reported per SD increase/decrease in models adjusted for confounders. Logistic regression was used to estimate the likelihood (odds ratio, OR) of recurrent falls in the year after the visit. Proportional hazards models were used to estimate the risk (hazard ratio, HR) of fractures. Results: One year after the visit, 417 men (14%) had recurrent (≥2) falls. Later acrophase (OR 1.18, 95% CI 1.06–1.32) was associated with a modestly greater likelihood of falls. In 8.6 years (SD 2.6 years) of >97% complete follow-up, 256 men (8.53%) had a major osteoporotic fracture, 85 (2.8%) had a clinical spine fracture, and 110 (3.7%) had a hip fracture. No consistent, significant associations were observed between RAR patterns and fractures. Conclusions: Later
acrophase was associated with a modestly greater risk of falls; this association did not translate into a higher fracture risk in this cohort of elderly men. © 2016 International Osteoporosis Foundation and National Osteoporosis Foundation

Chlorpyrifos is an organophosphorus (OP) pesticide widely used around the world for agricultural operations. Although studies have examined exposure in children, there is limited information on adolescents who are occupationally exposed. Furthermore, there is limited research addressing the change in exposure patterns and outcomes across the application season. The goal of the current study was to examine the impact of chlorpyrifos exposure on neurobehavioral performance in adolescents before, during and after the application season. The longitudinal study was conducted in Egypt from April 2010 to January 2011, quantifying exposure and neurobehavioral performance with repeated measures prior to, during, and following the application period. At each test session, participants completed a neurobehavioral test battery and urine was collected for analysis of the chlorpyrifos metabolite 3,5,6-trichloro-2-pyridinol (TCPy) (biomarker of exposure). Cumulative urinary TCPy over the study period was used to classify participants into low (<median) and high (>/= median) exposure groups. The urinary TCPy concentrations increased for both groups during the application season and decreased following the end of application. TCPy levels were significantly elevated in the high exposure group compared to the low exposure groups at all time intervals except baseline. Deficits in cumulative neurobehavioral performance were found among the high exposure group compared with the low exposure group. Additionally, changes in neurobehavioral performance across the application season indicate a pattern of impaired performance in the high exposure group compared to the low exposure group. Deficits increased during the application season and remained even months after application ceased. This study is the first to examine the impact of changes in pesticide exposure and neurobehavioral performance not only before and after the application season, but also within the application season. Furthermore, this study examines the impact of pesticide exposure on an adolescent population who may be at greater risk than adult populations.

STUDY DESIGN: This is a retrospective study. OBJECTIVE: Compare improvements in health status measures (HSMs) and surgical costs to determine whether use of more costly items has any relationship to clinical outcome and value in lumbar disc surgery. SUMMARY OF BACKGROUND DATA: Association between cost, outcomes, and value in spine surgery, including lumbar discectomy is poorly understood. Outcomes were calculated as difference in mean HSM scores between preoperative and postoperative timeframes. Prospective validated patient-reported HSMs studied were EuroQol quality of life index score (EQ-5D), Pain Disability Questionnaire (PDQ), and Patient Health Questionnaire (PHQ-9). Surgical costs consisted of disposable items and implants used in operating room. METHODS: We retrospectively identified all adult patients at Cleveland Clinic main campus between October 2009 and August 2013 who underwent lumbar discectomy (652) using administrative billing data, Current Procedural Terminology (CPT) code 63030. HSMs were obtained from Cleveland Clinic Knowledge Program Data Registry. RESULTS: In total, 67% of operations performed in the outpatient or ambulatory setting, 33% in the inpatient setting. Among 9 surgeons who performed >10 lumbar discectomies, there were 72.4 operations per surgeon, on average. Mean surgical costs of each surgeon differed (P<0.0001). In a multivariable regression, only the surgeon and surgery type (outpatient or inpatient) were statistically correlated with surgical costs (P<0.0001 and 0.046, respectively). Changes in EQ-5D, PDQ, and PHQ-9 were not correlated with surgical costs (P=0.76, 0.07, 0.76, respectively). In multivariable regression, only surgical cost was significantly correlated to mean difference in PDQ (P=0.030). More costly surgeries resulted in worse PDQ outcomes. CONCLUSIONS: Mean surgical costs varied statistically among 9 surgeons; costs were not shown to be positively correlated with patient outcomes. Performing an operation using more costly disposable supplies/implants does not seem to
improve patient outcomes and should be considered when constructing preference cards and during an operation.


OBJECTIVES: Families, clinicians and policymakers desire improved delivery of health and related services for children with special health care needs (CSHCN). We analyzed factors associated with ease of use in obtaining such services. We also explored what were specific difficulties or delays in receiving services. By examining data from the National Survey of Children with Special Health Care Needs (NS-CSHCN 2009-2010) and using the revised criteria for “ease of use,” we were able to assess the percentage of parents who reported that their experiences seeking services for their children met those criteria. METHODS: We performed Chi square tests to examine associations between the independent variables and their relationship to the difficulties or delays assessed in the survey, including: eligibility, availability of services, waiting lists, cost, and access to information. We used logistic regression to determine the association of meeting the “ease of use” criteria with socio-demographic, complexity of need, and access variables. RESULTS: Overall, a third of families of CSHCN (35.3 %) encounter difficulties, delays, or frustrations in obtaining health and related services. The lack of access to health and community services in this study fell most heavily on children from racial/ethnic minority backgrounds, those in poverty, and those with complex emotional/behavioral or developmental needs and functional limitations. CONCLUSIONS: for Practice CSHCN require services from a broad array of providers across multiple systems. Unfortunately, there are certain difficulties that hamper the accessibility of these systems. These findings underscore the need for both practice-level response and systems-level reform to ensure equitable distribution of health and community resources.


Arginine supplementation has the potential to improve the health of patients. Its use in hospitalized patients has been a controversial topic in the nutrition literature, especially concerning supplementation of septic patients. In this article, we review the relevant literature both for and against the use of arginine in critically ill, surgical, and hospitalized patients. The effect of critical illness on arginine metabolism is reviewed, as is its use in septic and critically ill patients. Although mounting evidence supports immunonutrition, there are only a few studies that suggest that this is safe in patients with severe sepsis. The use of arginine has been shown to benefit a variety of critically ill patients. It should be considered for inclusion in combinations of immunonutrients or commercial formulations for groups in whom its benefit has been reported consistently, such as those who have suffered trauma and those in acute surgical settings. The aims of this review are to discuss the role of arginine in health, the controversy surrounding arginine supplementation of septic patients, and the use of arginine in critically ill patients. © American Society for Nutrition.


BACKGROUND: A growing body of research has found that people with disabilities experience lower health status and an excess burden of disease relative to the general US population. However, the population of people with disabilities is quite diverse. Thus, it is important to understand health differences between subgroups of people with disabilities in order to most effectively target interventions to address disparities. An initial step in this process is reviewing and synthesizing available research addressing these subgroup differences. OBJECTIVES: To conduct a scoping review of literature to describe recent research activity that has examined health outcome disparities within populations of people with disabilities. METHODS: We searched for relevant articles in MEDLINE, PsycINFO, and CINAHL databases. Three staff independently reviewed abstracts according to inclusion criteria. Two authors then independently extracted data from each

Objective. To test the association between public health insurance and adequate prenatal care among female adolescents in Mexico. Materials and methods. Cross-sectional study, using the National Health and

OBJECTIVE To examine self-reported practices and policies to reduce infection and transmission of multidrug-resistant organisms (MDRO) in healthcare settings outside the United States. DESIGN Cross-sectional survey. PARTICIPANTS International members of the Society for Healthcare Epidemiology of America (SHEA) Research Network. METHODS Electronic survey of infection control and prevention practices, capabilities, and barriers outside the United States and Canada. Participants were stratified according to their country’s economic development status as defined by the World Bank as low-income, lower-middle-income, upper-middle-income, and high-income. RESULTS A total of 76 respondents (33%) of 229 SHEA members outside the United States and Canada completed the survey questionnaire, representing 30 countries. Forty (53%) were high-, 33 (43%) were middle-, and 1 (1%) was a low-income country. Country data were missing for 2 respondents (3%). Of the 76 respondents, 64 (84%) reported having a formal or informal antibiotic stewardship program at their institution. High-income countries were more likely than middle-income countries to have existing MDRO policies (39/64 [61%] vs 25/64 [39%], P=.003) and to place patients with MDRO in contact precautions (40/72 [56%] vs 31/72 [44%], P=.05). Major barriers to preventing MDRO transmission included constrained resources (infrastructure, supplies, and trained staff) and challenges in changing provider behavior. CONCLUSIONS In this survey, a substantial proportion of institutions reported encountering barriers to implementing key MDRO prevention strategies. Interventions to address capacity...
building internationally are urgently needed. Data on the infection prevention practices of low income countries are needed. © 2016 by The Society for Healthcare Epidemiology of America. All rights reserved.


OBJECTIVE: Sleep characteristics detected by electroencephalography (EEG) may be predictive of neurological recovery and rehabilitation outcomes after traumatic brain injury (TBI). We sought to determine whether sleep features were associated with greater access to rehabilitation therapies and better functional outcomes after severe TBI. METHODS: We retrospectively reviewed records of patients admitted with severe TBI who underwent 24 or more hours of continuous EEG (cEEG) monitoring within 14 days of injury for sleep elements and ictal activity. Patient outcomes included discharge disposition and modified Rankin Scale (mRS). RESULTS: A total of 64 patients underwent cEEG monitoring for a mean of 50.6 hours. Status epilepticus or electrographic seizures detected by cEEG were associated with poor outcomes (death or discharge to skilled nursing facility). Sleep characteristics were present in 19 (30%) and associated with better outcome (89% discharged to home/acute rehabilitation; P = .0002). Lack of sleep elements on cEEG correlated with a poor outcome or mRS > 4 at hospital discharge (P = .012). Of those patients who were transferred to skilled nursing/acute rehabilitation, sleep architecture on cEEG associated with a shorter inpatient hospital stay (20 days vs 27 days) and earlier participation in therapy (9.8 days vs 13.2 days postinjury). Multivariable analyses indicated that sleep features on cEEG predicted functional outcomes independent of admission Glasgow Coma Scale and ictal-interictal activity. CONCLUSION: The presence of sleep features in the acute period after TBI indicates earlier participation in rehabilitative therapies and a better functional recovery. By contrast, status epilepticus, other ictal activity, or absent sleep architecture may portend a worse prognosis. Whether sleep elements detected by EEG predict long-term prognosis remains to be determined.


Ulcerative dermatitis (UD) in C57BL/6 mice is poorly understood and challenging to treat. We sought to evaluate the evidence regarding commonly cited risk factors for UD and reported UD treatments. The terms ‘ulcerative dermatitis’ and ‘C57BL/6’ were used to search 3 electronic databases. The resulting 347 articles were screened to identify publications that compared the risk of spontaneous UD in wild-type C57BL/6 mice according to sex, season, diet, or age and those that compared the degree of healing or rate of lesion resolution according to the intervention used. Articles were evaluated by using published criteria for assessing methodologic quality, including study design, number of animals per study group, case definition, method of diagnosis, randomization, enrollment criteria, exclusion criteria, and outcomes. The search identified 11 publications on risk factors that met the inclusion criteria, and no publication on UD treatment met all of the criteria. Relaxing the inclusion criteria for reporting of risk factors and treatment outcomes to include both wild-type C57BL/6 mice and genetically engineered mice on a B6 background yielded 12 publications on risk factors and 3 publications on treatment. Dietary factors, particularly caloric restriction, appear to influence UD risk. Female sex was inconsistently associated with a higher risk of UD, which most often occurred in 13- to 24-mo-old mice in the studies that were reviewed. Only 1 of the 3 publications that evaluated UD treatments included an untreated group or alternative therapy control. Further research is needed to explore epidemiologic aspects of UD and to compare treatment options. Copyright 2015 by the American Association for Laboratory Animal Science.


Women are a consistent minority in the field of cardiology, with concerns regarding balancing career and parenting responsibilities often cited as a contributing factor to this under-representation. To investigate the impact that a career in cardiology may have on the family planning decisions of female cardiologists, the
Women in Cardiology section of the American College of Cardiology conducted a voluntary anonymous survey. The following perspective highlights lessons learned from the survey, and potential solutions to the issues surrounding maternity leave, radiation exposure during pregnancy, and breastfeeding accommodations raised by these data. Given that most female cardiologists are pregnant at some point during their careers, particularly during the vulnerable periods of training and early career, improving the experience of pregnancy and early parenthood for all cardiologists may secure the best possible candidates to the field of cardiology.


The quality and efficiency of American health care are increasingly measured using clinical and financial data with a goal of improving clinical practice. Proponents believe such efforts can improve outcomes, motivate clinicians, and inform the public about quality. Detractors point to problems with the accuracy of these measures and the risk of creating perverse incentives for both physicians and patients. Drawing on lessons from similar performance management policies in public education, we provide guidance about this trend for primary care physicians and health care policy makers. We argue that public school teacher evaluations that use value-added modeling foretell specific pitfalls for the use of similar models to evaluate physician effectiveness, and that unintended consequences of performance management in both education and health care can include the narrowing of purpose, depprofessionalization, and a loss of local/community control. © 2017, Annals of Family Medicine, Inc. All rights reserved.


Previously we reported that a 5-hour exposure of 6-day-old (P6) rhesus macaques to isoflurane triggers robust neuron and oligodendrocyte apoptosis. In an attempt to further describe the window of vulnerability to anesthetic neurotoxicity, we exposed P20 and P40 rhesus macaques to 5 h of isoflurane anesthesia or no exposure (control animals). Brains were collected 3 h later and examined immunohistochemically to analyze neuronal and glial apoptosis. Brains exposed to isoflurane displayed neuron and oligodendrocyte apoptosis distributed throughout cortex and white matter, respectively. When combining the two age groups (P20 + P40), the animals exposed to isoflurane had 3.6 times as many apoptotic cells as the control animals. In the isoflurane group, approximately 66% of the apoptotic cells were oligodendrocytes and 34% were neurons. In comparison, in our previous studies on P6 rhesus macaques, approximately 52% of the dying cells were glia and 48% were neurons. In conclusion, the present data suggest that the window of vulnerability for neurons is beginning to close in the P20 and P40 rhesus macaques, but continuing for oligodendrocytes. © 2016.


PURPOSE: Postoperative pneumothorax and effusion remain a concern following congenital diaphragmatic hernia (CDH) repair. Despite a recent trend away from intraoperative thoracostomy, few studies have actually compared outcomes with and without a chest tube. Rationale commonly cited for the more minimalistic approach include the presumed low likelihood of postoperative complications, potential risk of patch infection, and prolonged intubation. We evaluate these theories, as well as the implications of intraoperative chest tube (IOCT) placement. METHODS: We performed a retrospective chart review of 174 patients who underwent CDH repair at our academic children's hospital from 2004 to 2015. We compared incidence of clinically significant pleural events between patients who received an IOCT (n = 49) and those who did not (NIOCT, n = 124). We also evaluated time to extubation and rate of patch infections. RESULTS: Clinically significant pneumothorax or effusion occurred in 28% of NIOCT patients versus 10% of IOCT patients (P = .01). After thoracoscopic repair, time to extubation averaged 5.2 days in IOCT patients, 5.4 days in NIOCT patients with no postoperative complications, and 6.4 days in NIOCT patients requiring postoperative
After open repair, time to extubation averaged 13.8, 13.6, and 22.5 days, respectively. There were no documented patch infections. CONCLUSIONS: Chest tube placement during CDH repair is associated with significantly lower incidence of clinically significant pleural complications, does not delay extubation, and results in shorter ventilator times than cases that require postoperative intervention. Patch infections are extremely rare. There is no evidence that chest tube placement increases this risk.


Giant basal cell carcinomas (GBCCs) are large basal cell carcinomas (BCCs; <5 cm) with a greater propensity to invade and metastasize than standard BCCs. The presence of 2 GBCCs in a single individual is rare. We present the case of a 71-year-old Caucasian male with bilateral GBCCs on the dorsal forearms, measuring 130 cm² and 24 cm², respectively, that developed over a 21-year period. Over this period, the patient treated the tumors with herbal remedies. Histologic evaluation showed a conventional nodular BCC for both tumors. Computed tomography and magnetic resonance imaging revealed a T4N0M0 stage for the larger lesion. Surgical excision and grafting and reconstruction were offered, but he declined. This case highlights a shared belief in holistic treatments and rejection of Western medical interventions that are common among many patients with GBCC. Studies reporting nonsurgical treatments for GBCCs, including radiotherapy, vismodegib, topical imiquimod, and acitretin are reviewed.

Shastry, M. C., Asgari, M., Wan, E. A., Leitschuh, J., Preiser, N., Folsom, J., . . . Jacobs, P. G. (2016). Context-aware fall detection using inertial sensors and time-of-flight transceivers. Paper presented at the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2016. Automatic detection of falls is important for enabling people who are older to safely live independently longer within their homes. Current automated fall detection systems are typically designed using inertial sensors positioned on the body that generate an alert if there is an abrupt change in motion. These inertial sensors provide no information about the context of the person being monitored and are prone to false positives that can limit their ongoing usage. We describe a fall-detection system consisting of a wearable inertial measurement unit (IMU) and an RF time-of-flight (ToF) transceiver that ranges with other ToF beacons positioned throughout a home. The ToF ranging enables the system to track the position of the person as they move around a home. We describe and show results from three machine learning algorithms that integrate context-related position information with IMU based fall detection to enable a deeper understanding of where falls are occurring and also to improve the specificity of fall detection. The beacons used to localize the falls were able to accurately track to within 0.39 meters of specific waypoints in a simulated home environment. Each of the three algorithms was evaluated with and without the context-based false alarm detection on simulated falls done by 3 volunteer subjects in a simulated home. False positive rates were reduced by 50% when including context. © 2016 IEEE.


Thrombotic thrombocytopenia purpura (TTP) and the hemolytic uremic syndrome (HUS) are rare thrombotic microangiopathies that can be rapidly fatal. Although the acquired versions of TTP and HUS are generally highest on this broad differential, multiple rarer entities can produce a clinical picture similar to TTP/HUS, including microangiopathic hemolysis, renal failure, and neurologic compromise. More recent analysis has discovered a host of genetic factors that can produce microangiopathic hemolytic syndromes. This article discusses the current understanding of thrombotic microangiopathy and outlines the pathophysiology and causative agents associated with each distinct syndrome as well as the most accepted treatments. © 2016.

**Purpose** Suicide attempts by adolescents most commonly involve the overdose of medications. To date, there has been little information on the over-the-counter or prescription medicines that adolescents ingest for self-harm. Identification of medications chosen in suicide attempts may help guide anticipatory guidance to parents by primary care providers and Poison Centers in prevention programs. **Methods** This was a retrospective observational study using the American Association of Poison Control Center’s National Poison Data System. Data were collected on patients aged 13–19 years old at the time of their substance ingestion, between the years 2004 and 2013 and that were coded as reason for ingestion of “intentional-suspected suicide.” Results During the 10-year study period, there were 390,560 poison center calls for intentional-suspected suicide in the United States between 2004 and 2013, accounting for 80.3% of all “intentional” ingestion calls in the adolescent population. Over the entire age range, the most common substance ingested included acetaminophen (10.9%), ibuprofen (9%), selective serotonin reuptake inhibitors (7.7%), atypical antipsychotic (6%), and antihistamines (5%). The most common medications coded as resulting in major clinical effects or death were antidepressants and atypical antipsychotics. **Conclusions** Adolescent ingestion choices for suicide attempts have remained relatively consistent over the past 10 years. However, there was a recent decrease in selective serotonin reuptake inhibitor ingestions. The most common medications used in an overdose attempt were ibuprofen and acetaminophen. Further preventative efforts are needed in this at-risk population from multiple providers at various levels. © 2016 Society for Adolescent Health and Medicine


Marfan syndrome (MFS) is an autosomal dominant connective tissue disease associated with acute aortic dissection (AAD). We used 2 large registries that include patients with MFS to investigate possible trends in the chronobiology of AAD in MFS. We queried the International Registry of Acute Aortic Dissection (IRAD) and the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry to extract data on all patients with MFS who had suffered an AAD. The group included 257 patients with MFS who suffered an AAD from 1980 to 2012. The chi-square tests were used for statistical testing. Mean subject age at time of AAD was 38 years, and 61% of subjects were men. AAD was more likely in the winter/spring season (November to April) than the other half of the year (57% vs 43%, p = 0.05). Dissections were significantly more likely to occur during the daytime hours, with 65% of dissections occurring from 6 a.m. to 6 p.m. (p = 0.001). Men were more likely to dissect during the daytime hours (6 a.m. to 6 p.m.) than women (74% vs 51%, p = 0.01). These insights offer a glimpse of the times of greatest vulnerability for patients with MFS who suffer from this catastrophic event. In conclusion, the chronobiology of AAD in MFS reflects that of AAD in the general population.


Background Dupilumab, a human monoclonal antibody against interleukin-4 receptor alpha, inhibits signaling of interleukin-4 and interleukin-13, type 2 cytokines that may be important drivers of atopic or allergic diseases such as atopic dermatitis. Methods In two randomized, placebo-controlled, phase 3 trials of identical design (SOLO 1 and SOLO 2), we enrolled adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment. Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator’s Global Assessment and a reduction of 2
points or more in that score from baseline at week 16. Results We enrolled 671 patients in SOLO 1 and 708 in SOLO 2. In SOLO 1, the primary outcome occurred in 85 patients (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo (P<0.001 for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo (P<0.001 for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo (P<0.001 for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups. Conclusions In two phase 3 trials of identical design involving patients with atopic dermatitis, dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life, as compared with placebo. Trials of longer duration are needed to assess the long-term effectiveness and safety of dupilumab. (Funded by Sanofi and Regeneron Pharmaceuticals; SOLO 1 ClinicalTrials.gov number, NCT02277743; SOLO 2 ClinicalTrials.gov number, NCT02277769).


Studies of the prevalence of atopic dermatitis (AD) have provided insights into associated environmental risk factors, demonstrating the complex interactions between the presence of filaggrin (FLG) gene defects and environment. Among other important findings is that elevated transepidermal water loss (TEWL) in newborns is a strong predictor of AD, regardless of FLG status. Recently recognized predictors of disease course and severity include onset of AD signs and symptoms before 12 months of age and the presence of an FLG mutation and concomitant immunoglobulin E sensitization early in life. Semin Cutan Med Surg 35(supp5):S84-S88.


Purpose To evaluate tumor vasculature with optical coherence tomography angiography (OCTA) in malignant iris melanomas and benign iris lesions. Design Cross-sectional observational clinical study. Participants Patients with iris lesions and healthy volunteers. Methods Eyes were imaged using OCTA systems operating at 1050- and 840-nm wavelengths. Three-dimensional OCTA scans were acquired. Iris melanoma patients treated with radiation therapy were imaged again after 1-125 plaque brachytherapy at 6 and 18 months. Main Outcome Measures OCT and OCTA images, qualitative evaluation of iris and tumor vasculature, and quantitative vessel density. Results One eye each of 8 normal volunteers and 9 patients with iris melanomas or benign iris lesions, including freckles, nevi, and an iris pigment epithelial (IPE) cyst, were imaged. The normal iris has radially oriented vessels within the stroma on OCTA. Penetration of flow signal in normal iris depended on iris color, with best penetration seen in light to moderately pigmented irides. Iris melanomas demonstrated tortuous and disorganized intratumoral vasculature. In 2 eyes with nevi there was no increased vascularity; in another, fine vascular loops were noted near an area of ectropion uveae. Iris freckles and the IPE cyst did not have intrinsic vascularity. The vessel density was significantly higher within iris melanomas (34.5%±9.8%, P < 0.05) than in benign iris nevi (8.0%±1.4%) or normal irides (8.0%±1.2%). Tumor regression after radiation therapy for melanomas was associated with decreased vessel density. OCTA at 1050 nm provided better visualization of tumor vasculature and penetration through thicker tumors than at 840 nm. But in very thick tumors and highly pigmented lesions even 1050-nm OCTA could not visualize their full thickness. Interpretable OCTA images were obtained in 82% of participants in whom imaging was attempted. Conclusions This is the first demonstration of OCTA in iris tumors. OCTA may provide a dye-free, no-injection, cost-effective method for monitoring a variety of tumors, including iris melanocytic lesions, for
growth and vascularity. This could be helpful in evaluating tumors for malignant transformation and response to treatment. Penetration of the OCT beam remains a limitation for highly pigmented tumors, as does the inability to image the entire iris in a single field. © 2016 American Academy of Ophthalmology


Background: Evolutionary origins of derived morphologies ultimately stem from changes in protein structure, gene regulation, and gene content. A well-assembled, annotated reference genome is a central resource for pursuing these molecular phenomena underlying phenotypic evolution. We explored the genome of the Gulf pipefish (Syngnathus scovelli), which belongs to family Syngnathidae (pipefishes, seahorses, and seadragons). These fishes have dramatically derived bodies and a remarkable novelty among vertebrates, the male brood pouch. Results: We produce a reference genome, condensed into chromosomes, for the Gulf pipefish. Gene losses and other changes have occurred in pipefish hox and dlx clusters and in the tbx and pitx gene families, candidate mechanisms for the evolution of syngnathid traits, including an elongated axis and the loss of ribs, pelvic fins, and teeth. We measure gene expression changes in pregnant versus non-pregnant brood pouch tissue and characterize the genomic organization of duplicated metalloprotease genes (patristacins) recruited into the function of this novel structure. Phylogenetic inference using ultraconserved sequences provides an alternative hypothesis for the relationship between orders Syngnathiformes and Scombriformes. Comparisons of chromosome structure among percomorphs show that chromosome number in a pipefish ancestor became reduced via chromosomal fusions. Conclusions: The collected findings from this first syngnathid reference genome open a window into the genomic underpinnings of highly derived morphologies, demonstrating that de novo production of high quality and useful reference genomes is within reach of even small research groups. © 2016 The Author(s).


BACKGROUND AND PURPOSE: The backward push and release test (PRT) is a standardized clinical test of postural responses elicited by perturbations. Our goal was to determine reliability of administration and response. This will inform clinical administration and determine whether to develop an instrumented version.

METHODS: One examiner administered 10 backward PRT trials to adults with Parkinson disease (12), multiple sclerosis (14) and controls (12). We used three-dimensional motion analysis, force plates and instrumented gloves to measure administration and response. Administration variables were angle of posterior trunk lean and the distance of the centre of mass (CoM) behind the ankle. Postural response variables were latency of postural response from release to step initiation and first compensatory step length. Reliability was measured using the range of variables across trials, comparison of first and later trials, intraclass correlations (ICCs) to measure consistency and correlations between administration and response. RESULTS: There was inherent variability in administration, which affected postural response characteristics. Larger trunk angle and greater CoM-ankle distance were correlated with shorter postural response latencies and larger step lengths. Participant height also had an effect; taller participants had larger trunk angles prior to release resulting in longer latencies and larger step lengths. Using ICCs, consistency of trunk angle was likely acceptable and CoM-ankle distance was high. Consistency of latency was low, while step length was likely acceptable.

DISCUSSION: Despite variability in administration and inconsistency in response, different postural response characteristics were detected between patients with different disease states. Based on these results, we will create algorithms to instrument the PRT using inertial movement sensors to collect more sensitive measures of postural responses than observational clinical rating scales. Feedback for appropriate lean angle and calibration for participant height will improve consistency and usefulness of the instrumented PRT. Copyright (c) 2014 John Wiley & Sons, Ltd.

**OBJECTIVE:** Integrated (0 + 5) vascular surgery (VS) residency programs must include 24 months of training in core general surgery. The Accreditation Council for Graduate Medical Education currently does not require specific case numbers in general surgery for 0 + 5 trainees; however, program directors have structured this time to optimize operative experience. The aim of this study is to determine the case volume and type of cases that VS residents are exposed to during their core surgery training.

**DESIGN:** Accreditation council for graduate medical education operative logs for current 0 + 5 VS residents were obtained and retrospectively reviewed to determine general surgery case volume and distribution between open and laparoscopic cases performed. Standard statistical methods were applied.

**SETTING:** A total of 12 integrated VS residency programs provided operative case logs for current residents.

**PARTICIPANTS:** A total of 41 integrated VS residents in clinical years 2 through 5.

**RESULTS:** During the postgraduate year-1 training year, residents participated in significantly more open than laparoscopic general surgery cases (p < 0.0001). This difference was consistent over the first 3 years of training. The most frequently logged open general surgery cases are hernia repair (20%), skin and soft tissue (7.4%), and breast (6.3%). Residents in programs with core surgery over 3 years participated in significantly more general surgery operations compared with residents in programs with core surgery spread out over 4 years (p = 0.035).

**CONCLUSIONS:** 0 + 5 VS residents perform significantly more open operations than laparoscopic operations during their core surgery training. The majority of these operations are minor, nonabdominal procedures. The 0 + 5 VS residency program general surgery operative training requirements should be reevaluated and case minimums defined. The general surgery training component of 0 + 5 VS residencies may need to be restructured to meet the needs of current and future trainees.


The use of sanitary inspections combined with periodic water quality testing has been recommended in some cases as screening tools for fecal contamination. We conducted sanitary inspections and tested for thermotolerant coliforms (TTCs), a fecal indicator bacteria, among 7,317 unique water sources in West Bengal, India. Our results indicate that the sanitary inspection score has poor ability to identify TTC-contaminated sources. Among deep and shallow hand pumps, the area under curve (AUC) for prediction of TTC > 0 was 0.58 (95% confidence interval [CI] = 0.53-0.61) and 0.58 (95% CI = 0.54-0.62), respectively, indicating that the sanitary inspection score was only marginally better than chance in discriminating between contaminated and uncontaminated sources of this type. A slightly higher AUC value of 0.64 (95% CI=0.57-0.71) was observed when the sanitary inspection score was used for prediction of TTC > 0 among the gravity-fed piped sources. Among unprotected springs (AUC = 0.48, 95% CI = 0.38-0.55) and unprotected dug wells (AUC = 0.41, 95% CI = 0.20-0.66), the sanitary inspection score performed more poorly than chance in discriminating between sites with TTC < 1 and TTC > 0. Aggregating over all source types, the sensitivity (true positive rate) of a high/very high sanitary inspection score for TTC contamination (TTC > 1 CFU/100 mL) was 29.4% and the specificity (true negative rate) was 77.9%, resulting in substantial misclassification of the sites when using the established risk categories. These findings suggest that sanitary surveys are inappropriate screening tools for identifying TTC contamination at water points.


**BACKGROUND:** Olfactory loss is a cardinal symptom of chronic rhinosinusitis (CRS) and affects 40% to 80% of patients. However, common sinus-specific quality-of-life (QOL) instruments include only single questions...
related to olfaction. Few studies have explored olfactory outcomes after surgery utilizing validated, olfaction-specific QOL questionnaires. METHODS: Patients with CRS were enrolled from 3 centers across North America into a prospective cohort study. Patients completed the short modified version of the Questionnaire of Olfactory Disorders (QOD-NS) and the 40-item Smell Identification Test (SIT-40) before and at least 6 months after endoscopic sinus surgery (ESS). Multivariate linear regression was used to determine whether specific demographic, comorbidity, or disease severity measures were independently associated with QOD scores at baseline or predicted change after surgery. RESULTS: A total of 121 patients, equally split between genders, were enrolled with an average age of 47.9 years (range, 18-80 years). Baseline total QOD-NS scores were significantly associated with SIT-40 scores, with a moderate strength of correlation (Rs = 0.400; p < 0.001). The average QOD-NS score improved after ESS (35.7 +/- 13.0 vs 39.7 +/- 12.2; p = 0.006). Allergy, polyps, and steroid-dependent conditions were found to be independently associated with worse preoperative QOD-NS scores, whereas septal deviation was associated with better QOD-NS scores. Baseline computed tomography (CT) scores were the only variable that significantly predicted change in QOD-NS after surgery. CONCLUSION: Olfaction-specific QOL is worse in patients with polyps and comorbid allergy. Significant improvements in olfaction-specific QOL are seen after ESS, with the greatest gains seen in those with worse CT scores at baseline.


BACKGROUND AND AIMS: Gastrointestinal bleeding (GIB) may present as complication of multiorgan failure (MOF). The study aims to analyze the reasons for the limited success of hemostasis of GIB in MOF. METHODS: Using a Markov process, GIB is modeled as one of several complications associated with multiorgan breakdown to study how the reversal of GIB affects clinical outcome. RESULTS: Although endoscopic hemostasis can delay mortality in patients with severe systemic disease, its overall influence on survival is relatively small. In patients with a time-limited transition through an acute phase of increased mortality risk secondary to MOF, endoscopic hemostasis may substantially prolong survival in absolute terms. However, its relative contribution to overall survival still remains relatively small even in the scenario of transient risk only. The benefit of endoscopy is largest, if GIB is a major contributor to morbidity and mortality in comparison with all other disease complications. CONCLUSION: Because disease outcome in MOF is ultimately determined by other complications than GIB alone, the influence of endoscopic hemostasis on patient survival often remains disappointingly small.


Aim: Inflammatory bowel disease (IBD) and microscopic colitis are characterized by different geographical distributions across the USA. In this cross-sectional study we utilized demographic and socio-economic information associated with individual ZIP codes to further delineate the epidemiological characteristics of the two diseases. Method: A total of 813 057 patients who underwent colonoscopy between 2008 and 2014 were extracted from an electronic database of histopathology reports. The prevalence of patients with IBD or microscopic colitis was expressed as percentage of the population associated with specific demographic (age, sex, ethnicity) and socio-economic characteristics (population size, housing value, annual income, tertiary education). Results: Both diseases were more common among subjects from ZIP codes with predominantly White residents and less common among subjects from ZIP codes with predominantly non-White residents such as Black, Hispanic and Asian. These ethnic variations were more pronounced in microscopic colitis than IBD. Markers of affluence, such as average residential house value and annual income, were positively associated with IBD and negatively with microscopic colitis. The prevalence of both diseases was positively correlated with tertiary education. Conclusion: The occurrence of both IBD and microscopic colitis is influenced by environmental risk factors. The differences in the demographic, ethnic and socio-economic distributions of the two diseases suggest that different sets of risk factors affect the two diseases and that their aetiology is unrelated. Published [2016]. This article is a U.S. Government work and is in the public domain in the USA.

**BACKGROUND:** Previous studies found that microscopic colitis is inversely associated with *Helicobacter pylori* infection and that microscopic colitis is characterized by a marked ethnic variation. **AIM:** The aim of the present study was to test whether an underlying ethnic variation of *H. pylori* infection is responsible for the ethnic variation of microscopic colitis. **METHODS:** The Miraca Life Sciences Database is a large national electronic repository of histopathologic records of patients distributed throughout the entire USA. A cross-sectional study evaluated the influence of age, gender, ethnicity, and histologic diagnosis of *H. pylori* on the occurrence of microscopic colitis among subjects who underwent esophago-gastro-duodenoscopies plus colonoscopy. **RESULTS:** The total study population comprised 228,506 subjects, of whom 28,890 carried a diagnosis of *H. pylori* gastritis and 3460 microscopic colitis. Female sex, old age, and *H. pylori* infection exerted the strongest influence on the occurrence of microscopic colitis. In comparison with the population comprising Caucasians and African-Americans, microscopic colitis was less common among subjects of Hispanic (0.34, 0.27-0.47), East Asian (0.13, 0.06-0.22), Indian (0.31, 0.10-0.73), or Middle Eastern descent (0.28, 0.07-0.74). All these ethnic subgroups were also characterized by a higher prevalence of *H. pylori* than the comparison group. A low prevalence of *H. pylori* was significantly associated with a high prevalence of microscopic colitis (R² = 0.91, p < 0.001). **CONCLUSION:** Ethnic variations in the gastric infection with *H. pylori* may be partly responsible for the observed ethnic distribution of microscopic colitis.

Sourati, J., Kazmierczak, S. C., Akcakaya, M., Dy, J. G., Leen, T. K., & Erdogmus, D. (2016). Assessing subsets of analytes in context of detecting laboratory errors. Paper presented at the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2016. Laboratory error detection is a hard task yet plays an important role in efficient care of the patients. Quality controls are inadequate in detecting pre-analytic errors and are not frequent enough. Hence population- and patient-based detectors are developed. However, it is not clear what set of analytes leads to the most efficient error detectors. Here, we use three different scoring functions that can be used in detecting errors, to rank a set of analytes in terms of their strength in distinguishing erroneous measurements. We also observe that using evaluations of larger subsets of analytes in our analysis does not necessarily lead to a more accurate error detector. In our data set obtained from renal kidney disease inpatients, calcium, potassium, and sodium, emerged as the top-3 indicators of an erroneous measurement. Using the joint likelihood of these three analytes, we obtain an estimated AUC of 0.73 in error detection. © 2016 IEEE.


**OBJECTIVE:** To evaluate the gestational age (GA) at which perinatal mortality risk is minimized for fetuses with Down syndrome (DS). **METHODS:** Retrospective cohort of singleton pregnancies delivered between 24 and 41 weeks, using 2005-2006 United States linked birth and death certificate data. Among fetal DS cases, prospective risk of intrauterine fetal demise (IUD) and risk of infant death were calculated for each week, and composite risk of fetal/infant mortality with expectant management was compared to delivery. **RESULTS:** Of 3,113,098 pregnancies, 1766 had fetal DS (0.06%). IUD occurred in 7.4% with DS, and infant death in 6.5%. Prospective risk of IUD increased from 37 weeks onward to reach 50.7 per 1000 pregnancies (95% CI 33.2-68.3) at 42 weeks. Comparing mortality with expectant management to delivery, expectant management carried increasing risk from 38 (RR 1.18; 95% CI 1.05-1.33) to 41 weeks (RR 1.84; 95% CI 1.66-2.05). Further, number needed to deliver to avoid one excess death decreased from 38 (109.17; 95% CI 64.52-344.83) to 41 weeks (24.08; 95% CI 20.59-29.04). **CONCLUSIONS:** Although further research is needed to clarify risk factors for fetal and neonatal death in cases of DS, risk of perinatal mortality appears to be minimized with delivery at 38 weeks.

Mantle cell lymphoma (MCL) comprises around 6% of all non-Hodgkin’s lymphoma (NHL) diagnoses. In younger patients, age less than 60 to 65 years, aggressive induction often followed by consolidation with autologous stem cell transplant has suggested improved outcomes in this population. Less intensive therapies in older patients often followed by maintenance have been studied or are under active investigation. However, despite recent advances, MCL remains incurable, with a median overall survival of around five years. Patients with high-risk disease have particularly poor outcomes. Treatment varies widely across institutions, and to date no randomized trials comparing intensive vs less intensive approaches have been reported. Although recent data have highlighted the heterogeneity of MCL outcomes, patient assessment for treatment selection has largely been driven by patient age with little regard to fitness, disease biology, or disease risk. One critical advance is the finding that minimal residual disease status (MRD) after induction correlates with long-term outcomes. As such, its use as a potential end point could inform clinical trial design. In order to more rapidly improve the outcomes of MCL patients, clinical trials are needed that prospectively stratify patients on the basis of MCL biology and disease risk, incorporate novel agents, and use MRD to guide the need for additional therapy.


PURPOSE: To evaluate retinal blood flow measurements in normal eyes and eyes with varying levels of diabetic retinopathy (DR) using Doppler Fourier-domain optical coherence tomography (FD-OCT).

METHODS: Twenty-two eyes of 19 subjects, 10 with severe nonproliferative DR (NPDR) and 12 with proliferative DR (PDR), were compared with 44 eyes of 40 healthy control subjects. All eyes were scanned by RTvue FD-OCT. Color disk photographs and cube/volume scans of the optic nerve head were obtained. Doppler OCT scans and accessory imaging data were imported into Doppler OCT of Retinal Circulation grading software to calculate TRBF and vascular parameters (e.g., venous and arterial cross-sectional area). Measurements were compared between cases and controls using independent t-tests. RESULTS: Mean TRBF was 44.98 +/- 9.80 (range: 30.18-64.58) microL/minute for normal eyes, 35.80 +/- 10.48 (range: 20.69-49.56) microL/minute for eyes with severe NPDR, and 34.79 +/- 10.61 (range: 16.77-48.9) microL/minute for eyes with PDR. Mean TRBF was significantly lower in eyes with severe NPDR (P = 0.01) and PDR (P = 0.003) than in normal eyes. CONCLUSION: Total retinal blood flow was significantly lower in eyes with severe NPDR and PDR compared with normal eyes. Retinal blood flow determined by Doppler OCT may be a useful parameter for evaluating patients with DR.


OBJECTIVES: The goal of this study is to investigate whether prior exposure to reverberant listening environment improves speech intelligibility of adult cochlear implant (CI) users. METHODS: Six adult CI users participated in this study. Speech intelligibility was measured in five different simulated reverberant listening environments with two different speech corpuses. Within each listening environment, prior exposure was varied by either having the same environment across all trials (blocked presentation) or having different environment from trial to trial (unblocked). RESULTS: Speech intelligibility decreased as reverberation time increased. Although substantial individual variability was observed, all CI listeners showed an increase in the blocked presentation condition as compared to the unblocked presentation condition for both speech corpuses. CONCLUSION: Prior listening exposure to a reverberant listening environment improves speech intelligibility in adult CI listeners. Further research is required to understand the underlying mechanism of adaptation to listening environment.

BACKGROUND: Vitamin D deficiency is widespread in the world including the vulnerable group of pregnant women. Vitamin D deficiency during pregnancy is hypothesized to contribute to the cause of autism. Further, it is hypothesized that vitamin D supplementation during pregnancy and early childhood will reduce the recurrence rate of autism in newborn siblings. METHODS: To investigate the hypothesis an open label prospective study was performed prescribing vitamin D during pregnancy to mothers of children with autism at a dose of 5000IU/day. The newborn siblings were at high risk for the recurrence of autism. The newborn infants were also prescribed vitamin D, 1000IU/day to their third birthday. The newborn siblings were followed for three years and during that time, were assessed for autism on two separate occasions: at 18 months and 36 months of age. The results were compared to the reported recurrence rates in siblings of autistic children in the literature. RESULTS: The final outcome was 1 out of 19 (5%) developed autism in contrast to the recurrence rate of approximately 20% in the literature. We did not have a control group, nor was there blinding. CONCLUSIONS: The results are promising, however, this is a preliminary study with very small numbers and was uncontrolled. Further study with larger numbers is indicated. The ethics of prescribing a low dosage of vitamin D such as 400IU D3/day to a control group of mothers in comparison to a large dose such as 5000IU D3/day are problematic in our opinion.


BACKGROUND: Little is known about the role, extent, or effects of family member involvement in monitoring and managing opioid analgesics. Knowing when or how family members monitor prescribed opioid medication taking, whether it is acceptable to patients, or how family relationships may be affected by monitoring, are not well documented. METHODS: The study was conducted at Kaiser Permanente Northwest, an integrated health plan in Oregon and Washington. Semistructured in-depth interviews (N = 87) assessed circumstances surrounding overdose events among individuals who either experienced an opioid-related overdose or were family members of patients who died as a result of such an overdose. A subset of participants (n = 20) described family members' roles in monitoring opioid medications before or after overdoses. Interviews were transcribed verbatim and coded using Atlas.ti. We used a modified grounded theory approach to categorize emergent data and to identify common themes. RESULTS: When family members played roles in monitoring and managing opioid medications, clinicians were often unaware of their involvement. Patients and family members reported better outcomes when the patient, caregiver, and clinician developed a shared treatment plan. Negative outcomes included relationship stress, particularly when patients and caregivers had differing perspectives about what constituted effective pain management versus misuse and abuse. CONCLUSIONS: When families are concerned about opioid medications, coordination between clinicians, patients, and family carers appears to clarify roles and foster better outcomes. Increased stress and worse outcomes were reported when clinicians were not actively involved and when they did not attend to carers' concerns.


Purpose: Hemophagocytic syndrome (HS) is a rare disease with a spectrum of ocular findings. The authors report a unique funduscopic presentation of HS in a neonate and a discussion of diagnosis, typical features, management, and outcome. Methods: Single case report with retrospective analysis of the published literature of patients with HS and ocular findings from 1950 to present using the key terms hemophagocytic, lymphohistiocytosis, ocular, and ophthalmic. Literature search from 1950 to the present was performed through PubMed/MEDLINE and the Cochrane database. Requirement for inclusion was that the article or abstract was written in English. Results: A 4-week-old neonate with HS demonstrated bilateral discrete white dots within the retina, which resolved incompletely over the course of the next months but showed
increased pigmentation. Conclusion: With so few documented ophthalmic cases of HS in existence, the ocular findings at this point can be seen as diverse and variable. However as more cases are reported, hopefully this will allow for increased recognition of the ophthalmic manifestations and sequelae and in turn lead to improved treatment of this disease. Copyright © by Ophthalmic Communications Society, Inc.


Progressive neurodegenerative diseases like Alzheimer's disease (AD) or Parkinson's disease (PD) are an increasing threat to human health worldwide. Although mammalian models have provided important insights into the underlying mechanisms of pathogenicity, the complexity of mammalian systems together with their high costs are limiting their use. Therefore, the simple but well-established Drosophila model-system provides an alternative for investigating the molecular pathways that are affected in these diseases. Besides behavioral deficits, neurodegenerative diseases are characterized by histological phenotypes such as neuronal death and axonopathy. To quantify neuronal degeneration and to determine how it is affected by genetic and environmental factors, we use a histological approach that is based on measuring the vacuoles in adult fly brains. To minimize the effects of systematic error and to directly compare sections from control and experimental flies in one preparation, we use the ‘collar’ method for paraffin sections. Neurodegeneration is then assessed by measuring the size and/or number of vacuoles that have developed in the fly brain. This can either be done by focusing on a specific region of interest or by analyzing the entire brain by obtaining serial sections that span the complete head. Therefore, this method allows one to measure not only severe degeneration but also relatively mild phenotypes that are only detectable in a few sections, as occurs during normal aging.


Pit and fissure sealant is a clinical technique adopted to prevent caries lesion development. Ionomeric and/or resin-based materials are commonly used for this purpose. This article presents a case series of sealed teeth with 22-year follow-up evaluated by clinical, photographic, and microscopic analysis. In 1992, sixteen patients (9-14 years of age) had at least three teeth sealed with one of the following materials: resin-modified glass ionomer cement (RMGIC, Vitrebond or Fuji II LC) or polyacid-modified resin composite (PMRC, VariGlass VLC), totaling 86 sealed permanent teeth. After 22 years, 10 patients were recalled, representing 41 teeth. The retention of sealants was assessed by three methods: clinical analysis by visual inspection; photography; and scanning electron microscope (SEM) images and classified as retained (pits and fissures filled by sealant material); partially retained (pits and fissures partially filled by sealant material); or totally lost (no material was found in pits and fissures). The SEM images provided a higher number of retained sealants when compared with the clinical and photographic evaluations. Also, no totally lost scores were found with SEM analysis, regardless of the sealing material. No caries lesions were found. A fully or partially retained sealant in pits and fissures was capable of preventing caries lesions after 22 years within the patient pool analyzed.


The increasing number of older adults with blood-related disorders and the introduction of reduced-intensity conditioning regimens has led to increases in hematopoietic stem cell (HSC) transplantation among older adults and a corresponding increase in the age of siblings who donate HSCs to these patients. Data regarding the donation-related experiences of older donors are lacking. The Related Donor Safety Study aimed to examine/compare health-related quality of life (HRQoL) of older versus younger HSC donors. Sixty peripheral blood stem cell (PBSC) donors ages 18 to 60 years and 104 PBSC donors age >60 years completed validated questionnaires before donation and 4 weeks and 1 year after donation. Before donation, older donors had poorer general physical health (t = −3.27; P = .001) but better mental health (t = 2.11; P < .05). There were no age differences in multiple other donation-related factors. At 4 weeks after donation, there were no group differences in general physical/mental health, but older donors were less likely to report donation-related pain (t = −2.26; P < .05) and concerns (t = −3.38; P = .001). At both 4 weeks and 1 year after donation, there were no significant differences in the percentage of each age group feeling physically back to normal or in the number of days it took donors to feel completely well. There was no evidence that increasing age within the older donor group was associated with poorer donation-related HRQoL. Taken together, these data support the current practice of HSC donation by sibling donors above age 60, providing no evidence of worsening HRQoL up to 1 year after donation in individuals up to age 76.

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and idiopathic vulnerability for high MA preference and taking. We also confirmed that subchronic subtoxic MA experience elicits a hyperglutamatergic state within the NAC during protracted withdrawal, characterized by elevated metabotropic glutamate 1/5 receptor function and Homer2 receptor-scaffolding protein expression. A high MA-preferring phenotype was recapitulated by elevating endogenous glutamate within the NAC shell of mice and we reversed MA preference/taking by lowering endogenous glutamate and/or Homer2 expression within this subregion. Conclusions: Our data point to an idiopathic, genetic, or drug-induced hyperglutamatergic state within the NAC as a mediator of MA addiction vulnerability. © 2016 Society of Biological Psychiatry.


AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes the degradation of hepatic low-density lipoprotein (LDL) receptors (LDLR), thereby, decreasing hepatocyte LDL-cholesterol (LDL-C) uptake. However, it is unknown whether PCSK9 has effects on atherogenesis that are independent of lipid changes. The present study investigated the effect of human (h) PCSK9 on plasma lipids, hepatic lipogenesis, and atherosclerotic lesion size and composition in transgenic mice expressing hPCSK9 (hPCSK9tg) on wild-type (WT), LDLR(-)/(-), or apoE(-)/(-) background. METHODS AND RESULTS: hPCSK9 expression significantly increased plasma cholesterol (+91%), triglycerides (+18%), and apoB (+57%) levels only in WT mice. The increase in plasma lipids was a consequence of both decreased hepatic LDLR and increased hepatic lipid production, mediated transcriptionally and post-transcriptionally by PCSK9 and dependent on both LDLR and apoE. Despite the lack of changes in plasma lipids in mice expressing hPCSK9 and lacking LDLR (the main target for PCSK9) or apoE (a canonical ligand for the LDLR), hPCSK9 expression increased aortic lesion size in the absence of apoE (268 655 +/- 97 972 microm(2) in hPCSK9tg/apoE(-)/(-) vs. 189 423 +/- 65 700 microm(2) in apoE(-)/(-)) but not in the absence of LDLR. Additionally, hPCSK9 accumulated in the atheroma and increased lesion Ly6C(hi) monocytes (by 21%) in apoE(-)/(-) mice, but not in LDLR(-)/(-) mice.

CONCLUSIONS: PCSK9 increases hepatic lipid and lipoprotein production via apoE- and LDLR-dependent mechanisms. However, hPCSK9 also accumulate in the artery wall and directly affects atherosclerosis lesion size and composition independently of such plasma lipid and lipoprotein changes. These effects of hPCSK9 are dependent on LDLR but are independent of apoE.


BACKGROUND: Loop diuretic resistance is a common barrier to effective decongestion in acute heart failure (AHF), and is associated with poor outcome. Specific mechanisms underlying diuretic resistance are currently unknown in contemporary AHF patients. We therefore aimed to determine the relative importance of defects in diuretic delivery vs. renal tubular response in determining diuretic response (DR) in AHF. METHODS AND RESULTS: Fifty AHF patients treated with intravenous bumetanide underwent a 6-h timed urine collection for
sodium and bumetanide clearance. Whole-kidney DR was defined as sodium excreted per doubling of administered loop diuretic and represents the sum of defects in drug delivery and renal tubular response. Tubular DR, defined as sodium excreted per doubling of renally cleared (urinary) loop diuretic, captures resistance specifically in the renal tubule. Median administered bumetanide dose was 3.0 (2.0–4.0) mg with 52 (33–77)% of the drug excreted into the urine. Significant between-patient variability was present as the administered dose only explained 39% of variability in the quantity of bumetanide in urine. Cumulatively, factors related to drug delivery such as renal bumetanide clearance, administered dose, and urea clearance explained 28% of the variance in whole-kidney DR. However, resistance at the level of the renal tubule (tubular DR) explained 71% of the variability in whole-kidney DR. CONCLUSION: Defects at the level of the renal tubule are substantially more important than reduced diuretic delivery in determining diuretic resistance in patients with AHF.


Background The goal of this study was to compare the safety and effectiveness of individual antiembolic interventions in nonvalvular atrial fibrillation (AF): novel oral anticoagulants (NOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban); vitamin K antagonists (VKA); aspirin; and the Watchman device. Methods and Results A network meta-analysis of randomized, clinical trials (RCTs) was performed. RCTs that included patients with prosthetic cardiac valves or mitral stenosis, mean or median follow-up <6 months, <200 participants, without published report in English language, and NOAC phase II studies were excluded. The placebo/control arm received either placebo or no treatment. The primary efficacy outcome was the combination of stroke (of any type) and systemic embolism. All-cause mortality served as a secondary efficacy outcome. The primary safety outcome was the combination of major extracranial bleeding and intracranial hemorrhage. A total of 21 RCTs (96 017 nonvalvular AF patients; median age, 72 years; 65% males; median follow-up, 1.7 years) were included. In comparison to placebo/control, use of aspirin (odds ratio [OR], 0.75 [95% CI, 0.60-0.95]), VKA (0.38 [0.29-0.49]), apixaban (0.31 [0.22-0.45]), dabigatran (0.29 [0.20-0.43]), edoxaban (0.38 [0.26-0.54]), rivaroxaban (0.27 [0.18-0.42]), and the Watchman device (0.36 [0.16-0.80]) significantly reduced the risk of any stroke or systemic embolism in nonvalvular AF patients, as well as all-cause mortality (aspirin: OR, 0.82 [0.68-0.99]; VKA: 0.69 [0.57-0.85]; apixaban: 0.62 [0.50-0.78]; dabigatran: 0.62 [0.50-0.78]; edoxaban: 0.62 [0.50-0.77]; rivaroxaban: 0.58 [0.44-0.77]; and the Watchman device: 0.47 [0.25-0.88]). Apixaban (0.89 [0.80-0.99]), dabigatran (0.90 [0.82-0.99]), and edoxaban (0.89 [0.82-0.96]) reduced risk of all-cause death as compared to VKA. Conclusions--The entire spectrum of therapy to prevent thromboembolism in nonvalvular AF significantly reduced stroke/systemic embolism events and mortality. © 2016 The Authors.


Dietary potassium deficiency activates thiazide-sensitive sodium chloride cotransport along the distal nephron. This may explain, in part, the hypertension and cardiovascular mortality observed in individuals who consume a low-potassium diet. Recent data suggest that plasma potassium affects the distal nephron directly by influencing intracellular chloride, an inhibitor of the with-no-lysine kinase (WNK)-Ste20p-related proline- and alanine-rich kinase (SPAK) pathway. As previous studies used extreme dietary manipulations, we sought to determine whether the relationship between potassium and NaCl cotransporter (NCC) is physiologically relevant and clarify the mechanisms involved. We report that modest changes in both dietary and plasma potassium affect NCC in vivo. Kinase assay studies showed that chloride inhibits WNK4 kinase activity at lower concentrations than it inhibits activity of WNK1 or WNK3. Also, chloride inhibited WNK4 within the range of distal cell chloride concentration. Mutation of a previously identified WNK chloride-binding motif converted WNK4 effects on SPAK from inhibitory to stimulatory in mammalian cells. Disruption of this motif in WNKs 1, 3, and 4 had different effects on NCC, consistent with the three WNKs having different chloride sensitivities. Thus, potassium effects on NCC are graded within the physiological range,
which explains how unique chloride-sensing properties of WNK4 enable it to mediate effects of potassium on NCC in vivo.


Issue: Medical educators and educational researchers continue to improve their processes for managing medical student and program evaluation data using sound ethical principles. This is becoming even more important as curricular innovations are occurring across undergraduate and graduate medical education.

Dissemination of findings from this work is critical, and peer-reviewed journals often require an institutional review board (IRB) determination. Approach: IRB data repositories, originally designed for the longitudinal study of biological specimens, can be applied to medical education research. The benefits of such an approach include obtaining expedited review for multiple related studies within a single IRB application and allowing for more flexibility when conducting complex longitudinal studies involving large datasets from multiple data sources and/or institutions. In this paper, we inform educators and educational researchers on our analysis of the use of the IRB data repository approach to manage ethical considerations as part of best practices for amassing, pooling, and sharing data for educational research, evaluation, and improvement purposes.

Implications: Fostering multi-institutional studies while following sound ethical principles in the study of medical education is needed, and the IRB data repository approach has many benefits, especially for longitudinal assessment of complex multi-site data. © 2016 Erin K. Thayer et al.


Effectively treating addiction is a challenge among any population, and treatment for adolescents may be particularly challenging in the context of ongoing neurodevelopment, which may alter the brain’s initial response to substances as well as its response to treatment. One way to improve treatment outcomes for youth is to use a translational perspective that explicitly connects cognitive and neurodevelopmental fields with the field of behavioral therapies. This integrative approach is a potential first step to inform the correspondence between the neurocognitive and behavioral fields in youth addiction. This chapter seeks to provide context for neurocognitive treatment studies by first discussing recent structural and functional neuroimaging studies showing associations with substance use or behavioral addictions. Several regions of interest are then proposed that appear to also be associated with addiction treatment across multiple studies, namely, the accumbens/striatum, precuneus, insula, anterior cingulate cortex, and dorsolateral prefrontal cortex. This research suggests that reward, self-reflective, and executive control areas might be especially relevant in youth behavioral treatment response, and preliminary evidence suggests that existing treatments may encourage neurocognitive changes in these areas.


PURPOSE: To describe the retinal findings in two cases of Alport syndrome. METHODS: Observational case series. The clinical findings of the two patients were documented with color fundus photography and high resolution spectral domain optical coherence tomography. RESULTS: Patient 1 was found to have fleck retinopathy in both eyes, inner retinal thinning in the right eye and a full-thickness macular hole in the left eye. Patient 2 was found to have a full-thickness macular hole in the right eye as well as retinoschisis in the temporal macula in the right eye. The left eye revealed inner retinal thinning involving the fovea, a vitelliform lesion of the temporal macula and midperipheral retinoschisis involving multiple retinal layers.

CONCLUSION: Retinal abnormalities including fleck retinopathy, retinal thinning, macular holes, retinoschisis, and vitelliform lesions are variably present in Alport syndrome. This is only the second report of a vitelliform lesion in a patient with Alport syndrome and the first report of midperipheral retinoschisis. The array of
Retinal findings is believed to reflect a dysfunctional Type IV collagen present in the internal limiting membrane and Bruch membrane.

Tian, P., Ataer-Cansizoglu, E., Kalpathy-Cramer, J., Ostmo, S., Jonas, K., Chan, R. V. P., . . . Erdogmus, D. (2016). Toward a severity index for ROP: An unsupervised approach. Paper presented at the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2016. Retinopathy of prematurity (ROP) is a disease affecting low birth-weight infants and is the major cause of childhood blindness. Although accurate diagnosis is important, there is a high variability among expert decisions mostly due to subjective thresholds. Existing work focused on automated diagnosis of ROP. In this study, we construct a continuous severity index as an alternative to discrete classification. We follow an unsupervised approach by performing nonlinear dimensionality reduction. Instead of extracting several statistics of image features, each image is represented by the probability distribution of its features. The distance between distributions are then used in manifold learning methods as the distance between samples. The experiments are carried out on a dataset of 104 wide-angle retinal images. The results are promising and they reflect the challenges of the discrete classification. © 2016 IEEE.

BACKGROUND: G protein-gated inwardly rectifying potassium (GIRK) channels contribute to the effects of a number of drugs of abuse, including ethanol. However, the roles of individual subunits in the rewarding effects of ethanol are poorly understood. METHODS: We compare conditioned place preference (CPP) in GIRK3 subunit knock-out (GIRK3(-/-)), heterozygote (GIRK3(+/-)), and wild-type (WT) mice. In addition, the development of locomotor tolerance/sensitization and the effects of EtOH intoxication on associative learning (fear conditioning) are also assessed. RESULTS: Our data show significant EtOH CPP in GIRK3(-/-) and GIRK3(+/-) mice, but not in the WT littermates. In addition, we demonstrate that these effects are not due to differences in EtOH metabolism, the development of EtOH tolerance/sensitivity, or associative learning abilities. While there were no consistent genotype differences in the fear conditioning assay, our data do show a selective sensitization of the impairing effects of EtOH intoxication on contextual learning, but no effect on cued learning. CONCLUSIONS: These findings suggest that GIRK3 plays a role in EtOH reward. Furthermore, the selectivity of this effect suggests that GIRK channels could be an effective therapeutic target for the prevention and/or treatment of alcoholism.

BACKGROUND: Functional imaging by thoracic electrical impedance tomography (EIT) is a non-invasive approach to continuously assess central stroke volume variation (SVV) for guiding fluid therapy. The early available data were from healthy lungs without injury-related changes in thoracic impedance as a potentially influencing factor. The aim of this study was to evaluate SVV measured by EIT (SVVEIT) against SVV from pulse contour analysis (SVVPC) in an experimental animal model of acute lung injury at different lung volumes. METHODS: We conducted a randomized controlled trial in 30 anaesthetized domestic pigs. SVVEIT was calculated automatically analysing heart-lung interactions in a set of pixels representing the aorta. Each initial analysis was performed automatically and unsupervised using predefined frequency domain algorithms that had not previously been used in the study population. After baseline measurements in normal lung conditions, lung injury was induced either by repeated broncho-alveolar lavage (n=15) or by intravenous administration of oleic acid (n=15) and SVVEIT was remeasured. RESULTS: The protocol was completed in 28 animals. A total of 123 pairs of SVV measurements were acquired. Correlation coefficients (r) between SVVEIT and SVVPC were 0.77 in healthy lungs, 0.84 after broncho-alveolar lavage, and 0.48 after lung injury from oleic acid. CONCLUSIONS: EIT provides automated calculation of a dynamic preload index
of fluid responsiveness (SVVEIT) that is non-invasively derived from a central haemodynamic signal. However, alterations in thoracic impedance induced by lung injury influence this method.


Colorectal cancer and adenoma adjacent to cancer exhibit distinct microRNA (miRNA) alterations in an apparent mucosato-adenocarcinoma sequence. The pattern of microRNAs in screen-detected polyps in relation to histologic features and cancer risk has not been investigated. miRNA expression analysis was performed on normal mucosa (NM), hyperplastic polyps (HP), tubular adenomas (TA), tubulovilious adenomas or high-grade dysplasia (TVHG), and serrated polyps [sessile serrated adenoma/polyps (SSA/P) and traditional serrated adenomas (TSA)] in biopsy specimens from 109 patients undergoing screening/surveillance colonoscopy. Generalized linear models were used to identify differentially expressed miRNAs by histologic type and logistic regression to identify miRNA predictors of histopathology. False discovery rate (FDR) was used to control for multiple comparisons. We identified 99 miRNAs differing in at least one of five histopathologic groups (FDR ≤0.05). In a comparison of HPNM versus TVHG, the top most upregulated and downregulated miRNAs in HPNM included miR-145, -143, -107, -194, and -26a (upregulated), and miR-663, -1268, -320b, -1275, and -320b (downregulated; FDR P 0.05). miR-145 and -619 showed high accuracy to discriminate low-from highrisk polyps without serrated histology (TVHG vs. HPNM \+ TA; CI, 95.6%), whereas miR-124, -143, and -30a showed high accuracy of separating high-risk polyps (TVHG \+ TSA) from low-risk polyps (HPNM \+ TA \+ SSA/P; CI, 96.0%). For TSAs, miR-125b and -199a were uniquely downregulated relative to HPNMs, and miR-335, -222, and -214 discriminated between non-serrated and serrated histology. Our data support the presence of colorectal cancer-associated miRNA alterations in screen-detected adenomas that may be useful for risk stratification for surveillance interval planning. © 2016 American Association for Cancer Research.


Computerized cognitive training (CCT) may counter the impact of aging on cognition, but both the efficacy and neurocognitive mechanisms underlying CCT remain controversial. In this study, 35 older individuals were randomly assigned to Cogmed adaptive working memory (WM) CCT or an active control CCT, featuring five weeks of five ~40 min sessions per week. Before and after the 5-week intervention, event-related potentials were measured while subjects completed a visual n-back task with three levels of demand (0-back, 1-back, 2-back). The anterior P3a served as an index of directing attention and the posterior P3b as an index of categorization/WM updating. We hypothesized that adaptive CCT would be associated with decreased P3 amplitude at low WM demand and increased P3 amplitude at high WM demand. The adaptive CCT group exhibited a training-related increase in the amplitude of the anterior P3a and posterior P3b in response to target stimuli across n-back tasks, while subjects in the active control CCT group demonstrated a post-training decrease in the anterior P3a. Performance did not differ between groups or sessions. Larger overall P3 amplitudes were strongly associated with better task performance. Increased post-CCT P3 amplitude correlated with improved task performance; this relationship was especially robust at high task load. Our findings suggest that adaptive WM training was associated with increased orienting of attention, as indexed by the P3a, and the enhancement of categorization/WM updating processes, as indexed by the P3b. Increased P3 amplitude was linked to improved performance; however, there was no direct association between adaptive training and improved performance. © 2016 Tusch, Alperin, Ryan, Holcomb, Mohammed and Dafnner.

OBJECTIVES: The purpose of this study was to evaluate the accuracy of sonographic estimations of fetal weight (FW) and signed percent error between pregnant patients with and without diabetes mellitus (DM).

METHODS: We conducted a retrospective cohort study of all singleton nonanomalous live births who delivered after 34 weeks and received a sonographic estimation of FW within 2 weeks of delivery at the University of Cincinnati Medical Center between 2008 and 2011. Our primary outcome compared the DeltaFW and signed percent error between DM and non-DM pregnancies. Sensitivity and specificity were calculated for the prediction of FW greater than 4000 g in each study group. Linear regression analysis assessed correlation coefficients, R² values, and variance of the DeltaFW by live birth weight.

RESULTS: The mean DeltaFWs were 62 and 103 g for non-DM and DM pregnancies, respectively (P = .04). However, the signed percent error (mean +/- SD, 1.7% +/- 9.8% versus 2.6% +/- 9.9%; P = .15) was similar between the study groups. Linear regression comparing the DeltaFW to the live birth weight revealed a weak correlation in DM (r = 0.34; R² = 0.11) and non-DM pregnancies, (r = 0.17; R² = 0.03) pregnancies. Overall sensitivity for the prediction of FW greater than 4000 g was poor (0.41 and 0.62 in non-DM and DM pregnancies). However, the specificity was high (0.97 and 0.99 for both groups).

CONCLUSIONS: Although DM alters the biometric measurements of the fetus with increasing thoracoabdominal size, there are no clinically significant alterations in the accuracy of sonography for FW prediction when performed near delivery. Sonography is highly specific for birth weight greater than 4000 g, which is helpful for delivery planning and management.


Background: Fingernail psoriasis is difficult to treat. Objective: The objective was to evaluate the effect of ixekizumab, a monoclonal antibody selectively targeting IL-17A, on fingernail psoriasis. Methods: This Phase 3, double-blind trial (UNCOVER-3) randomized patients to placebo, etanercept (50-mg twice weekly), or 80 mg ixekizumab as one injection every 4 (IXE Q4W) or 2 weeks (IXE Q2W) after a 160-mg starting dose. At Week 12, ixekizumab patients received open-label IXE Q4W through Week 60; placebo patients received a 160-mg starting ixekizumab dose and etanercept patients a 4-week placebo washout before starting IXE Q4W. Efficacy was assessed by mean percent Nail Psoriasis Severity Index (NAPSI) improvement at Weeks 12 and 60. Results: Of 1346 patients in the UNCOVER-3 trial, this subgroup analysis included only patients with baseline fingernail psoriasis: 116 (60.1%) placebo, 236 (61.8%) etanercept, 228 (59.1%) IXE Q4W and 229 (59.5%) IXE Q2W. At Week 12, greater mean percent NAPSI improvements were achieved in IXE Q4W (36.7%) and IXE Q2W (35.2%) vs. placebo (-34.3%, P < 0.001 each comparison) and etanercept (20.0%, P = 0.048 vs. Q4W, P = 0.072 vs. Q2W). At Week 60, mean percent NAPSI improvement was >80% regardless of initial treatment. At Week 12 (nonresponder imputation), complete resolution (NAPSI = 0) was achieved in 19.7% (IXE Q4W), 17.5% (IXE Q2W), 4.3% (placebo, P < 0.001 each comparison) and 10.2% (etanercept, P < 0.05 each comparison) of patients. By Week 60, >50% of patients achieved complete resolution. Conclusions: At Week 12, significant improvements in fingernail psoriasis were achieved with ixekizumab therapy. With IXE Q4W maintenance dosing, additional improvement was demonstrated through 60 weeks, and >50% of patients achieved complete resolution. Registered at clinicaltrials.gov: NCT01646177 Journal of the European Academy of Dermatology and Venereology © 2016 European Academy of Dermatology and Venereology.
encodes an N-terminally truncated protein missing a predicted 254 amino acids. ΔN-ASPP2 suppresses p53 target gene transactivation, promoter occupancy, and endogenous p53 target gene expression in response to DNA damage. Moreover, ΔN-ASPP2 promotes progression through the cell cycle, as well as resistance to genotoxic stress-induced growth inhibition and apoptosis. Additionally, we found that ΔN-ASPP2 expression is increased in human breast tumors as compared to adjacent normal breast tissue; in contrast, ASPP2 is suppressed in the majority of these breast tumors. Together, our results provide insight into how this new ASPP2 isoform may play a role in regulating the ASPP2-p53 axis. © 2016.


Objective The neutrophil-to-lymphocyte ratio (NLR) has been used as a surrogate marker of systemic inflammation. We sought to investigate the association between NLR and wound healing in diabetic wounds. Methods The outcomes of 120 diabetic foot ulcers in 101 patients referred from August 2011 to December 2014 were examined retrospectively. Demographic, patient-specific, and wound-specific variables as well as NLR at baseline visit were assessed. Outcomes were classified as ulcer healing, minor amputation, major amputation, and chronic ulcer. Results The subjects' mean age was 59.4 ± 13.0 years, and 67 (66%) were male. Final outcome was complete healing in 24 ulcers (20%), minor amputation in 58 (48%) and major amputation in 16 (13%), and 22 chronic ulcers (18%) at the last follow-up (median follow-up time, 6.8 months). In multivariate analysis, higher NLR (odds ratio, 13.61; P = .01) was associated with higher odds of nonhealing. Conclusions NLR can predict odds of complete healing in diabetic foot ulcers independent of wound infection and other factors. © 2016 Society for Vascular Surgery


This study investigates if different diabetic treatment regimens affects diabetic foot ulcer healing. From January 2013 to December 2014, 107 diabetic foot ulcers in 85 patients were followed until wound healing, amputation or development of a non-healing ulcer at the last follow-up visit. Demographic data, diabetic treatment regimens, presence of peripheral vascular disease, wound characteristics and outcome were collected. Non-healing wound was defined as major or minor amputation or those who didn’t have complete healing until the last observation. Median age was 60.0 years (range: 31.1-90.1) and 58 cases (68.2%) were males. Twenty-four cases reached a complete healing (healing rate: 22.4%). Median follow-up period in subjects with classified as having chronic wounds was 6.0 months (range: 0.7-21.8). Insulin treatment was a part of diabetes management in 52 (61.2%) cases. Insulin therapy significantly increased the wound healing rate (30.3% [20/66 ulcers] vs. 9.8% [4/41 ulcers]) (P=0.013). In multivariate random-effect logistic regression model, adjusting for age, gender, smoking status, type of diabetes, hypertension, chronic kidney disease, peripheral arterial disease, oral hypoglycemic use, wound infection, involved side, presence of Charcot’s deformity, gangrene, osteomyelitis on x-ray, and serum hemoglobin A1C levels, insulin treatment was associated with a higher chance of complete healing (beta+/SE: 15.2+/6.1, P=0.013). Systemic insulin treatment can improve wound healing in diabetic foot ulcers after adjusting for multiple confounding covariates. This article is protected by copyright. All rights reserved.


OBJECTIVE: To identify psychiatric diagnoses and psychosocial factors associated with intentional male genital self-mutilation (GSM) of specific injury subtypes. METHODS: A search of MEDLINE, EMBASE, PsycINFO, PubMed, Web of Science and CINAHL for cases of GSM was conducted until December 2015, based on GSM and related terms. Cases were examined for injury subtype, psychiatric diagnosis and psychosocial factors. Chi-square analyses were employed to determine differences in frequency of such factors across injury subtypes. RESULTS: Data were obtained from 173 cases: genital mutilation (n=21), penile amputation (n=62), castration (n=56) and combined amputation/castration (n=34). Common psychiatric disorders included schizophrenia spectrum (49%), substance use (18.5%), personality (15.9%) and gender dysphoric disorders (15.3%). Chi-square analyses revealed that schizophrenia spectrum disorders occurred significantly more often among auto-amputes as compared with self-castrators or mutilators. Gender dysphoria occurred significantly more often among self-castrators than auto-amputes. No significant differences emerged regarding psychosocial factors across GSM subtypes. However, associations were observed between psychosocial factors and psychiatric diagnoses. Although altogether not commonly
reported, experiential factors were reported in 82% of psychotic individuals. Treatment inaccessibility was noted among 71% of gender dysphorics engaging in auto-castration. CONCLUSION: Clinicians must consider the diverse range of psychiatric disorders and psychosocial factors underlying GSM.


In this essay, I borrow the idea of universal precautions from infection control and suggest that family physicians use a set of considerations, based on the mnemonic UNIVERSAL, to nurture cultural humility, enter a metaphorical “space-in-between” in cross-cultural encounters, and foster global fluency. These UNIVERSAL considerations I base on my experiences in global family medicine, attending to economically poor and socially marginalized patients in both international and domestic settings. They are informed by readings in transcultural psychiatry, medical anthropology, development studies, and primary care. I invite others involved in global family medicine to reflect on what they have learned along their own professional paths, so as to enhance their therapeutic abilities as global family physicians, wherever they may be.


Fanconi anemia (FA) is an autosomal recessive not, multisystem DNA repair disorder with prominent defects in hematopoietic stem cell maintenance that result in their progressive attrition and failure in early school age. Allogeneic stem cell transplantation has proved curative for patients with suitable donors. This, along with the characteristic survival advantage of phenotypically normal over non-corrected FA stem cells underscores the compelling rationale for stem cell gene therapy in FA. While integrating lentiviral vectors (LV) have become the preferred platform for genetic correction in several hematologic and immunodeficiency disorders, the residual oncogenic potential by these vectors raises concerns in FA stem cells with potentially preexisting genetic lesions. On this backdrop, investigators are developing a new generation of non-integrating viral vectors capable of nuclear persistence through serial mitotic cycles and stable under selection to offset the comparatively lower transduction rates. Here, we review the competing approaches to develop such non-integrating lentiviral (NILV) episome vectors that faithfully replicate in stem cells.


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Polyphosphate is an inorganic polymer that can potentiate several interactions in the blood coagulation system. Blood platelets contain polyphosphate, and the secretion of platelet-derived polyphosphate has been associated with increased thrombus formation and activation of coagulation factor XII. However, the small polymer size of secreted platelet polyphosphate limits its capacity to activate factor XII in vitro. Thus, the mechanism by which platelet polyphosphate contributes to thrombus formation remains unclear. Using live-cell imaging, confocal- and electron microscopy, we show that activated platelets expose polyphosphate on their cell surface. The apparent polymer size of membrane-associated polyphosphate largely exceeds that of secreted polyphosphate. Ultracentrifugation fractionation experiments revealed that membrane-associated platelet polyphosphate is condensed into insoluble spherical nanoparticles with divalent metal ions. In contrast to soluble polyphosphate, membrane-associated polyphosphate nanoparticles potently activate factor XII. Our findings identify the presence of membrane-associated polyphosphate in a nanoparticle state on the surface of activated platelets. We propose that these polyphosphate nanoparticles mechanistically link the procoagulant activity of platelets with the activation of coagulation factor XII.

Purpose For inoperable stage I (T1-T2N0) small cell lung cancer (SCLC), national guidelines recommend chemotherapy with or without conventionally fractionated radiation therapy. The present multi-institutional cohort study investigated the role of stereotactic ablative radiation therapy (SABR) for this population.

Methods and Materials The clinical and treatment characteristics, toxicities, outcomes, and patterns of failure were assessed in patients with histologically confirmed stage T1-T2N0 SCLC. Kaplan-Meier analysis was used to evaluate the survival outcomes. Univariate and multivariate analyses identified predictors of outcomes. Results From 24 institutions, 76 lesions were treated in 74 patients (median follow-up 18 months). The median age and tumor size was 72 years and 2.5 cm, respectively. Chemotherapy and prophylactic cranial irradiation were delivered in 56% and 23% of cases, respectively. The median SABR dose and fractionation was 50 Gy and 5 fractions. The 1- and 3-year local control rate was 97.4% and 96.1%, respectively. The median disease-free survival (DFS) duration was 49.7 months. The DFS rate was 58.3% and 53.2% at 1 and 3 years, respectively. The median, 1-year, and 3-year disease-specific survival was 52.3 months, 84.5%, and 64.4%, respectively. The median, 1-year, and 3-year overall survival (OS) was 17.8 months, 69.9%, and 34.0% respectively. Patients receiving chemotherapy experienced an increased median DFS (61.3 vs 9.0 months; P=.02) and OS (31.4 vs 14.3 months; P=.02). The receipt of chemotherapy independently predicted better outcomes for DFS/OS on multivariate analysis (P=.01). Toxicities were uncommon; 5.2% experienced grade ≥2 pneumonitis. Post-treatment failure was most commonly distant (45.8% of recurrence), followed by nodal (25.0%) and “elsewhere lung” (20.8%). The median time to each was 5 to 7 months. Conclusions From the findings of the largest report of SABR for stage T1-T2N0 SCLC to date, SABR (≥50 Gy) with chemotherapy should be considered a standard option. © 2016


Purpose To report two cases of pediatric choroidal neovascularization (CNV) and the associated neovascular and retinal findings identified on Optical Coherence Tomography Angiography (OCTA) imaging. Methods A 14-year-old boy with handheld laser-induced maculopathy-related CNV and a 13-year-old boy with idiopathic CNV were evaluated with visual acuity testing, slit-lamp exam, fundus photography, fluorescein angiography, indocyanine green angiography, spectral domain optical coherence tomography, and OCTA. Results Macular CNV were identified in both pediatric patients using OCTA imaging. The first case demonstrated a classic pediatric type II CNV with a “tree-like” pattern and a single vessel in-growth site, while the second case demonstrated a type I CNV with a “glomerular” pattern. Conclusion Distinct choroidal neovascular patterns were visualized in these two cases of pediatric CNV when compared to adult subtypes. OCTA is a noninvasive imaging modality capable of evaluating and characterizing pediatric CNV and their associated vascular patterns. © 2016 The Authors


Background: Text message interventions are feasible, preferable, and sometimes effective for youth with diabetes. However, few, if any studies, have examined the personalized use of text messages with youth repeatedly hospitalized for diabetic ketoacidosis (DKA) and their caregivers. This study characterizes the use of personalized text messages in Novel Interventions in Children’s Healthcare (NICH). Methods: Approximately 2 months of text messages sent to youth with repeat DKA and their caregivers were logged regarding the following text characteristics: (1) content, (2) intervention type, (3) timing, and (4) recipient characteristics. Results: NICH interventionists sent 2.3 and 1.5 texts per day to patients and caregivers, respectively. Approximately 59% of outgoing texts occurred outside of typical business hours, and roughly 68% of texts contained some form of support and/or encouragement. The relation between type of intended intervention and day/time of text was significant, χ2(2, N = 5,808) = 266.93, P <.001. Interventionists were more likely to send behavioral intervention text messages outside of business hours, whereas they were more likely to send care coordination and case management text messages during business hours. Conclusions: To our knowledge, this is the first study to specifically categorize and describe the personalized
use of text messages with youth repeatedly hospitalized for DKA and their caregivers. Findings indicate that a promising treatment program for these youth frequently used text interventions to deliver praise and encouragement to patients and caregivers alike, often outside of typical business hours, and tailored text content based on patient and caregiver characteristics. © 2015 Diabetes Technology Society.


**OBJECTIVE:** This study’s objective was to evaluate the effect of two common components of meditation (mindfulness and slow breathing) on potential mechanistic pathways. **METHODS:** A total of 102 combat veterans with posttraumatic stress disorder (PTSD) were randomized to (a) the body scan mindfulness meditation (MM), (b) slow breathing (SB) with a biofeedback device, (c) mindful awareness of the breath with an intention to slow the breath (MM+SB), or (d) sitting quietly (SQ). Participants had 6 weekly one-on-one sessions with 20 minutes of daily home practice. The mechanistic pathways and measures were as follows: (a) autonomic nervous system (hyperarousal symptoms, heart rate [HR], and heart rate variability [HRV]); (b) frontal cortex activity (attentional network task [ANT] conflict effect and event-related negativity and intrusive thoughts); and (c) hypothalamic-pituitary-adrenal axis (awakening cortisol). PTSD measures were also evaluated. **RESULTS:** Meditation participants had significant but modest within-group improvement in PTSD and related symptoms, although there were no effects between groups. Perceived impression of PTSD symptom improvement was greater in the meditation arms compared with controls. Resting respiration decreased in the meditation arms compared with SQ. For the mechanistic pathways, (a) subjective hyperarousal symptoms improved within-group (but not between groups) for MM, MM+SB, and SQ, while HR and HRV did not; (b) intrusive thoughts decreased in MM compared with MM+SB and SB, while the ANT measures did not change; and (c) MM had lower awakening cortisol within-group (but not between groups).

**CONCLUSION:** Treatment effects were mostly specific to self-report rather than physiological measures. Continued research is needed to further evaluate mindfulness meditation’s mechanism in people with PTSD.


Given shifting trends of religious identities in the USA, better understanding the impact of patients’ religious identities on health-related quality of life (QOL) may help tailor the use of psychological interventions. Men with prostate cancer (N = 43) completed measures of quality of life (QOL), spiritual well-being in two domains (i.e., Faith and Meaning/Peace), psychological state, and psychological trait before undergoing radiotherapy. We hypothesized that (1) higher existential Meaning/Peace would correlate with higher QOL and psychological trait protective factors (e.g., Agreeableness) and that (2) higher existential Meaning/Peace would correlate with lower depression, anxiety, and Neuroticism (i.e., a psychological trait risk factor). We did not anticipate similar relationships between religious Faith and QOL, depression, anxiety, or psychological traits and consider related analyses to be exploratory in nature. Meaning/Peace was indeed negatively associated with depression, anxiety, and Neuroticism. Meaning/Peace was positively correlated with Physical, Social, Functional, and Emotional well-being, as well as Extraversion. Religious Faith was positively associated with Functional well-being, but not the other state, trait, or QOL domains. In sum, prostate cancer patients’ sense of existential Meaning/Peace prior to radiotherapy was associated with well-being in many domains, whereas religious Faith appeared less so.


The Developmental Origins of Health and Disease and the related science of epigenetics redefines the meaning of what constitutes upstream approaches to significant social and public health problems. An increasingly frequent concept being expressed is “When it comes to your health, your zip code may be more important than your genetic code”. Epigenetics explains how the environment-our zip code-literally gets under our skin, creates biological changes that increase our vulnerability for disease, and even children’s
prospects for social success, over their life course and into future generations. This science requires us to rethink where disease comes from and the best way to promote health. It identifies the most fundamental social equity issue in our society: that initial social and biological disadvantage, established even prior to birth, and linked to the social experience of prior generations, is made worse by adverse environments throughout the life course. But at the same time, it provides hope because it tells us that a concerted focus on using public policy to improve our social, physical, and economic environments can ultimately change our biology and the trajectory of health and social success into future generations.


Genetic factors significantly affect vulnerability to alcohol dependence (alcoholism). We previously identified quantitative trait loci on distal mouse chromosome 1 with large effects on predisposition to alcohol physiological dependence and associated withdrawal following both chronic and acute alcohol exposure in mice (Alcdp1 and Alcw1, respectively). We fine-mapped these loci to a 1.1-1.7 Mb interval syntenic with human 1q23.2-23.3. Alcw1/Alcdp1 interval genes show remarkable genetic variation among mice derived from the C57BL/6J and DBA/2J strains, the two most widely studied genetic animal models for alcohol-related traits. Here, we report the creation of a novel recombinant Alcw1/Alcdp1 congenic model (R2) in which the Alcw1/Alcdp1 interval from a donor C57BL/6J strain is introgressed onto a uniform, inbred DBA/2J genetic background. As expected, R2 mice demonstrate significantly less severe alcohol withdrawal compared to wild-type littermates. Additionally, comparing R2 and background strain animals, as well as reciprocal congenic (R8) and appropriate background strain animals, we assessed Alcw1/Alcdp1 dependent brain gene expression using microarray and quantitative PCR analyses. To our knowledge this includes the first Weighted Gene Co-expression Network Analysis using reciprocal congenic models. Importantly, this allows detection of co-expression patterns limited to one or common to both genetic backgrounds with high or low predisposition to alcohol withdrawal severity. The gene expression patterns (modules) in common contain genes related to oxidative phosphorylation, building upon human and animal model studies that implicate involvement of oxidative phosphorylation in alcohol use disorders (AUDs). Finally, we demonstrate that administration of N-acetylcysteine, an FDA-approved antioxidant, significantly reduces symptoms of alcohol withdrawal (convulsions) in mice, thus validating a phenotypic role for this network. Taken together, these studies support the importance of mitochondrial oxidative homeostasis in alcohol withdrawal and identify this network as a valuable therapeutic target in human AUDs.


Airway management is an important component of resuscitation from out-of-hospital cardiac arrest (OHCA). The optimal approach to advanced airway management is unknown. The Pragmatic Airway Resuscitation Trial (PART) will compare the effectiveness of endotracheal intubation (ETI) and Laryngeal Tube (LT) insertion upon 72-h survival in adult OHCA. Encompassing United States Emergency Medical Services agencies affiliated with the Resuscitation Outcomes Consortium (ROC), PART will use a cluster-crossover randomized design. Participating subjects will include adult, non-traumatic OHCA requiring bag-valve-mask ventilation. Trial interventions will include (1) initial airway management with ETI and (2) initial airway management with LT. The primary and secondary trial outcomes are 72-h survival and return of spontaneous circulation. Additional clinical outcomes will include airway management process and adverse events. The trial will enroll a total of 3000 subjects. Results of PART may guide the selection of advanced airway management strategies in OHCA.

Stroke induces a catastrophic immune response that involves the global activation of peripheral leukocytes, especially T cells. The human leukocyte antigen-DRα1 domain linked to MOG-35-55 peptide (DRα1-MOG-35-55) is a partial major histocompatibility complex (MHC) class II construct which can inhibit neuroantigen-specific T cells and block binding of the cytokine/chemokine macrophage migration inhibitory factor (MIF) to its CD74 receptor on monocytes and macrophages. Here, we evaluated the therapeutic effect of DRα1-MOG-35-55 in a mouse model of permanent distal middle cerebral artery occlusion (dMCAO). DRα1-MOG-35-55 was administered to WT C57BL/6 mice by subcutaneous injection starting 4 h after the onset of ischemia followed by three daily injections. We demonstrated that DRα1-MOG-35-55 post treatment significantly reduced brain infarct volume, improved functional outcomes, and inhibited the accumulation of CD4+ and CD8+ T cells and expression of pro-inflammatory cytokines in the ischemic brain 96 h after dMCAO. In addition, DRα1-MOG-35-55 treatment shifted microglia/macrophages in the ischemic brain to a beneficial M2 phenotype without changing their total numbers in the brain or blood. This study demonstrates for the first time the therapeutic efficacy of the DRα1-MOG-35-55 construct in dMCAO across MHC class II barriers in C57BL/6 mice. This MHC-independent effect obviates the need for tissue typing and will thus greatly expedite treatment with DRα1-MOG-35-55 in human stroke subjects. Taken together, our findings suggest that DRα1-MOG-35-55 treatment may reduce ischemic brain injury by regulating post-stroke immune responses in the brain and the periphery. © 2016 Springer Science+Business Media New York


The recruitment of motoneurons during force generation follows a general pattern that has been confirmed across diverse species [1-3]. Motoneurons are recruited systematically according to synaptic inputs and intrinsic cellular properties and corresponding to movements of different intensities. However, much less is known about the output properties of individual motoneurons and how they affect the translation of motoneuron recruitment to the strength of muscle contractions. In larval zebrafish, spinal motoneurons are recruited in a topographic gradient according to their input resistance (Rin) at different swimming strengths and speeds. Whereas dorsal, lower-Rin primary motoneurons (PMns) are only activated during behaviors that involve strong and fast body bends, more ventral, higher-Rin secondary motoneurons (SMns) are recruited during weaker and slower movements [4-6]. Here we perform in vivo paired recordings between identified spinal motoneurons and skeletal muscle cells in larval zebrafish. We characterize individual motoneuron outputs to single muscle cells and show that the strength and reliability of motoneuron outputs are inversely correlated with motoneuron Rin. During repetitive high-frequency motoneuron drive, PMn synapses undergo depression, whereas SMn synapses potentiate. We monitor muscle cell contractions elicited by single motoneurons and show that the pattern of motoneuron output strength and plasticity observed in electrophysiological recordings is reflected in muscle shortening. Our findings indicate a link between the recruitment pattern and output properties of spinal motoneurons that can together generate


In pyramidal neurons such as hippocampal area CA1 and basolateral amygdala, a slow afterhyperpolarization (sAHP) follows a burst of action potentials, which is a powerful regulator of neuronal excitability. The sAHP amplitude increases with aging and may underlie age related memory decline. The sAHP is due to a Ca(2+)-dependent, voltage-independent K(+) channel, IK1 (KCNN4) as the sAHP channel in CA1 pyramidal neurons. The signature pharmacology of IK1, blockade by TRAM-34, was reported for the sAHP and underlying current. We have examined the sAHP and find no evidence that TRAM-34 affects either the current underlying the sAHP or excitability of CA1 or basolateral amygdala pyramidal neurons. In addition, CA1 pyramidal neurons from IK1 null mice exhibit a characteristic sAHP current. Our results indicate that IK1 channels do not mediate the sAHP in pyramidal neurons.
appropriate intensities for muscle contractions. We demonstrate that motoneuron output properties provide an additional peripheral mechanism for graded locomotor control at the neuromuscular junction.


Altered macroscopic anatomical characteristics of the cerebral cortex have been identified in individuals affected by various neurodevelopmental disorders. However, the cellular developmental mechanisms that give rise to these abnormalities are not understood. Recently, advances in image reconstruction of diffusion magnetic resonance imaging (diffusion MRI) have made possible high resolution in utero measurements of water diffusion anisotropy in the fetal brain. Here, diffusion anisotropy within the developing fetal cerebral cortex is longitudinally characterized in the rhesus macaque, focusing on gestation days (G) 85 through G135 of the 165 day term. Additionally, for subsets of animals characterized at G90 and G135, immunohistochemical staining was performed, and 3D structure tensor analyses were used to identify the cellular processes that most closely parallel changes in water diffusion anisotropy with cerebral cortical maturation. Strong correlations were found between maturation of dendritic arbors on the cellular level, and the loss of diffusion anisotropy with cortical development. In turn, diffusion anisotropy changes were strongly associated both regionally and temporally with cortical folding. Notably, the regional and temporal dependence of diffusion anisotropy and folding were distinct from the patterns observed for cerebral cortical surface area expansion. These findings strengthen the link proposed in previous studies between cellular-level changes in dendrite morphology and non-invasive diffusion MRI measurements of the developing cerebral cortex, and support the possibility that, in gyroencephalic species, structural differentiation within the cortex is coupled to the formation of gyri and sulci. SIGNIFICANCE STATEMENT: Abnormal brain morphology has been found in populations with neurodevelopmental disorders. However, the mechanisms linking cellular level and macroscopic maturation are poorly understood, even in normal brains. This study contributes new understanding to this subject using serial in utero MRI measurements of rhesus macaque fetuses, from which macroscopic and cellular information can be derived. We found that morphological differentiation of dendrites was strongly associated both regionally and temporally with folding of the cerebral cortex. Interestingly, parallel associations were not observed with cortical surface area expansion. These findings support the possibility that perturbed morphological differentiation of cells within the cortex may underlie abnormal macroscopic characteristics of individuals affected by neurodevelopmental disorders.


The importance of the Gallus gallus (chicken) as a model organism and agricultural animal merits a continuation of sequence assembly improvement efforts. We present a new version of the chicken genome assembly (Gallus_gallus-5.0, GCA_000002315.3), built from combined long single molecule sequencing technology, finished BACs, and improved physical maps. In overall assembled bases, we see a gain of 183 Mb, including 16.4 Mb in placed chromosomes with a corresponding gain in the percentage of intact repeat elements characterized. Of the 1.21 Gb genome, we include three previously missing autosomes, GGA30, 31, and 33, and improve sequence contig length 10-fold over the previous Gallus_gallus-4.0. Despite the significant base representation improvements made, 138 Mb of sequence is not yet located to chromosomes. When annotated for gene content, Gallus_gallus-5.0 shows an increase of 4679 annotated genes (2768 noncoding and 1911 protein-coding) over those in Gallus_gallus-4.0. We also revisited the question of what genes are missing in the avian lineage, as assessed by the highest quality avian genome assembly to date, and found that a large fraction of the original set of missing genes are still absent in sequenced bird species. Finally, our new data support a detailed map of MHC-B, encompassing two segments: one with a highly stable gene copy number and another in which the gene copy number is highly variable. The chicken model has been a critical resource for many other fields of study, and this new reference assembly will substantially further these efforts. © 2017 Warren et al.

**BACKGROUND:** High-dose opioids prescribed for the treatment of chronic pain have been associated with increased risk of opioid overdose. Health systems and states have responded by developing opioid dose limitation policies. Little is known about how these policies affect prescribing practices or characteristics of patients who respond best to opioid tapers from high-dose opioids. **METHODS:** We conducted a retrospective cohort study to evaluate change in total opioid dose after the implementation of a provider education intervention and a 120 mg morphine equivalents per day (MED) opioid dose limitation policy in one academic primary care clinic. We compared opioid prescriptions 1 year before and 1 year after the intervention. We used univariate and multivariate logistic regression to assess which patient characteristics predicted opioid dose reduction from high opioid dose. **RESULTS:** Out of a total of 516 patients prescribed chronic opioid therapy, 116 patients (22%) were prescribed high-dose opioid therapy (>120 mg MED). After policy adoption, the average daily dose of opioids declined by 64 mg MED (95% confidence interval [CI]: 32-96; P < .001) and 41 patients (37%) on high-dose opioids tapered their doses below 120 mg MED (Tapered to Safer Dose group). In multivariate analyses, female sex was the only significant association with dose taper; female patients were less likely to taper to a safer dose (adjusted odds ratio [aOR] = 0.28, 95% CI: 0.11-0.70). **CONCLUSIONS:** A combined intervention of education and a practice policy that limits opioid doses for patients prescribed chronic opioid therapy may be an important component of system-level strategies to reduce opioid misuse and overdose; it may also help identify patients suitable for medication-assisted treatment for opioid use disorder. Specific strategies may be needed to assist women with opioid dose tapers.


**Background:** Recent guidelines recommend a systolic blood pressure (SBP) goal of less than 150 mm Hg for adults aged 60 years or older, but the balance of benefits and harms is unclear in light of newer evidence. **Purpose:** To systematically review the effects of more versus less intensive BP control in older adults. **Data Sources:** Multiple databases through January 2015 and MEDLINE to September 2016. **Study Selection:** 21 randomized, controlled trials comparing BP targets or treatment intensity, and 3 observational studies that assessed harms. **Data Extraction:** Two investigators extracted data, assessed study quality, and graded the evidence using published criteria. **Data Synthesis:** Nine trials provided high-strength evidence that BP control to less than 150/90 mm Hg reduces mortality (relative risk [RR], 0.90 [95% CI, 0.83 to 0.98]), cardiac events (RR, 0.77 [CI, 0.68 to 0.89]), and stroke (RR, 0.74 [CI, 0.65 to 0.84]). Six trials yielded low- to moderate-strength evidence that lower targets (<140/85 mm Hg) are associated with marginally significant decreases in cardiac events (RR, 0.82 [CI, 0.64 to 1.00]) and stroke (RR, 0.79 [CI, 0.59 to 0.99]) and nonsignificantly fewer deaths (RR, 0.86 [CI, 0.69 to 1.06]). Low- to moderate-strength evidence showed that lower BP targets do not increase falls or cognitive impairment. **Limitation:** Data relevant to frail elderly adults and the effect of multimorbidity are limited. **Conclusion:** Treatment to at least current guideline standards for BP (<150/90 mm Hg) substantially improves health outcomes in older adults. There is less consistent evidence, largely from 1 trial targeting SBP less than 120 mm Hg, that lower BP targets are beneficial for high-risk patients. Lower BP targets did not increase falls or cognitive decline but are associated with hypotension, syncope, and greater medication burden. Primary Funding Source: U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. (PROSPERO 2015: CRD42015017677).

Heterozygous Neurofibromatosis 1 (NF1) loss of function mutations occur in approximately 90% of patients with neurofibromatosis. A major, disabling phenotypic consequence of reduced NF1 function is cognitive impairment; a possibly related behavioral phenotype is impaired sleep. Recent results in Drosophila have demonstrated a genetic interaction between Anaplastic Lymphoma Kinase (Alk) and NF1 for both associative learning and sleep. Inhibition of Alk improves associative learning and sleep in heterozygous NF1 mutant flies. The results in Drosophila provide a strong motivation to investigate NF1/Alk genetic interactions in mice. In Drosophila, activation of Alk by its ligand, Jelly belly (Jeb), is the physiologically relevant target of negative regulation by NF1. Therefore, we tested whether genetic inhibition of Alk in heterozygous NF1 mutant mice attenuates or rescues cognitive impairments in mice. Our results are consistent with the hypothesis that NF1 functions in mice biochemically to inhibit signaling from Alk through Ras. The cognitive phenotypes observed in heterozygous NF1 mutant mice are rescued or ameliorated by genetic inhibition of Alk activity. In two tests of hippocampus-dependent learning, the Morris water maze and extinction of contextual fear, mutation of one or both alleles of Alk was sufficient to improve performance to wild type or near wild type levels in NF1-/+ mice. In addition, in NF1 mice genetic inhibition of Alk improves circadian activity levels. These data are intriguing in light of the circadian alterations seen in NF1 patients and indicate that inhibition of Alk activity may cognitively benefit patients with Neurofibromatosis 1.


Pityriasis rosea (PR) is an acute exanthematous skin disease that is likely due to reactivation of human herpesviruses (HHVs) 6b and 7. In contrast to herpes simplex and zoster (alphaherpesviruses), HHV-6b and -7 (betaherpesviruses) are not found predominantly in skin lesions. This difference in virion location may decrease the possibility of causing central nervous system infection through skin contamination, but the risk for hematogenous spread likely remains the same. This article uses the first-known epidural placement through active PR to illustrate risk-benefit considerations when deciding between neuraxial and general anesthesia for obstetric patients with PR.


National guidelines call for health care organizations to provide around-the-clock coaching for medical error disclosure. However, frontline clinicians may not always seek risk managers for coaching. As part of a demonstration project designed to improve patient safety and reduce malpractice liability, we trained multidisciplinary disclosure coaches at 8 health care organizations in Washington State. The training was highly rated by participants, although not all emerged confident in their coaching skill. This multisite intervention can serve as a model for other organizations looking to enhance existing disclosure capabilities. Success likely requires cultural change and repeated practice opportunities for coaches.


BACKGROUND: Understanding the relationship between alcohol abuse, a common and theoretically modifiable condition, and the most common cause of death in the world, cardiovascular disease, may inform potential prevention strategies. OBJECTIVES: The study sought to investigate the associations among alcohol abuse and atrial fibrillation (AF), myocardial infarction (MI), and congestive heart failure (CHF). METHODS: Using the Healthcare Cost and Utilization Project database, we performed a longitudinal analysis of California residents >/=21 years of age who received ambulatory surgery, emergency, or inpatient medical care in California between 2005 and 2009. We determined the risk of an alcohol abuse diagnosis on incident AF, MI, and CHF. Patient characteristics modifying the associations and population-attributable risks were determined. RESULTS: Among 14,727,591 patients, 268,084 (1.8%) had alcohol abuse. After multivariable adjustment, alcohol abuse was associated with an increased risk of incident AF (hazard ratio [HR]: 2.14; 95% confidence interval [CI]: 2.08 to 2.19; p < 0.0001), MI (HR: 1.45; 95% CI: 1.40 to 1.51; p < 0.0001), and CHF
(HR: 2.34; 95% CI: 2.29 to 2.39; p < 0.0001). In interaction analyses, individuals without conventional risk factors for cardiovascular disease exhibited a disproportionately enhanced risk of each outcome. The population-attributable risk of alcohol abuse on each outcome was of similar magnitude to other well-recognized modifiable risk factors. CONCLUSIONS: Alcohol abuse increased the risk of AF, MI, and CHF to a similar degree as other well-established risk factors. Those without traditional cardiovascular risk factors are disproportionately prone to these cardiac diseases in the setting of alcohol abuse. Thus, efforts to mitigate alcohol abuse might result in meaningful reductions in cardiovascular disease.


An estimated 40,000 deaths will be attributed to breast cancer in 2016, underscoring the need for improved therapies. Evading cell death is a major hallmark of cancer, driving tumor progression and therapeutic resistance. To evade apoptosis, cancers use anti-apoptotic Bcl-2 proteins to bind to and neutralize apoptotic activators, such as Bim. Investigation of anti-apoptotic Bcl-2 family members in clinical breast cancer datasets, revealed greater expression and more frequent gene amplification of MCL1 as compared to BCL2 or BCL2L1 (Bcl-xL) across three major molecular breast cancer subtypes, Luminal (A and B), HER2-enriched, and Basal-like. While Mcl-1 protein expression was elevated in estrogen receptor alpha (ERAlpha)-positive and ERAlpha-negative tumors as compared to normal breast, Mcl-1 staining was higher in ERAlpha+ tumors. Targeted Mcl-1 blockade using RNAi increased caspase-mediated cell death in ERAlpha+ breast cancer cells, resulting in sustained growth inhibition. In contrast, combined blockade of Bcl-2 and Bcl-xL only transiently induced apoptosis, as cells rapidly acclimated through Mcl-1 upregulation and enhanced Mcl-1 activity, as measured in situ using Mcl-1/Bim proximity ligation assays. Importantly, MCL1 gene expression levels correlated inversely with sensitivity to pharmacological Bcl-2/Bcl-xL inhibition in luminal breast cancer cells, whereas no relationship was seen between gene expression of BCL2 or BCL2L1 and sensitivity to Bcl-2/Bcl-xL inhibition. These results demonstrate that breast cancers rapidly deploy Mcl-1 to promote cell survival, particularly when challenged with blockade of other Bcl-2 family members, warranting the continued development of Mcl-1 selective inhibitors for targeted tumor cell killing. IMPLICATIONS: Mcl-1 levels predict breast cancer response to inhibitors targeting other Bcl-2 family members, and demonstrate the key role played by Mcl-1 in resistance to this drug class.


PURPOSE: To develop a novel surgical approach to provide consistent delivery of cell suspension into the subretinal space without cell leakage into the vitreous. METHODS: Cell viability was assessed following mock injections to determine the optimal size cannula for delivery of the cells. A pars plana without vitrectomy approach was used to create a subretinal bleb with balanced salt solution using a 41-gauge cannula. GFP-labeled retinal pigment epithelium cells were injected through transretinal (n = 8) and transscleral (n = 16) injection approaches. Optical coherence tomography, fundus photography and autofluorescence, and histological analysis were used to evaluate surgical success. RESULTS: The 30-gauge cannula yielded the highest recovery of cells with highest viability. The transretinal approach consistently resulted in transplanted cells in the vitreous, with some cells coming to rest on the inner limiting membrane. Conversely, the transscleral approach resulted in transplantation of cells into the subretinal space in 100% of cases. Histological analysis confirmed these results. CONCLUSION: We have developed a novel surgical approach that resulted in encapsulation of transplanted cells into the subretinal space with a 100% success rate. This approach will provide a useful tool for further cell transplantation study and may provide an approach for clinical application of delivering cells to the subretinal space.

With newer-generation ceramic components used in total hip arthroplasty, component fracture is a rare complication. However rare, when ceramic component fracture does occur, prompt identification and revision is necessary as delay can lead to dramatic failure with resultant metallosis as the extremely hard ceramic debris abrades remaining components. We present a case of a 70-year-old woman with ceramic liner fracture and an estimated 10-year delay in intervention with failure resulting in pelvic discontinuity and massive metallosis with associated cutaneous manifestation. She was treated with a complex revision and reconstruction and is 2 years postrevision without major complication. © 2016 The Authors.


Objectives The provisional criteria of the American College of Rheumatology (ACR) 2010 and the 2011 self-report modification for survey and clinical research are widely used for fibromyalgia diagnosis. To determine the validity, usefulness, potential problems, and modifications required for the criteria, we assessed multiple research reports published in 2010–2016 in order to provide a 2016 update to the criteria. Methods We reviewed 14 validation studies that compared 2010/2011 criteria with ACR 1990 classification and clinical criteria, as well as epidemiology, clinical, and databank studies that addressed important criteria-level variables. Based on definitional differences between 1990 and 2010/2011 criteria, we interpreted 85% sensitivity and 90% specificity as excellent agreement. Results Against 1990 and clinical criteria, the median sensitivity and specificity of the 2010/2011 criteria were 86% and 90%, respectively. The 2010/2011 criteria led to misclassification when applied to regional pain syndromes, but when a modified widespread pain criterion (the “generalized pain criterion”) was added misclassification was eliminated. Based on the above data and clinic usage data, we developed a (2016) revision to the 2010/2011 fibromyalgia criteria. Fibromyalgia may now be diagnosed in adults when all of the following criteria are met: (1) Generalized pain, defined as pain in at least 4 of 5 regions, is present. (2) Symptoms have been present at a similar level for at least 3 months. (3) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9. (4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses. Conclusions The fibromyalgia criteria have good sensitivity and specificity. This revision combines physician and questionnaire criteria, minimizes misclassification of regional pain disorders, and eliminates the previously confusing recommendation regarding diagnostic exclusions. The physician-based criteria are valid for individual patient diagnosis. The self-report version of the criteria is not valid for clinical diagnosis in individual patients but is valid for research studies. These changes allow the criteria to function as diagnostic criteria, while still being useful for classification. © 2016 Elsevier Inc.


Background: The frontal sinus is considered the most challenging sinus to address surgically. There are no current classifications of the degree of surgical complexity of different frontal sinus configurations. The aim of this study is to develop a classification system of the degree of complexity of frontal recess surgery based on preoperative computed tomography (CT) scans. Methods: Authors were asked to submit a classification system. These were circulated to all authors. Selection of the final 3 classifications was based on a majority consensus. These classifications were compared further for time-taken, ease-of-use, and interrater
agreement. These were assessed by the authors on 10 CT scans representing a range of anticipated surgical difficulty. Results: Out of 3 compared classifications, classification A was the quickest to score (1.44 minutes vs 1.57 minutes and 2.25 minutes), subjectively easiest (3.23 vs 4.07 and 5 on a visual analogue scale [VAS]), and had a moderate interrater agreement (0.52 vs 0.42 and 0.79). In addition, the grading of complexity was as good whether measurements were taken on the CT scans or whether size of the frontal ostium was visually estimated. Conclusion: We propose a fast, easy classification to anticipate the complexity of surgery in the frontal sinus and recess, for patients undergoing primary surgery. © 2016 ARS-AAOA, LLC.


Nuclear lamins are the major components of the nuclear lamina at the periphery of the nucleus, supporting the nuclear envelope and participating in many nuclear processes, including DNA replication, transcription and chromatin organization. A group of diseases, the laminopathies, is associated with mutations in lamin genes. One of the most striking cases is Hutchinson-Gilford progeria syndrome (HGPS) which is the consequence of a lamin A dominant negative mutant named progerin. Due to the abnormal presence of a permanent C-terminal farnesyl tail, progerin gradually accumulates on the nuclear membrane, perturbing a diversity of signalings and transcriptional events. The accumulation of progerin has led to the speculation that progerin possesses higher stability than the wild type lamin A protein. However, the low solubility of lamin proteins renders traditional immunoprecipitation-dependent methods such as pulse-chase analysis ineffective for comparing the relative stabilities of mutant and wild type lamins. Here, we employ a novel platform for inferring differences in lamin stability, which is based on normalization to a co-translated reporter protein following porcine teschovirus-1 2A peptide-mediated co-translational cleavage. The results obtained using this method support the notion that progerin is more stable than lamin A. Moreover, treatment of FTI reduces progerin relative stability to the level of wild type lamin A. © 2016 The Author(s). Published with license by Taylor & Francis. © Di Wu, Phillip A. Yates, Haoyue Zhang, and Kan Cao.


Objectives: Liver disease is an important contributor to morbidity and mortality in patients after Fontan surgery. There has been no large-scale survey of liver health in this population. We sought to explore the prevalence and predictors of liver disease in a multicenter cohort of adults with Fontan physiology. Methods: Subjects were recruited from 6 adult congenital heart centers. Demographics; clinical history; and laboratory, imaging, and histopathology data were obtained. Results: Of 241 subjects (median age 25.8 years [11.8-59.4], median time since Fontan 20.3 years [5.4-34.5]), more than 94% of those who underwent testing (208 of 221) had at least 1 abnormal liver-related finding. All hepatic imaging (n = 54) and liver histology (n = 68) was abnormal. Subjects with abnormal laboratory values had higher sinusoidal fibrosis stage (2 vs 1, . P = .007) and higher portal fibrosis stage (3 vs 1, . P = .003) compared with those with all normal values. Low albumin correlated with lower sinusoidal fibrosis stage (1 vs 2, . P = .02) and portal fibrosis stage (0 vs 3, . P = .002); no other liver studies correlated with fibrosis. Regenerative nodules were seen on 33% of histology specimens. Conclusions: Regardless of modality, findings of liver disease are common among adults with Fontan circulation, even those appearing clinically well. Cirrhosis is present in up to one-third of subjects. Correlations between hepatic fibrosis stage and clinical history or findings on noninvasive testing are few. Further research is needed to identify patients at risk for more severe liver disease and to determine the best methods for assessing liver health in this population. © 2016 The American Association for Thoracic Surgery.


CAMP-response element binding protein (CREB) is a nuclear transcription factor that has been implicated in the pathogenesis and maintenance of various types of human cancers. Identification of small molecule inhibitors of CREB-mediated gene transcription has been pursued as a novel strategy for developing cancer therapeutics. We recently discovered a potent and cell-permeable CREB inhibitor called 666-15. 666-15 is a bisnaphthamide and has been shown to possess efficacious anti-breast cancer activity without toxicity in vivo. In this study, we designed and synthesized a series of analogs of 666-15 to probe the importance of regiochemistry in naphthalene ring B. Biological evaluations of these analogs demonstrated that the substitution pattern of the alkoxy and carboxamide in naphthalene ring B is very critical for maintaining potent CREB inhibition activity, suggesting that the unique bioactive conformation accessible in 666-15 is critically important.


Fever and leukocytosis have many possible etiologies in injection drug users. We present a case of a 22-year-old woman with fever and leukocytosis that were presumed secondary to cotton fever, a rarely recognized complication of injection drug use, after an extensive workup. Cotton fever is a benign, self-limited febrile syndrome characterized by fevers, leukocytosis, myalgias, nausea and vomiting, occurring in injection drug users who filter their drug suspensions through cotton balls. While this syndrome is commonly recognized amongst the injection drug user population, there is a paucity of data in the medical literature. We review the case presentation and available literature related to cotton fever.


Quantifying the carbon footprints of grain crops is of great importance to the mitigation of agricultural greenhouse gases. Previous studies revealed that the agricultural greenhouse gas emissions of China kept increasing in the past few years. In this study, the life cycle assessment method was used to calculate the product and farm carbon footprints of rice, wheat and maize based on the governmental statistical datasets and published results. The spatial and temporal patterns of carbon footprint was analyzed, and the impacts of environmental and socioeconomic factors on carbon footprints were evaluated using canonical correspondence analysis. The results showed that the product carbon footprints of rice, wheat and maize corresponded to 1.06 ± 0.03, 0.50 ± 0.04 and 0.40 ± 0.03 kg CO2 eq/kg, while the farm carbon footprints were 7285 ± 78, 2800 ± 222 and 2707 ± 151 kg CO2 eq/ha. The total greenhouse gas emissions from three crops increased by 1.94%/y from 2004 to 2013. The farm carbon footprints of grain crops in the southern provinces were higher than those in the northern provinces. Topsoil clay fraction, latitude, arable land per capita in the rural areas, and longitude significantly affected the spatial distribution of carbon footprints. This study provides a novel insight into the spatial and temporal patterns of carbon footprint from grain crops in China. The results can serve as references for the development of mitigation measures of greenhouse gas in China. © 2016 Elsevier Ltd.


PURPOSE OF REVIEW: This report examines recent publications identifying phenotypic and functional heterogeneity among pancreatic beta cells and investigating their potential roles in normal and abnormal islet function. The development of new methods and tools for the study of individual islet cells has produced a surge of interest in this topic. RECENT FINDINGS: Studies of beta cell maturation and pregnancy-induced proliferation have identified changes in serotonin and transcription factors SDX2/3 expression as markers of temporal heterogeneity. Structural and functional heterogeneity in the form of functionally distinct ‘hub’ and ‘follower’ beta cells was found in mouse islets. Heterogeneous expression of Fltp (in mouse beta cells) and ST8SIA1 and CD9 (in human beta cells) were associated with distinct functional potential. Several impressive
reports describing the transcriptomes of individual beta cells were also published in recent months. Some of these reveal previously unknown beta cell subpopulations. SUMMARY: A wealth of information on functional and phenotypic heterogeneity has been collected recently, including the transcriptomes of individual beta cells and the identities of functionally distinct beta cell subpopulations. Several studies suggest the existence of two broad categories: a more proliferative but less functional and a less proliferative but more functional beta cell type. The identification of functionally distinct subpopulations and their association with type 2 diabetes underlines the potential clinical importance of these investigations.


Macrophage migration inhibitory factor (MIF) is a key cytokine/chemokine in the activation and recruitment of inflammatory T lymphocytes known to exacerbate experimental stroke severity. MIF effects are mediated through its primary cellular receptor, CD74, the MHC class II invariant chain present on all class II expressing cells, including monocytes, macrophages and dendritic cells (DC). We demonstrated previously that partial MHC class II/peptide constructs (pMHC) can effectively treat mice with experimental stroke, in part through their ability to competitively inhibit MIF/CD74 interactions and downstream signaling. However, the role of MIF and CD74 in human ischemic stroke is not yet well established. To evaluate the therapeutic potential for pMHC, we assessed MIF and CD74 expression levels and their association with disease outcome in subjects with ischemic stroke. MIF levels were assessed in blood plasma by ELISA and CD74 expression was quantified by flow cytometry and qRT-PCR in peripheral blood mononuclear cells (PBMCs) obtained from subjects with ischemic stroke and age and sex-matched healthy controls (HC). MIF levels were increased in plasma and the number of CD74+ cells and CD74 mRNA expression levels were significantly increased in PBMC of subjects with ischemic stroke versus HC, mainly on CD4+ T cells, monocytes and DC. Greater increases of CD74+ cells were seen in subjects with cortical vs. subcortical infarcts and the number of CD74+ cells in blood correlated strongly with infarct size and neurological outcomes. However, differences in MIF and CD74 expression were not affected by age, gender or lesion laterality. Increased CD74 expression levels may serve as a useful biomarker for worse stroke severity and predicted outcomes in subjects with ischemic stroke and provide a rationale for potential future treatment with pMHC constructs. © 2016 Elsevier Ltd.


AIM AND OBJECTIVES: To explore risk factors for a single fall and multiple falls in the first and second postoperative years among older people hip fracture patients. BACKGROUND: Older people hip fracture patients have a high probability of falling again after a fall incident. Risk factors for postoperative falls among older people hip fracture patients in Taiwan remain to be confirmed. DESIGN: Secondary analysis. METHODS: Data collected from control groups of two clinical trials conducted during 2001-2004 and during 2005-2009 were selected. Overall, 181 older adults who underwent hip fracture surgery were assessed at predischarge and postdischarge. Participant data were collected through home visits. RESULTS: Decline in unaffected limb quadriceps muscle endurance was a crucial predictor of a single fall in the first postoperative year for older people hip fracture patients. Advanced age and more severe depressive symptoms were the crucial predictor for multiple falls. Engagement in activities of daily living was the crucial predictor for falls during the first to second postoperative years among older people hip fracture patients. CONCLUSION: In Taiwan, postoperative falls that occur within 1-2 years of a hip fracture are associated with a high incidence of single and multiple falls in older people. The crucial predictors of falls in the first and second year after a hip fracture include unaffected limb quadriceps endurance, age, depression status and postdischarge ADLs in older people. This article is protected by copyright. All rights reserved.

The release of dopamine from terminals in the nucleus accumbens (NAc) is regulated by a number of factors, including voltage gated ion channels, D2-autoreceptors and nicotinic acetylcholine receptors (nAChRs). Cholinergic interneurons (CINs) drive dopamine release through activation of nAChRs on dopamine terminals. Using cyclic voltammetry in mouse brain slices, nAChR-dependent spontaneous dopamine transients and the mechanisms underlying the origin were examined in the NAc. Spontaneous events were infrequent (0.3 per minute), but the rate and amplitude were increased after blocking Kv channels with 4-aminopyridine. Although, the firing frequency of CINs was increased by blocking glutamate reuptake with TBOA and the Sk blocker apamin, only 4-aminopyridine increased the frequency of dopamine transients. In contrast, inhibition of CIN firing with the mu/delta selective opioid [Met5]enkephalin (1 nM) decreased spontaneous dopamine transients. Cocaine increased the rate and amplitude of dopamine transients, suggesting that the activity of the dopamine transporter limits the detection of these events. In the presence of cocaine, the rate of spontaneous dopamine transients was further increased after blocking D2-autoreceptors. Blockade of muscarinic receptors had no effect on evoked dopamine release suggesting that feedback inhibition of acetylcholine release was not involved. Thus, while spontaneous dopamine transients are reliant on nAChRs, the frequency was not strictly governed by the activity of CINs. The increase in frequency of spontaneous dopamine transients induced by cocaine was not due to an increase in cholinergic tone and are likely a product of an increase in detection resulting from decreased dopamine reuptake.

SIGNIFICANCE STATEMENT: The actions of dopamine in the nucleus accumbens are thought to be responsible for endogenous reward and the reinforcing properties of drugs of abuse, such as psychostimulants. The present work examines the mechanisms underlying nicotinic acetylcholine receptor induced spontaneous dopamine release. This study demonstrates that spontaneous dopamine release is (1) dependent of the activation of nicotinic receptors (2) independent on the spontaneous activity of cholinergic interneurons and (3) that cocaine increased the detection of dopamine transients by prolonging the presence and increasing the diffusion of dopamine in the extracellular space. The release of acetylcholine is therefore responsible for spontaneous dopamine transients and cocaine augments dopamine tone without altering activity of cholinergic interneurons.


Ectoine has osmoprotective effects on Sinorhizobium meliloti that differ from its effects in other bacteria. Ectoine does not accumulate in S. meliloti cells; instead, it is degraded. The products of the ehuABCD-eutABCDE operon were previously discovered to be responsible for the uptake and catabolism of ectoine in S. meliloti. However, the mechanism by which ectoine is involved in the regulation of the ehuABCD-eutABCDE operon remains unclear. The ehuR gene, which is upstream of and oriented in the same direction as the ehuABCD-eutABCDE operon, encodes a member of the MocR/GntR family of transcriptional regulators. Quantitative reverse transcription-PCR and promoter-lacZ reporter fusion experiments revealed that EhuR represses transcription of the ehuABCD-eutABCDE operon, but this repression is inhibited in the presence of ectoine. Electrophoretic mobility shift assays and DNase I footprinting assays revealed that EhuR bound specifically to the DNA regions overlapping the -35 region of the ehuA promoter and the +1 region of the ehuR promoter. Surface plasmon resonance assays further demonstrated direct interactions between EhuR and the two promoters, although EhuR was found to have higher affinity for the ehuA promoter than for the ehuR promoter. In vitro, DNA binding by EhuR could be directly inhibited by a degradation product of ectoine. Our work demonstrates that EhuR is an important negative transcriptional regulator involved in the regulation of ectoine uptake and catabolism and is likely regulated by one or more end products of ectoine catabolism. © 2016 American Society for Microbiology.


Fluorescence microscopy is an essential tool for the biosciences, enabling the direct observation of proteins in their cellular environment. New methods that facilitate attachment of photostable synthetic fluorophores with genetic specificity are needed to advance the frontiers of biological imaging. Here, we describe a new
set of small, selective, genetically encoded tags for proteins based on a heterodimeric coiled-coil interaction between two peptides: CoilY and CoilZ. Proteins expressed as a fusion to CoilZ were selectively labeled with the complementary CoilY fluorescent probe peptide. Fluorophore-labeled target proteins were readily detected in cell lysates with high specificity and sensitivity. We found that these versatile interacting peptide (VIP) tags allowed rapid and specific delivery of bright organic dyes or quantum dots to proteins displayed on living cells. Additionally, we validated that either CoilY or CoilZ could serve as the VIP tag, which enabled us to observe two distinct cell-surface protein targets with this one heterodimeric pair.

Purpose: A retrospective analysis of tonal and speech loudness discomfort levels (LDLs) relative to a subjective report of sound tolerance (SRST) was performed to explore the relation between the 2 commonly used clinical measures. Method: Tonal LDLs and SRST were measured for 139 U.S. military veterans who were recruited into a study providing intervention for tinnitus. Spearman's rank correlation coefficients were computed to assess the relation between the tonal and speech LDLs and the SRST. Results: Only weak correlations were found between tonal LDLs and SRST and between speech LDLs and SRST. Conclusion: If LDLs ratings of SRST measured the same phenomenon, the measures would be strongly negatively correlated. The weak correlations found between the measures suggest that LDLs do not accurately represent a patient's ability to tolerate sound in daily life. © 2016 American Speech-Language-Hearing Association.


The vestibular blood-labyrinth barrier (BLB) is comprised of perivascular-resident macrophage-like melanocytes (PVM/Ms) and pericytes (PCs), in addition to endothelial cells (ECs) and basement membrane (BM), and bears strong resemblance to the cochlear BLB in the stria vascularis. Over the past few decades, in vitro cell-based models have been widely used in blood-brain barrier (BBB) and blood-retina barrier (BRB) research, and have proved to be powerful tools for studying cell-cell interactions in their respective organs. Study of both the vestibular and strial BLB has been limited by the unavailability of primary culture cells from these barriers. To better understand how barrier component cells interact in the vestibular system to control BLB function, we developed a novel culture medium-based method for obtaining EC, PC, and PVM/M primary cells from tiny explants of the semicircular canal, sacculus, utriculus, and ampullae tissue of young mouse ears at post-natal age 8-12 d. Each phenotype is grown in a specific culture medium which selectively supports the phenotype in a mixed population of vestibular cell types. The unwanted phenotypes do not survive passaging. The protocol does not require additional equipment or special enzyme treatment. The harvesting process takes less than 2 h. Primary cell types are generated within 7-10 d. The primary culture ECs, PCs, and PVM/M have consistent phenotypes more than 90% pure after two passages (approximately 3 weeks). The highly purified primary cell lines can be used for studying cell-cell interactions, barrier permeability, and angiogenesis.


OBJECTIVE: To examine the relationship between dietary cruciferous vegetable intake and selected tumour biomarkers for histone acetylation (H3K9ac, H3K18ac, HDAC3 and HDAC6), proliferation (Ki-67) and cell-cycle regulation (p21) from breast tissue. DESIGN: The study used baseline data of women recruited to participate in a clinical trial of sulforaphane supplement. Dietary cruciferous vegetable intake was collected through a validated Arizona Cruciferous Vegetable Intake Questionnaire. Breast tissue was obtained from biopsy samples. Spearman correlations were calculated between intake of specific cruciferous vegetables and biomarkers. Tissue biomarkers were log2-transformed to obtain approximate normality. Linear regression analyses were conducted to examine associations between cruciferous vegetable intake and biomarkers adjusting for age and use of non-steroidal anti-inflammatory drugs. False discovery rate (FDR) was used to account for multiple comparisons. SETTING: Clinical trial baseline. SUBJECTS: Fifty-four women who had abnormal mammogram findings and were scheduled for breast biopsy. RESULTS: Mean intake of total cruciferous vegetables from all food sources was 81.7 (sd 57.3) g/d. Mean urinary total sulforaphane metabolites was 0.08 (sd 0.07) microm/mm creatinine. Total cruciferous vegetable intake was inversely associated with Ki-67 protein expression in breast ductal carcinoma in situ (DCIS) tissue (beta=-0.004; se=0.001; FDR q value=0.03), but not in benign or invasive ductal carcinoma (IDC) tissue. No association was found for other biomarkers measured (HDAC3, HDAC6, H3K9, H3K18 and p21) in all tissues examined (benign, DCIS and IDC). CONCLUSIONS: The present study sought to provide additional evidence for the potential role of sulforaphane in histone acetylation and cell proliferation. Here, we report that total cruciferous vegetable intake is associated with decreased cell proliferation in breast DCIS tissue.
an example of the utility of a platform to study platelet activation and microaggregate formation in the bloodstream (convection-limited regime) relative to the local site of thrombus formation.


Objective: This study assessed the relationship of timeliness of autism spectrum disorder (ASD) diagnosis with current use of ASD-related services in a nationally representative sample of U.S. children. Methods: The Centers for Disease Control's (CDC's) Survey of Pathways to Diagnosis and Services was used to assess experiences of 722 children ages six to 11 with ASD. Bivariate and multivariate analyses were used to explore associations between age at ASD diagnosis and delay in ASD diagnosis and use of health services. Health services included current use of behavioral intervention (BI) therapy, school-based therapy, complementary and alternative medicine (CAM), and psychotropic medications. Results: Mean age at ASD diagnosis was 4.4 years, and mean diagnostic delay was 2.2 years. In adjusted analysis, older age at diagnosis (4 versus 4) was associated with lower likelihood of current BI or school-based therapy use and higher likelihood of current psychotropic medication use. Analyses that treated age at diagnosis as a continuous variable found that likelihood of current psychotropic medication use increased with older age at diagnosis. A delay of two or more years between parents' first discussion of concerns with a provider and ASD diagnosis was associated with higher likelihood of current CAM use. Likelihood of current CAM use increased as delay in diagnosis became longer. Conclusions: Both older age at diagnosis and longer delay in diagnosis were associated with different health services utilization patterns among younger children with ASD. Prompt and early diagnosis may be associated with increased use of evidence-based therapies for ASD.